A novel palladium-catalysed approach to functionalised N-heterocycles

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A Novel Palladium-Catalysed Approach to Functionalised *N*-Heterocycles

by

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BForSc. (Hons)

Submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy

Deakin University

April, 2011

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"Die organische Chemie kann einen jetzt ganz toll machen. Sie kommt mir wie ein Urwald der Tropenländer vor, voll der merkwürdigsten Dinge, ein ungeheures Dickicht, ohne Ausgang und Ende, in das man sich nicht hinein wagen mag."

Friedrich Wöhler (1835)

"At this time organic chemistry can drive one completely crazy. It seems to me like a primeval tropical jungle, full of the most remarkable things, an amazing thicket, without escape or end, into which one would not dare to enter."

Acknowledgments

First of all I would like to thank my principal supervisor Dr Fred Pfeffer for the time, support, friendship, tennis matches, building projects and many other opportunities he has provided me during my time at Deakin University. In addition to being an excellent mentor and role model, Fred has bestowed on me what it means to be a scientist of the highest standard, both in the lab and with written communication, and for this I thank him.

Thankyou to my research supervisor Scott Stewart and his wife Marta for teaching me all about the wonderful world of palladium chemistry, and for their friendship and hospitality during the numerous weeks I spent in Perth at the University of Western Australia.

I would like to thank a number of my colleagues at Deakin University incluing Professor Neil Barnett and Dr Luke Henderson for the many useful discussions we have held over the past few years. Thankyou to Gail Dyson (NMR spectroscopy) and Dr Xavier Conlan (Mass Spectrometry) for their assistance with my project. Also a big thankyou to my fellow postgraduate students and lab colleagues for their friendship and the many laughs we have shared over the past 7 years at Deakin University.

A wise man by the name of Georg C. Lichtenberg (1742-1799), a professor of physics at Göttingen University once said: “He who knows nothing but chemistry does not know chemistry either”. To this end, I would like to thank all my friends and family, in particular my parents, who have supported me over the years and helped me to maintain a life outside of chemistry. I would especially like to thank my wife Carly for her love and support during the challenging time of my PhD.

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

δ (ppm)	Chemical shift
^{o}C	Degrees Celsius
π	pi-bond
σ	sigma-bond
µL	Microlitre
Ac	Acetyl
Ar	Aromatic
AR	Analytical reagent
ATP	Adenosine triphosphate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
br	Broad peak
Bs	Benzenesulfonyl
Bn	Benzyl
Bz	Benzoyl
Cbz	Carboxybenzyl
$CDCl_3$	Deuterated chloroform
Co.	Company
Cy_2NMe	*N,N*-dicyclohexylmethylamine
d	Doublet
de	Diastereomeric excess
dig	Digonal
dr	Diastereomeric ratio
DavePhos	2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	*N,N*-diisopropylmethylamine
DMF	Dimethylformamide
DM	Diabetes Mellitus

DMAP	4-Dimethylaminopyridine
DMEDA	*N,N'*-dimethylethylenediamine
DNBz	Dinitrobenzoyl
DNBS	Dinitrobenzenesulfonyl
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dba	Dibenzylideneacetone
DMSO-*d6*	Deuterated dimethylsulfoxide
ee	Enantiomeric excess
EDG	Electron donating group
EWG	Electron withdrawing group
EDCI	*N*-3-dimethylaminopropyl-*N'*-ethyl carbodiimide hydrochloride
ESI	Electronspray Ionisation
Et	Ethyl
EtOAc	Ethyl Acetate
EtOH	Ethanol
g	grams
h.	hours
HDAC	Histone deacetylase
HPLC	High performance liquid chromatography
Hz	Hertz
HRMS	High Resolution Mass Spectrometry
HOBt	1-hydroxybenzotriazole hydrate
HIV-1	Human Immunodeficiency Virus Type 1
J	Coupling constant
L	Litres
L	Ligand
m	Multiplet
mM	Millimolar
mins	Minutes
Me	Methyl
MeOH	Methanol

MeCN	Acetonitrile
MHz	Megahertz
mg	Milligram
mL	Millilitres
mmol	Millimoles
mol	Mole
Mp	Melting point
MW	Microwave irradiation
m/z	Mass to charge ratio
m	Meta
m-CPBA	*meta*-Chloroperoxybenzoic acid
mRNA	Messenger ribonucleic acid
NEt_3	Triethylamine
NMR	Nuclear magnetic resonance
NBS	*N*-bromosuccinimide
NHC	N-Heterocyclic carbene
NOE	Nuclear Overhauser Effect
*n*Bu	*n*-butyl
Ns	2-nitrobenzenesulfonyl
Nosyl	2-nitrobenzenesulfonyl
nm	Nanometre
OAc	Acetate
o	Ortho
p	Para
PPAR	Peroxisome-proliferator activated receptor
Pet Sp.	Petroleum Spirits (40-60 ^{o}C)
Ph	Phenyl
pH	Potential of hydrogen
PhMe	Toluene
ppm	Parts per million
PPA	Polyphosphoric acid

$PyBr_3$	Pyridinium tribromide
q	Quartet
quin	Quintet
rt	Room temperature
RCM	Ring closing metathesis
s	Singlet
SEM	[2-(trimethylsilyl)ethoxy]methyl
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T2D	Type 2 diabetes
THF	Tetrahydrofuran
Ts	*p*-toluenesulfonyl
Tosyl	*p*-toluenesulfonyl
Tf	Trifluoromethanesulfonyl
TFP	Trifuryl phosphine
Trig	Trigonal
t_r	Retention time
tert	Tertiary
*t*Bu	*tert*-butyl
TBACl	Tetra-*n*-butylammonium chloride
TBAF	Tetra-*n*-butylammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
THβC	Tetrahydro-β-carboline
THIQ	Tetrahydroisoquinoline
TMS	Trimethylsilane
TMEDA	Tetramethylethylenediamine
TBDMS	*tert*-butyldimethylsilyl
TZD	Thiazolidinedione
TOFMS	Time of flight mass spectrometry
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Publications

Parts of this work have been or will be published (publications appear in their entirety in Appendix One):

Domino Heck-aza-Michael Reactions:
Efficient Access to 1-Substituted Tetrahydro-*β*-carbolines
Daniel L. Priebbenow, Luke C. Henderson, Frederick M. Pfeffer, Scott G. Stewart
Journal of Organic Chemistry, **2010**, *75*, 1787-1790.

A General Approach to *N*-Heterocyclic Scaffolds Using Domino Heck-aza-Michael Reactions
Daniel L. Priebbenow, Scott G. Stewart, Frederick M. Pfeffer
Organic & Biomolecular Chemistry, **2011**, *9*, 1508-1515.

A One-pot, Three Component Approach to Functionalised Tetrahydroisoquinolines Using Domino Heck-aza-Michael Reactions
Daniel L. Priebbenow, Frederick M. Pfeffer, Scott G. Stewart
European Journal of Organic Chemistry, **2011**, *9*, 1632-1635.

Asymmetric Domino Heck-aza-Michael Reactions
Daniel L. Priebbenow, Scott G. Stewart, Frederick M. Pfeffer
Submitted, May 2011.

Abstract

The central core of a number of biologically active natural products and pharmaceuticals often contain an *N*-heterocycle. The development of new, efficient methodology for the synthesis of indole-based *N*-heterocycles (for example tetrahydro-*β*-carbolines, azepinoindoles and indoloazocines) was investigated during this research project. Two approaches were explored, employing either an *intramolecular* Heck reaction or *intermolecular* Heck reaction at the indole-2-position.

Although the intramolecular Heck reaction proved unsuccessful, research into the intermolecular Heck reaction ultimately lead to the development of a domino Heck-aza-Michael reaction for the preparation of a series of C1-substituted tetrahydro-*β*-carboline scaffolds. This domino Heck-aza-Michael methodology was then successfully applied to the synthesis of both tetrahydroisoquinoline and isoindoline heterocycles.

A one-pot, three-component method incorporating a domino Heck–aza-Michael reaction was developed for the rapid synthesis of functionalised tetrahydroisoquinolines. Following the *in situ* generation of an acrylamide, a domino process involving intermolecular Heck reaction and subsequent intramolecular aza-Michael addition afforded tetrahydroisoquinolines bearing C1-acetamide functionality.

Using chiral amine substrates, an asymmetric domino Heck-aza-Michael reaction was developed for the preparation of chiral 1,3-disubstituted *N*-heterocycles in good yields and with moderate to high diastereoselectivity.

A range of the current methods available were then employed in the synthesis of indole-based *N*-heterocyclic scaffolds, which were further derivatised as potential PPARγ agonists for the treatment of type 2 diabetes.

Plain English Summary

The efficient preparation of molecules used for the treatment of a number of diseases is highly sought after by the pharmaceutical industry. This report details the development of a new, rapid and efficient method for the synthesis of the central core of a number of these pharmaceuticals. This new methodology allows for a reduction in the time, money, effort and minimises the generation of waste during the synthetic process. The preparation of a series of molecules for the treatment of type 2 diabetes is also described herein.

Chapter One
Introduction

Thesis Overview

The research presented in this thesis details efforts to develop new palladium-catalysed methodology to access *N*-heterocyclic scaffolds. A brief investigation into the further functionalisation of selected indole-based *N*-heterocycles as potential PPARγ agonists for the treatment of type 2 diabetes is also presented.

The introductory chapter (*Chapter One*) presents a review of the current synthetic methodologies available to access indole-based *N*-heterocycles from tryptamine. Palladium chemistry at the indole-2-position and the Heck reaction in particular are discussed in detail in addition to a brief review of domino reactions and their many advantages. The design and synthesis of indole-based PPARγ agonists is introduced in this chapter and the project aims complete this chapter.

Chapter Two details attempts to develop new methodology to access a range of indole-based scaffolds differing in both ring size and functionality introduced during *N*-heterocycle formation. The preparation of the new ring system employing an intramolecular Heck reaction subsequent to the tethering of the appropriate olefin from the N_{10}-amine of tryptamine was investigated.

To further expand the methodology for the synthesis of indole-based *N*-heterocycles, the intermolecular Heck reaction at the indole-2-position, followed by addition of the N_{10}-amine of tryptamine was explored. The successful development of a domino Heck-aza-Michael reaction for the synthesis of C1-substituted tetrahydro-*β*-carbolines is described in *Chapter Three*.

In addition to the synthesis of tetrahydro-*β*-carbolines, the extension of the domino Heck-aza-Michael process for the synthesis of a number of other *N*-heterocycles is presented in *Chapter Four*. The development of both a multicomponent and an asymmetric variant of this domino Heck-aza-Michael methodology are also described.

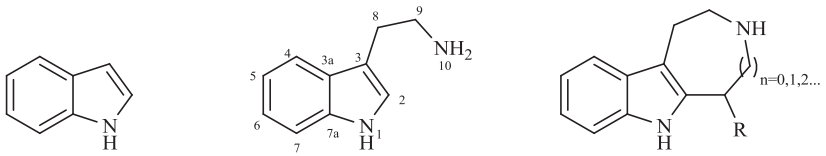
Chapter Five discusses the recent use of indole-based compounds as PPARγ agonists for the treatment of type-2-diabetes. Our contribution to this burgeoning field focused on a number of indole-based *N*-heterocyclic scaffolds, readily accessed from tryptamine. The selection of several of these scaffolds and further functionalisation as PPARγ agonists is presented.

Chapter Six provides the concluding remarks for this research project and presents some ideas for the future work. Also included in this thesis are experimental details for all of the reactions carried out during this research project (*Chapter Seven*), as well as a copy of the publications resulting from the work contained within this thesis in *Appendix One*.

1.1 Chapter Overview

Indole-based *N*-heterocycles are ubiquitous and many exhibit interesting biological activity.[1] There are several different forms of these heterocyclic scaffolds present in nature, differing in both ring size and functionality and these are introduced in the following chapter. This chapter also evaluates a number of the synthetic strategies currently available to access indole-based *N*-heterocycles from tryptamine.

Although the indole moiety is itself an *N*-heterocycle, the terminology "*N*-heterocycle" as used in the remainder of this document refers to the C-N heterocycle attached to the indole scaffold at the indole-2- and indole-3-position (Figure 1.1). Where reference is made to the N_{10}-amine of tryptamine (**2**), it refers to the amine tethered to the indole scaffold at the indole-3-position (Figure 1.1)



Indole **1** *Tryptamine* **2** *Indole-based N-heterocycle*

Figure 1.1 A graphical depiction of the terms used frequently within this thesis

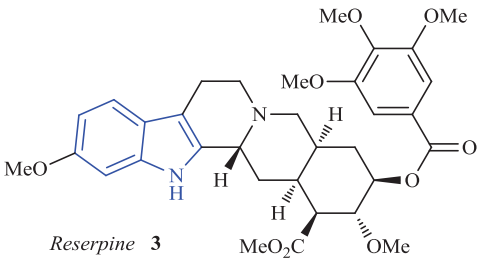
This introductory chapter details previous approaches to the application of palladium chemistry at the indole-2-position, palladium-mediated domino reactions and provides a comprehensive review of the Heck reaction including catalytic considerations.

This chapter also briefly introduces the synthesis of indole-based PPARγ agonists. Previous research by the Pfeffer group identified indole-based PPARγ agonists possessing a modest level of insulin-sensitising activity.[2-3] Attention turned to the indole-scaffold in an attempt to increase the insulin-sensitising activity of these potential PPARγ agonists by varying the size and functionality contained within the indole-based *N*-heterocycle.

1.2 Indole Alkaloids

The importance of heterocycles is evident due to their wide use in chemical, biological and industrial settings. Heterocycles form the central core of numerous biologically active natural products and pharmaceutical agents, and many are applied in other settings as herbicides and corrosion inhibitors.[1] Currently, over one half of the 20 million or more chemical compounds registered contain heterocyclic systems.[1]

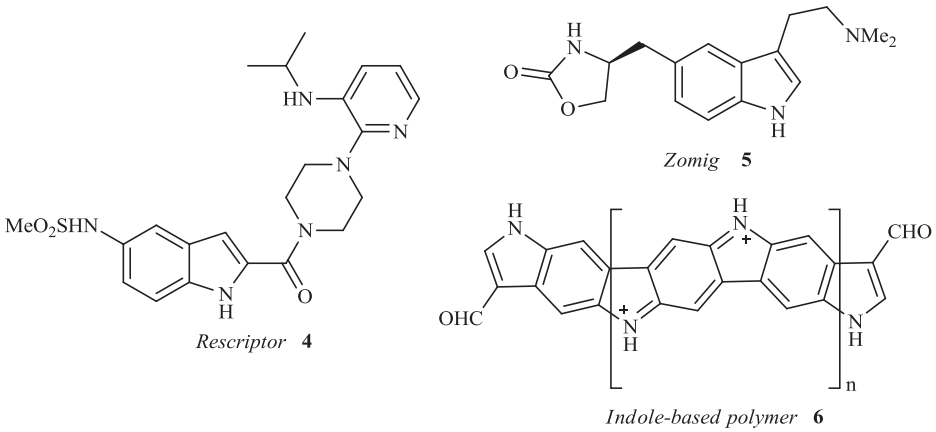
The benzo[*b*]pyrrole heterocycle (known trivially as indole) is one of the most commonly observed heterocycles. The indole moiety is present in a large number of natural products, many of which exhibit interesting biological activity,[4-7] for example reserpine (**3** - Figure 1.2), introduced in the 1950's as one of the first drugs to treat diseases of the central nervous system.[8] The natural incorporation of an indole group into the biologically important amino acid tryptophan is further evidence of its implicit relevance to life.



Reserpine **3**

Figure 1.2 The indole scaffold as found in the natural products reserpine[8]

The indole scaffold has been successfully employed in numerous pharmaceutical agents, for example HIV-1 reverse transcriptase inhibitors (Rescriptor **4**, Figure 1.3) and new antimigraine drugs (Zomig **5**, Figure 1.3). This indole functionality has also been utilised in other areas of chemistry, including polymer chemistry for the fabrication of micro pH sensors (indole polymer **6**, Figure 1.3).[9]



Rescriptor **4**

Zomig **5**

Indole-based polymer **6**

Figure 1.3 The indole heterocycle employed in a number of pharmaceutical agents and polymers

1.2.1 The Synthesis of Indole-Based *N*-Heterocycles from Tryptamine

The abundance of both serotonin and tryptophan derivatives in nature have inspired organic chemists to design and synthesise thousands of indole-containing pharmaceuticals.[9] An

important subset of these indole alkaloids possess a third ring (more specifically a C-N heterocycle) fused at the indole-2 and indole-3 position (Figure 1.4).

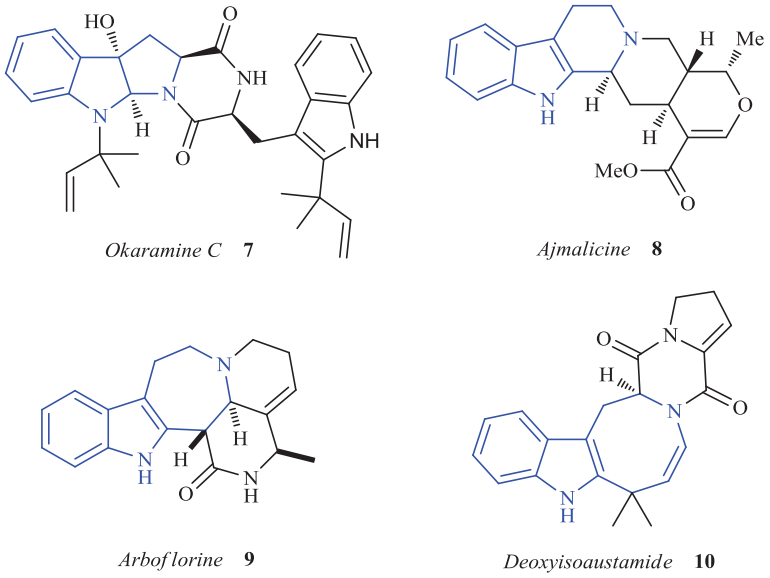


Figure 1.4 Indole-based natural products that contain additional C-N heterocycles of varying sizes

The pyrrolo[2,3-*b*]indole skeleton (containing an additional 5-membered *N*-heterocycle) is found in a number of naturally occurring compounds[10-11] (for example the insecticide okaramine C (**7**) - Figure 1.4).[12] This pyrroloindole scaffold is central to several other biologically active natural products, showing potential as anticancer agents and potent vasodilators.[13-17]

The tetrahydro-*β*-carboline (containing an additional 6-membered *N*-heterocycle) forms the central core of numerous pharmaceutical targets developed for the treatment of medical conditions including breast cancer, type-2-diabetes and bacterial infections.[6, 18-21] This ring system is also prevalent in several more structurally complex natural products including the secologanin-type terpinoid indole alkaloid ajmalicine (**8** - Figure 1.4) and the antihypertensive agent reserpine (**3** - Figure 1.2).[8, 18, 22-25]

The azepino[4,5-*b*]indole skeleton containing an additional 7-membered *N*-heterocycle has been identified in a number of recently isolated natural products including arboflorine (**9** - Figure 1.4).[26-27] The indoloazocine scaffold (which contains an additional 8-membered ring) is central to numerous natural products including the lundurines, okaramine N, and deoxyisoaustamide **10** (Figure 1.4).[28-33] These indoloazocines have also been employed as useful intermediates in the synthesis of larger molecules.[34]

Due to their high level of biological activity, it is important that the aforementioned indole scaffolds can be rapidly accessed synthetically. The use of methodology that facilitates the installation of a variety of functional groups is also highly desirable in a medicinal chemistry setting, with a simple common starting point for the synthesis of such *N*-heterocyclic systems being advantageous.

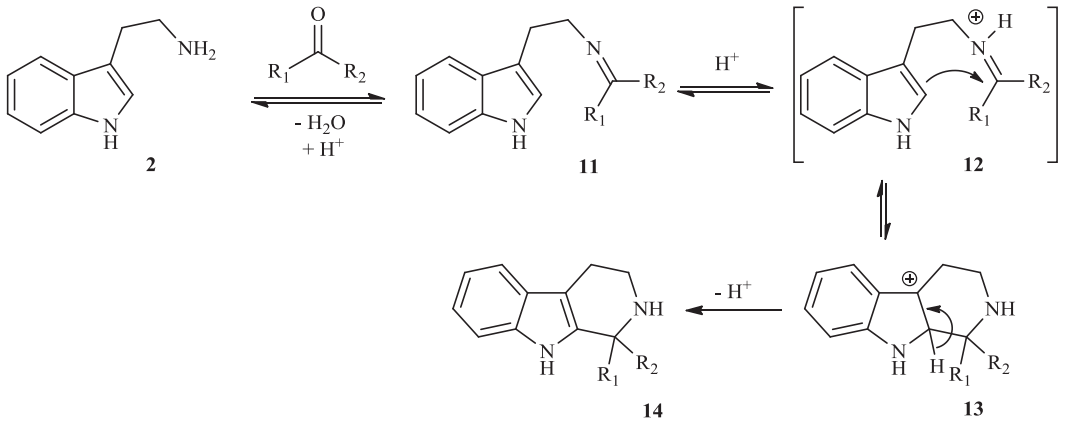
The synthesis of indole-based *N*-heterocycles within this research project was limited to those where the tricyclic scaffolds are accessible from tryptamine or similar tryptophan derivatives. Tryptamine (**2**) is a readily available source of the indole ring system and is commonly used as a starting material for the synthesis of indole-based *N*-heterocycles, as it already contains multiple sites for further functionalisation.

Current methods to prepare tricyclic indole-based scaffolds from tryptamine include the Pictet-Spengler reaction, the Bischler-Napieralski reaction, and numerous transition-metal catalysed cyclisations. The following section describes these relevant synthetic approaches available for the synthesis of indole-based *N*-heterocycles.

1.2.2 The Pictet-Spengler Reaction

The Pictet-Spengler reaction is the most common method for the synthesis of tetrahydro-*β*-carbolines (TH*β*Cs).[35-36] This method involves the acid-catalysed reaction of an appropriate aryl-amine and a carbonyl compound (usually an aldehyde or ketone) to form a new C-N heterocycle.[37] This reaction was originally developed by Pictet and Spengler in 1911 for the synthesis of tetrahydroisoquinolines from phenethylamine, however it was soon realised that this reaction also took place using tryptamine to form the tetrahydro-*β*-carboline scaffold in high yields (Scheme 1.1).[38]

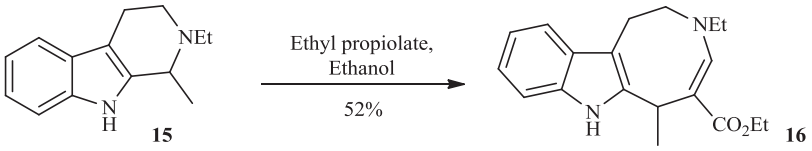
The Pictet-Spengler reaction includes the formation of a Schiff base **11** (imine) from the condensation of the amine and a carbonyl compound. The imine is then attacked by the indole-scaffold, promoted by the acid catalyst to form intermediate **13**.[39] Deprotonation of **13** follows to form the tetrahydro-*β*-carboline scaffold **14** (Scheme 1.1).



Scheme 1.1 The acid-catalysed Pictet-Spengler reaction for the synthesis of tetrahydro-*β*-carbolines

This reaction performs well for the synthesis of 6-membered *N*-heterocycles using simple acid catalysts (for example trifluoroacetic acid). To expand the scope of this reaction sequence, several modifications to the Pictet-Spengler reaction have been developed in recent years include the synthesis of oxygen containing heterocyclic systems,[40-42] the use of non-acid catalysts[43-46] and modified aldehyde reagents, [22-23, 25, 47] microwave-assisted synthesis[48-50] and asymmetric variants.[51-54]

The Pictet-Spengler reaction has been employed to great effect in the total synthesis of natural products as well as in the preparation of a number of potential pharmaceutical agents.[55-56] Tetrahydro-*β*-carbolines synthesised using the Pictet-Spengler reaction (for example TH*β*C **15**) have also been employed as useful intermediates in the synthesis of natural products and medicinal chemistry targets containing larger indole-based *N*-heterocycles (for example indoloazocine **16** - Scheme 1.2).[33, 57-61]

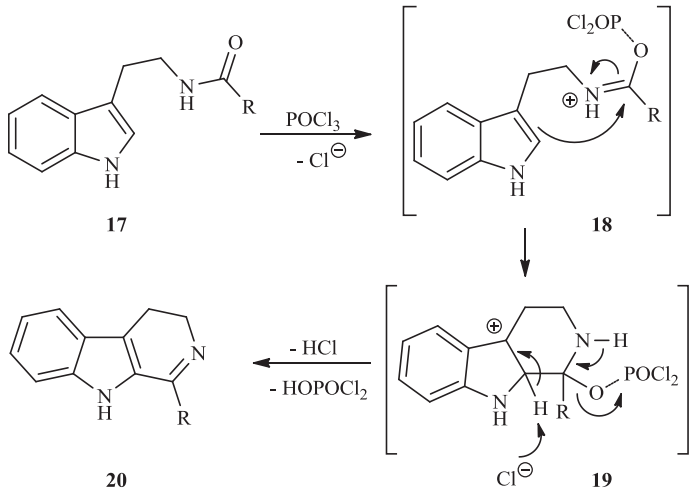


Scheme 1.2 The synthesis of an indoloazocine from a tetrahydro-*β*-carboline intermediate

The Pictet-Spengler reaction allows for the synthesis of 6-membered *N*-heterocycles with the possibility of introducing a wide variety of functional groups at the C1-position of the newly formed tetrahydro-*β*-carboline, depending on the availability and stability of the carbonyl compounds required.

1.2.3 The Bischler-Napieralski Reaction

An alternative method to access tetrahydro-*β*-carboline scaffolds is the Bischler-Napieralski reaction. As in the case of the Pictet-Spengler reaction, this methodology was first developed for the synthesis of isoquinolines, but in this instance involves the cyclodehydration of an amide to form the new 6-membered *N*-heterocycle (Scheme 1.3).[37, 62]



Scheme 1.3 The formation of an indole-based *N*-heterocyclic system through the Bischler-Napieralski reaction

This reaction follows a very similar mechanism to the Pictet-Spengler reaction, through formation of intermediate **18** following reaction of an amide **17** with a dehydrating agent ($POCl_3$, P_2O_5, PPA, TFAA, Tf_2O or similar),[63] which is then attacked by the electron-rich indole scaffold. Deprotonation of **19** leads to formation of the new C1-substituted 6-membered *N*-heterocycle **20** (Scheme 1.3).[64]

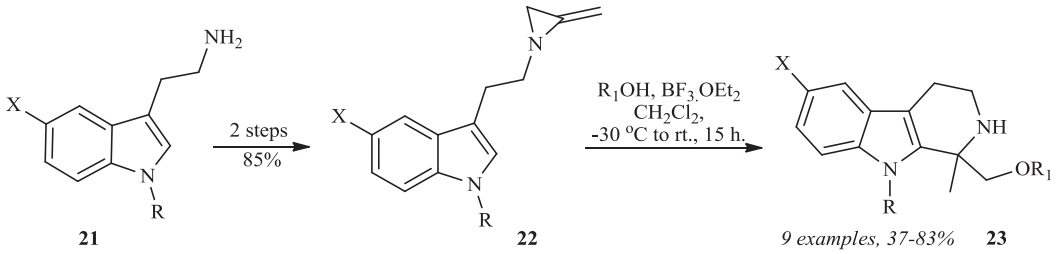
The imine of the resultant product **20** can be readily reduced (asymmetrically if required)[65-67] to form the secondary amine, which can then be functionalised for the preparation of potential pharmaceutical agents,[68] or as the key step in the total synthesis of natural products.[69-73]

In comparison to the Pictet-Spengler and Bischler-Napieralski reactions developed over 100 years ago, efficient methodology to access 5-, 7-, and 8-membered rings attached to the indole scaffold have only been developed in recent years. A number of these methods are described in the following section.

1.2.4 Acid-Catalysed Cyclisations

Acid-catalysed methodology (either a Brønsted-Lowry or Lewis acid) to access 6-, 7-, and 8-membered indole-based *N*-heterocycles has been recently developed, often for the synthesis of intermediates as part of larger total syntheses.

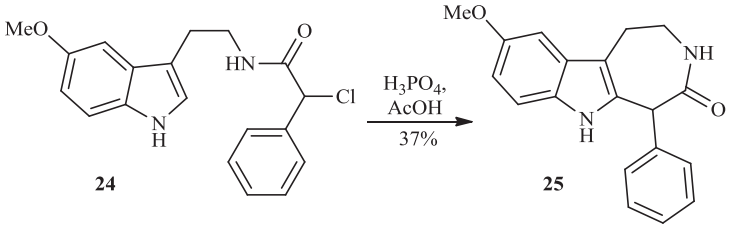
The synthesis of 1,1-disubstituted tetrahydro-*β*-carbolines **23** from 2-methylaziridines **22** was reported recently by Mumford *et al.*[74] This methodology allowed access to a range of ether substituted TH*β*Cs from tryptamine **21**, in moderate to excellent yields using a Lewis acid catalysed electrophilic cyclisation (Scheme 1.4). An asymmetric version of this reaction using α-methyl tryptamine was also reported.[74]



21 **22** *9 examples, 37-83%* **23**

Scheme 1.4 The synthesis of disubstituted tetrahydro-*β*-carbolines from 2-methylaziridines

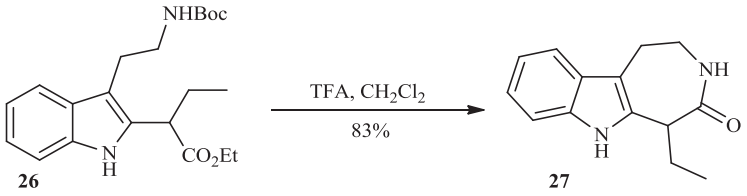
The use of traditional acid-catalysis has also been employed in the formation of functionalised azepinoindoles. The synthesis of 5-phenylhexahydroazepino[4,5-*b*]indoles **25** from tryptamines as potential neuroleptic agents was reported by Elliot *et al*. using a phosphoric acid mediated alkylation (Scheme 1.5).[75]



24 **25**

Scheme 1.5 Acid-medicated cyclisation to form the azepinoindole scaffold

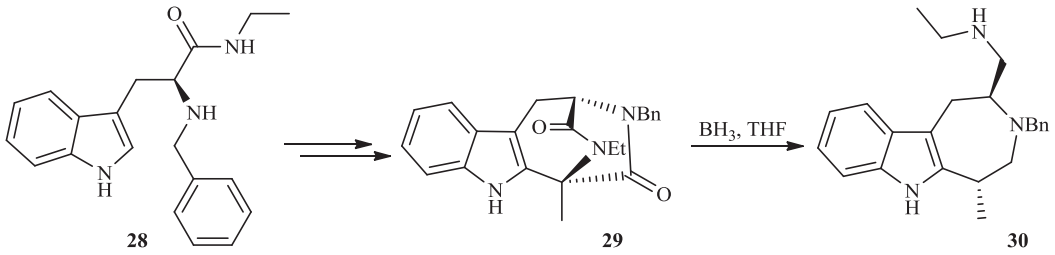
The formation of the azepinoindolone **27** was recently published by Miranda *et al.* (Scheme 1.6) which, following functionalisation of the indole-2-position, involved an acid-mediated lactamisation reaction.[76] This particular reaction sequence allowed the introduction of various alkyl and ester substituents onto the azepinoindole scaffold.[76]



26 **27**

Scheme 1.6 Acid-mediated lactamisation to form the functionalised azepinoindolone scaffold

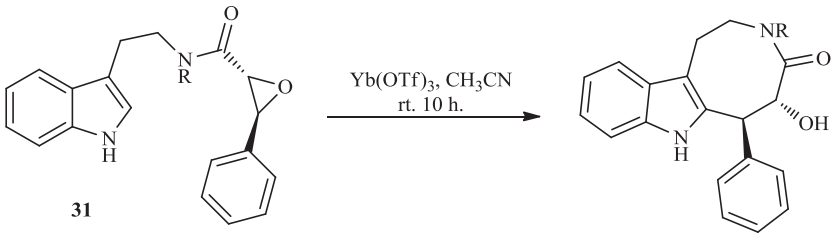
A fascinating example of an azepinoindole synthesis through a Pictet-Spengler type cyclisation was reported by the group of Giger which involved the formation of a diazabicyclo[3.2.2]nonedione intermediate **29**, which was subsequently reduced using a borane-THF solution to afford azepinoindole **30** (Scheme 1.7).[77]



28 **29** **30**

Scheme 1.7 A Pictet-Spengler type cyclisation followed by reductive fragmentation of a diazabicyclo[3.2.2]nonedione intermediate leads to the formation of the azepinoindole scaffold

Recent advances in the chemistry of lanthanides have lead to the development of an epoxide ring opening cyclisation sequence catalysed by ytterbium(III) triflate (Scheme 1.8).[78] The functionalised indoloazocines (**32** and **33)** were produced in good yield and excellent *ee*, providing an efficient route for the total synthesis of two natural products from tryptamine.



31

R = H (50%) (-)-(*5R,6S*)-norbalasubramide 96% *ee* **32**
R = Me (76%) (-)-(*5R,6S*)-balasubramide 86% *ee* **33**

Scheme 1.8 Synthesis of functionalised indoloazocines using ytterbium-catalysis

Although the acid-catalysed processes mentioned above provide access to a range of functionalised indole-based *N*-heterocycles, organometallic-catalysed processes are by far

the most efficient means for the synthesis of *N*-heterocyclic systems and are described in the following section.

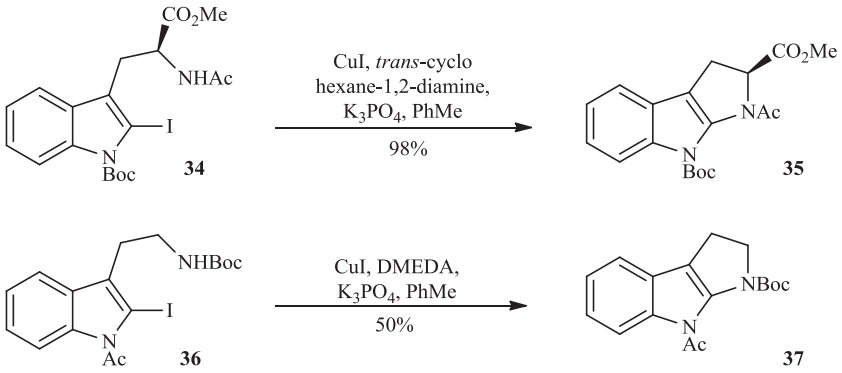
1.2.5 Transition-Metal Catalysed Cyclisations

Transition metals are classified as metallic elements that have valence electrons in two shells instead of one. This electron configuration bestows the unique property to accept or donate electrons, allowing these metals to readily change oxidation states during a catalytic cycle. The more important and extensively studied transition metals in homogenous catalysis are found among the "late transition metals" which include ruthenium, palladium, nickel and platinum. The use of ligands to form transition metal complexes allows their catalytic properties to be fine-tuned. The many advantages of transition-metal catalysis has lead to its use in the development of many new synthetic transformations offering enhanced chemoselectivity, regioselectivity and perhaps most importantly enantioselectivity over conventional organic reactions.[79] The following section describes the use of ruthenium, copper, gold, mercury and palladium catalysed cyclisation processes.*

Copper-Catalysed Cyclisations

Copper-catalysis has emerged as a cheap and efficient method for achieving the arylation (or vinylation) of O-, S- and N-nucleophiles. A number of copper-catalysed Ullmann type processes have recently been developed for the synthesis of *N*-heterocycles.[82] The synthesis of pyrroloindoles from tryptamine or tryptophan has been studied extensively (often involving an oxidative cyclisation process), however a number of these methods result in decomposition of the aromaticity of the indole ring system.[83-86] The development of a copper-catalysed C-N cross-coupling process for the synthesis of pyrroloindoles (for example **35** and **37**), has provided access to these 5-membered indole-based *N*-heterocycles in good yield from tryptamine or tryptophan derivatives (Scheme 1.9), allowing the indole ring system to remain intact.[13]

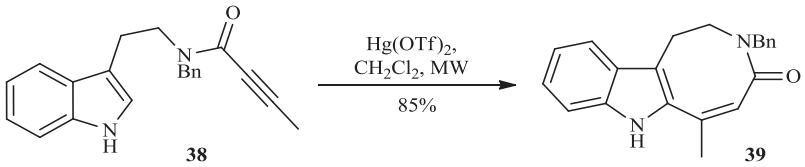
* For a more comprehensive review of transition-metals and their use in organic chemistry refer to *Transition Metals for Organic Synthesis* (Beller, M.; Bolm, C., 2 ed. WlLEY-VCH Verlag GmbH: Weinheim, 2004.), *Metal-Catalysed Cross-Coupling Reactions* (de Meijere, A.; Diederich, F., 2 ed.; WILEY-VCH Verlag GmbH.: Weinheim, 2004)[80] and *The Organometallic Chemistry of the Transition Metals* (Crabtree, R. H., John Wiley & Sons, Inc.: Hoboken, New Jersey, 2005.).[81]



Scheme 1.9 The copper-mediated synthesis of pyrroloindoles

Mercury-Catalysed Cyclisations

The synthesis of indoloazocine ring **39** from tryptamine using a mercury-catalysed cyclisation process was recently reported by Donets *et al.* (Scheme 1.10).[87]

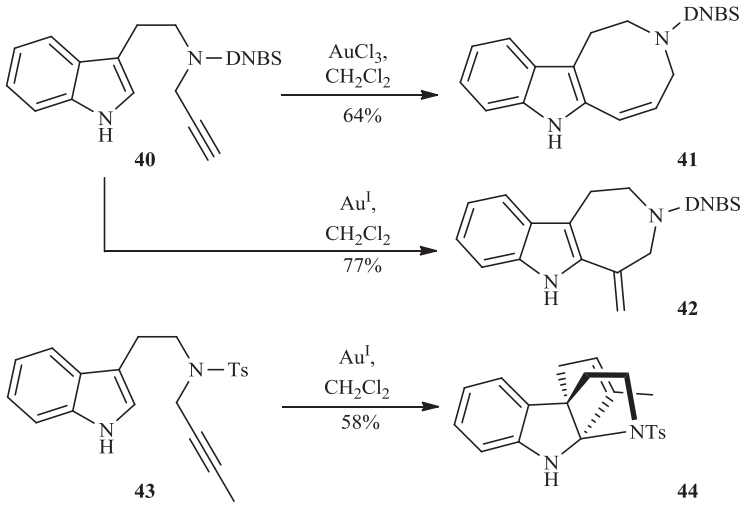


Scheme 1.10 The synthesis of indoloazocines using a mercury-catalysed process

In this process a new 8-membered *N*-heterocycle is formed in excellent yield. In the early stages of this reaction it was proposed that mercury forms a complex with the alkyne **38**, activating it for nucleophilic attack from the indole-2-position. Significantly, this mercury mediated process tolerates a range of simple alkyl substituents tethered to the alkyne.

Gold-Catalysed Cyclisations

The use of gold-catalysed processes in synthetic chemistry has rapidly increased over the past decade.[88-92] A greater understanding of how gold can activate both alkynes and alkenes has resulted in the use of gold-catalysis to effect difficult transformations.[93-98] To this end, Echvarren *et al.* in 2006 reported the gold-catalysed cyclisation of functionalised tryptamines (for example **40** and **43)** to afford indole-based *N*-heterocyclic scaffolds (using either Au^{I} or Au^{III} catalysts) where the newly formed ring differed in size from a 5- to an 8-membered ring (Scheme 1.11).[99-100]

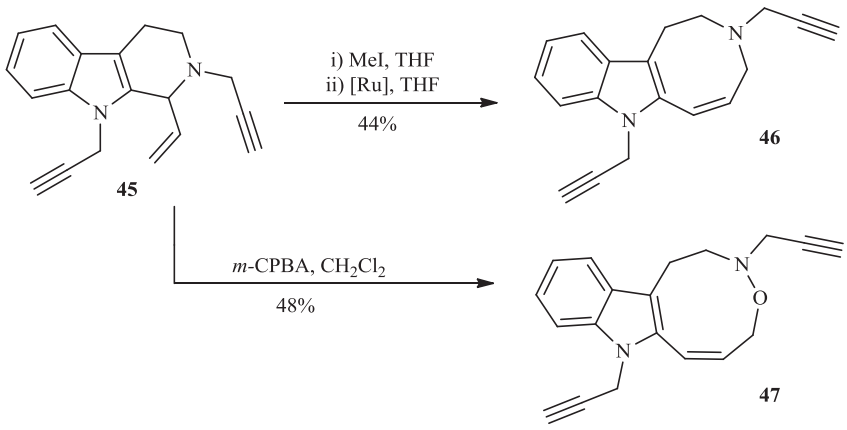


Scheme 1.11 Gold catalysed cyclisation to form indole-based heterocyclic scaffolds
Au^I = (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate, DNBS = Dinitrobenzenesulfonyl

The authors propose that the cationic gold(I) complex leads solely to the formation of the azepino[4,5-*b*]indole **42** (Scheme 1.11). When the same substrate was subject to the more electrophilic $AuCl_3$ catalyst, formation of the indoloazocine scaffold **41** took place *via* an 8-*exo*-*dig* process. In the presence of the tosyl-amine **43**, which functioned as a leaving group, formation of the pyrroloindole tetracycle **44** occurred. This was proposed to be the result of (i) formation of the 8-membered ring, (ii) rearrangement to form a conjugated gold-carbene species, and (iii) readdition of the sulfonamide to form the tetracycle **44**.[99]

Ruthenium-Catalysed Cyclisations

During their investigations into ring closing metathesis (RCM) for the synthesis of *β*-carboline alkaloids, González-Gómez *et al.* reported the formation of an indoloazocine scaffold **46** and a 9-membered *N,O*-heterocycle **47** (Scheme 1.12).[101]



Scheme 1.12 A ruthenium-catalysed cyclisation to form indole-based heterocyclic scaffolds

For the synthesis of the indoloazocine **46**, formation of the THβC ammonium salt was facilitated by reaction of **45** with an excess of methyl iodide. Allylic rearrangement to form the new 8-membered *N*-heterocycle then took place in the presence of the Hoveyda–Grubbs ruthenium complex.[102] A similar allylic rearrangement, this time following the synthesis of the *N*-oxide using *m*-CPBA, lead to formation of the 9-membered indole-based heterocycle **47** (Scheme 1.12).[101]

1.2.6 Palladium-Mediated Cyclisations

The Nobel Prize for chemistry in 2010 was awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki for their contribution to the development of palladium-catalysed carbon-carbon bond forming reactions. Palladium is unique as a catalyst as it is able to facilitate diverse synthetic transformations under mild reaction conditions, is tolerant to a range of functional groups, and is extremely atom economical.[103-104]

The element palladium was first discovered in 1803 by the British chemist William Hyde Wollaston who named it after the asteroid *Pallas*, discovered a year earlier. Palladium is a silvery-white precious metal predominantly found in Russia, the USA and South Africa and has found use in a variety of applications including jewellery and electronics.[103] Palladium was not employed in organic chemistry until the 20th century, following invention of the Wacker process (the palladium- and copper-catalysed oxidation of ethylene to acetaldehyde). Following mechanistic studies of this process by Tsuji *et al.* the modern era of organopalladium chemistry was born.[105]

A number of palladium(0) catalysed processes were developed during the 1970s to facilitate the formation of carbon-carbon bonds including the Negishi coupling with the alkyl zinc reagent and the Suzuki reaction using functionalised boronic acids and esters (Figure 1.5).[106-108] [80, 103, 109-119]

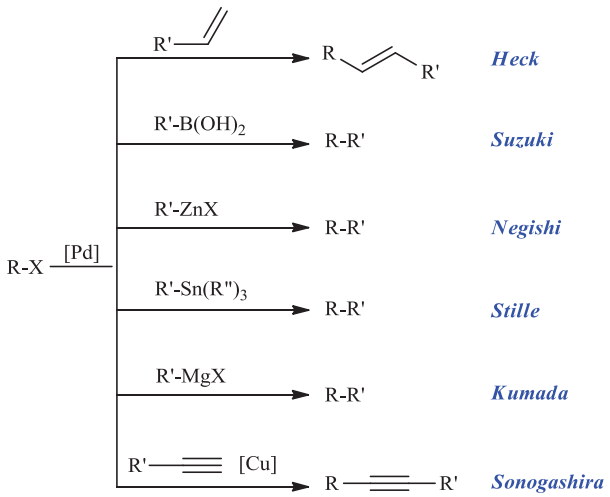


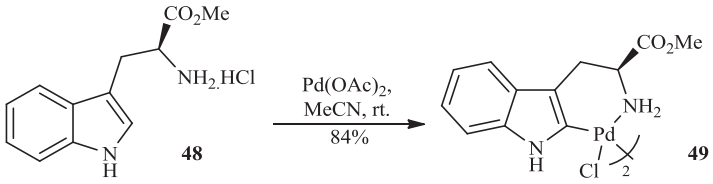
Figure 1.5 Palladium-catalysed processes for the formation of new carbon-carbon bonds

Palladium is located in group 8 of the periodic table and is classed as a late transition metal. This means that the *d* orbital of palladium in only partially filled, a property essential to its ability to both donate and accept electrons. The judicious choice of electron-rich or electron-poor ligands can be employed to tailor the reactive nature of palladium to facilitate a range of synthetic transformations as required. Additional fundamental characteristics that make palladium-catalysis ideal for a range of cross-coupling reactions are detailed below.[103, 105]

- Palladium is a second row transition metal of moderately large atomic size. The size of palladium appears to govern the stability and the general reactivity of palladium catalysts. The other complexes comprising of elements from the same periodic table group such as nickel are quite reactive but lack selectivity where on the other hand platinum derivatives are considered too stable.
- Palladium favours the 0 and +2 oxidation states (although the +1, +3 and +4 oxidation states of palladium have also been observed). This important characteristic of palladium complexes means that palladium does not readily undergo radical or single-electron processes, minimising the occurrence of side reactions.
- Palladium has a high affinity for non-polar π-compounds (such as alkenes and alkynes). The relatively high electronegativity of palladium also allows a carbon-palladium bond formed during the catalytic cycle and also this species remains unreactive towards other polar functional groups present.
- A majority of the palladium-complexes available do not require the vigorous exclusion of air and/or moisture from the reaction.

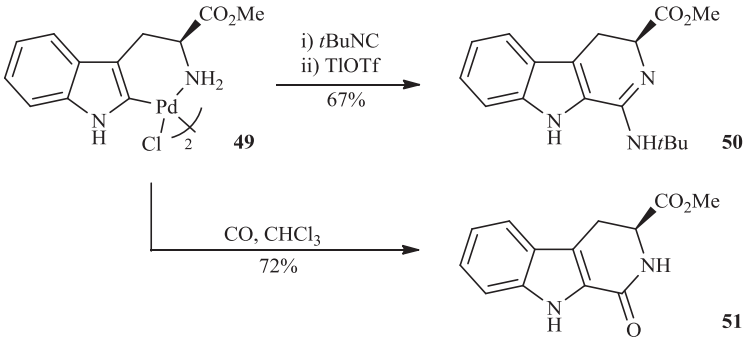
Not limited to only carbon-carbon bond forming reactions, palladium complexes have recently been employed to catalyse many other synthetic transformations including hydrogenation, amination, amidation, cyanation, and carbonylation to name a few.[120-130] Due to this ever growing number of synthetic transformations catalysed by palladium, many of the methods utilised for the construction and subsequent functionalisation of heterocycles employ palladium catalysts.[9] Palladium-catalysis also facilitates a much greater level of chemo-, regio- and stereoselectivity in the formation of *N*-heterocycles than many other bond-forming processes available.[9, 103, †]

A recent report by Vicente *et al*. described the formation of a tryptophan-based palladacycle **49** following reaction of L-tryptophan methyl ester (**48**) with a stoichiometric amount of palladium acetate (Scheme 1.13).[134-135]



Scheme 1.13 The synthesis of an L-tryptophan based palladacycle

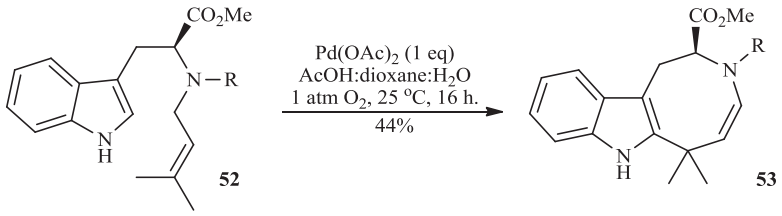
This intermediate was then able to be used in the halogenation of the indole-2-position, as well as the synthesis of a number of *β*-carboline analogues (for example **50** and **51**) through the insertion of isocyanides or carbon monoxide into the Pd-C2 bond of the cyclopalladated complex **49** (Scheme 1.14).[135]



Scheme 1.14 The synthesis of functionalised *β*-carbolines from a palladacycle intermediate

† A full review of palladium-catalysed heterocycle synthesis is beyond the scope of this report; however several excellent reports are available in the literature including *Palladium in Heterocyclic Chemistry. A Guide for the Synthetic Chemist* (Li, J. J.; Gribble, G. W. Elsevier Science Ltd., 2000).[9, 79, 131-133]

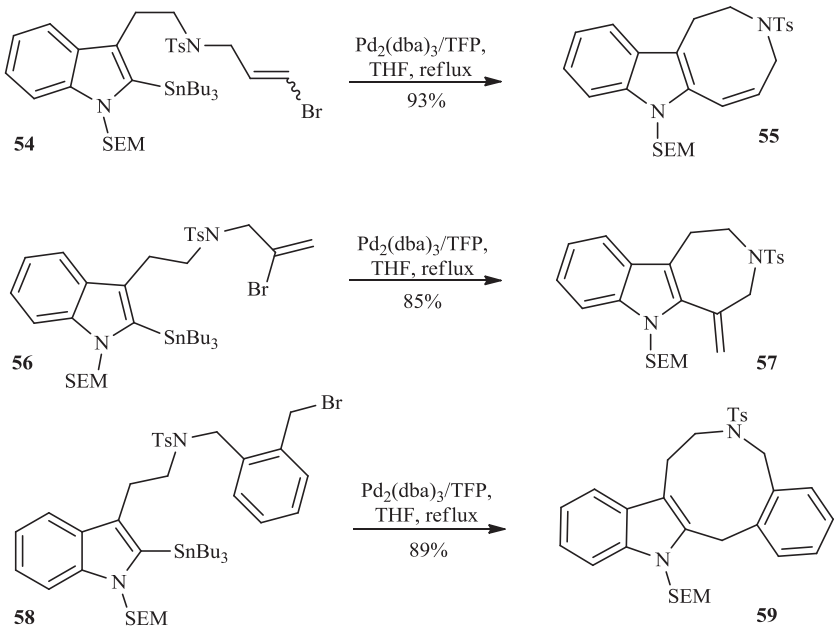
Palladium has also been employed for the formation of the indoloazocine framework **53** as a key step in the total synthesis of (+)-austamide, (+)-deoxyisoaustamide and okaramine N (Scheme 1.15).[28, 31] In the first two examples (Scheme 1.14 and 1.15) the use of a stoichiometric amount of palladium was needed to facilitate formation of the new *N*-heterocycle. The preparation of indole-based *N*-heterocycles using only a catalytic amount of palladium is discussed in the following section.



Scheme 1.15 A palladium-mediated key step in the total synthesis of natural products

Stille-Coupling

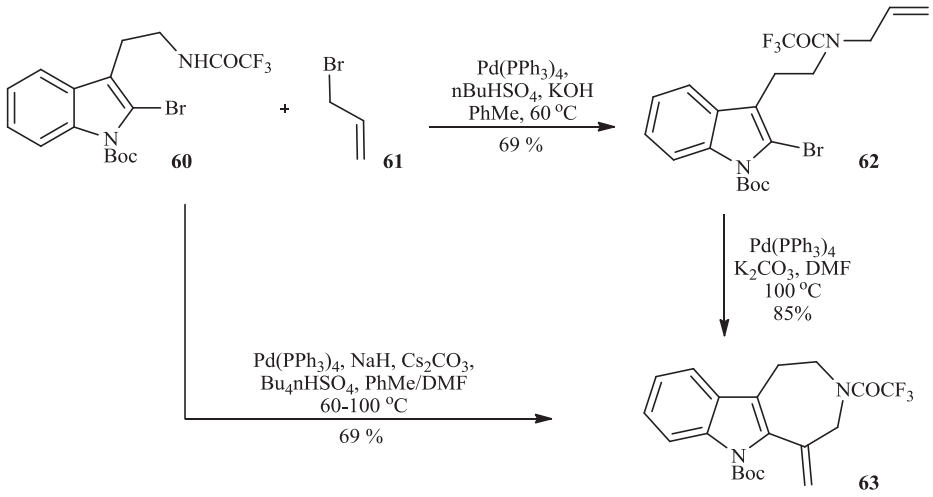
The palladium-catalysed Stille coupling of an indole-stannane to afford tryptamines functionalised at the indole-2-position was reported in 1993 by Palmisano and Santagostino.[136] Initially, to further extend the scope of this reaction, several vinyl-bromides were tethered from the N_{10}-amine of a tryptamine-tin derivative. Subsequent treatment with a catalytic amount of palladium(0) facilitated an intramolecular Stille cross-coupling reaction to afford the polycyclic ring systems (Scheme 1.16).[136]



Scheme 1.16 The synthesis of indole-based *N*-heterocycles through a Stille cross-coupling

Domino Tsuji-Trost/Heck Reactions

The synthesis of an azepino[4,5-*b*]indole **63** using a palladium-catalysed single step or domino Tsuji-Trost/Heck reaction was reported by Stewart *et al.* in 2009 (Scheme 1.17).[137]



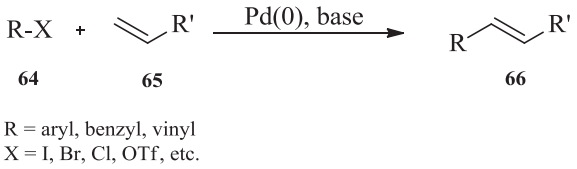
Scheme 1.17 The synthesis of azepino[4,5-*b*]indoles using a Tsuji-Trost/Heck reaction sequence

This carefully controlled reaction sequence involved the initial functionalisation of the trifluoroacetate protected N_{10}-amine of tryptamine **60** through palladation of allyl bromide **61**, known as the Tsuji-Trost reaction. Following installation of the olefin, an additional portion of base is added and the temperature increased to allow intramolecular Heck reaction at the indole-2-position to take place, forming the new 7-membered *N*-heterocycle **63** in good yield. As the Heck reaction at the indole-2-position appears to occur at a slower rate than that of other aryl halides, the use of palladium-catalysis for the first reaction in this domino sequence allows the allylation step to proceed much faster, allowing sufficient time for the intramolecular Heck reaction to take place.[137]

1.3 The Heck Cross-Coupling Reaction

The formation of *N*-heterocycles utilising both intramolecular and intermolecular Heck reactions was studied extensively during this project and as such a more detailed description of this reaction is warranted. The Heck reaction (or Mizoroki-Heck reaction) was first discovered independently by the groups of Heck[138-144] and Moritani-Fujiwara[145-146] in the late 1960s; however these pioneering reactions required a stoichiometric amount of palladium. The development of a catalytic version of this reaction was first reported by Mizoroki (in 1971)[108, 147] and then refined by Heck (in 1972).[107] The Heck-Mizoroki reaction traditionally takes place between an aryl (or vinyl) halide **64** and an alkene **65** in the presence of a

catalytic amount of palladium(0),[103] and can be defined as a vinylic substitution reaction where the vinylic hydrogen is replaced by an aryl, benzyl or vinyl group (Scheme 1.18).[103-104]

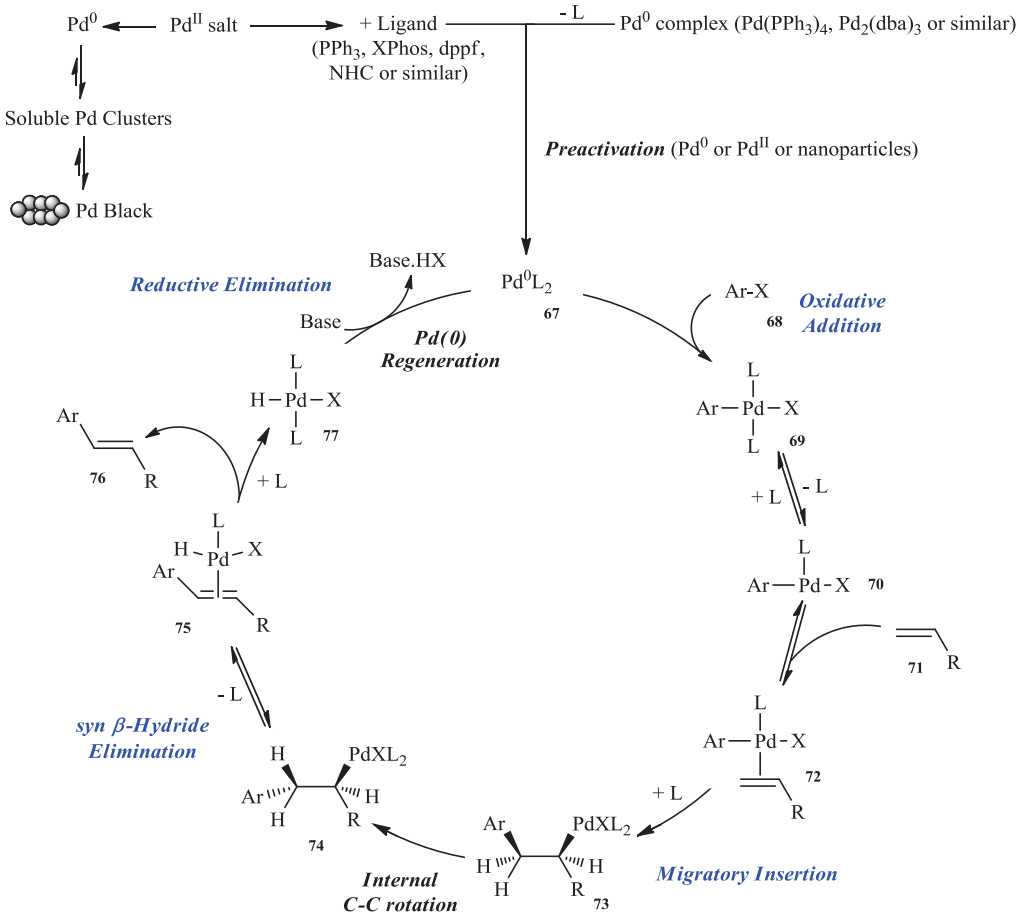


Scheme 1.18 The Heck reaction is classified as a vinylic substitution reaction

The gradual refinement of the Heck reaction over the past 40 years has lead to this powerful reaction finding a range of applications including in the total synthesis of natural products and pharmaceuticals, the preparation of hydrocarbons, and the synthesis of novel polymers and dyes.[80, 104, 148-150]

1.3.1 The Catalytic Cycle

The Heck reaction is based on a Pd(0)/Pd(II) catalytic cycle and the original cycle proposed by Heck is still generally accepted (although some parts of the mechanistic cycle are still not fully understood and alternative mechanisms have been proposed[151]). The Heck reaction involves four main processes, namely oxidative addition, migratory insertion, *β*-hydride elimination and reductive elimination (Scheme 1.19).[80, 152]



Scheme 1.19 The catalytic cycle of the Heck reaction[104]

The first step of the sequence involves oxidative addition of the aryl-halide **68** to the coordinatively unsaturated palladium(0) complex **67** (which can either be a 14 or 12 electron species depending on the number of ligands attached). Following oxidative addition, the electrophilicity of this complex is greatly enhanced, and as such it readily coordinates an alkene **71**. Migratory insertion of the σ-arylpalladium(II) complex **72** into the C=C double bond *via* a four membered transition state affords the σ-(*β*-aryl)alkylpalladium complex **73** (Scheme 1.19). Internal rotation occurs such that a *β*-hydrogen is aligned s*yn*-periplanar to the palladium (see **74**), allowing *β*-hydride elimination to take place to afford the more thermodynamically stable (*E*)-alkene **76**. Regeneration of the active Pd(0) catalyst **67** through base-mediated reductive elimination completes the catalytic cycle (Scheme 1.19). A number of the key considerations of this cross-coupling process are discussed in more detail below.

Preactivation

For the palladium to be catalytically active, it is required in its highly reactive Pd(0) state.[152] However, this Pd(0) species is unstable and must be prepared *in situ*, from either the more stable Pd(II) salts (e.g. $Pd(OAc)_2$ or $PdCl_2$) or the less stable Pd(0) complexes (e.g. Pd_2dba_3 or $Pd(PPh_3)_4$). When the Pd(II) salts are employed, they are generally used in combination with phosphine ligands or other additives that reduce the Pd(II) to the $Pd(0)L_2$ species **67**.[153-158] There is also evidence to suggest that the base,[159] alkene[107] or even solvent[160] may play a role in reducing the Pd(II) to the Pd(0), however when present, it is considered that the phosphine ligands are the most active and hence, the most likely to facilitate this reduction.

To satisfy the 18-electron rule, the Pd(0) species typically coordinates to four ligands. Some recent reports propose that Pd(IV) may be involved in certain palladium-mediated transformations.[161-163] There is also evidence to suggest that the formation of palladium nanoparticles occurs at higher temperatures and these nanoparticles may also play a role in facilitating the Heck reaction, especially under ligand free conditions.[164-167]

Oxidative Addition

During the oxidative addition step, the catalytically active Pd(0) species **67** is oxidised to Pd(II) **69** as it binds an aryl or vinyl group and a halide (or pseudohalide) leaving group. The rate of oxidative addition depends on the halide or pseudohalide present with the general order for reactivity being: diazonium salts > iodide > triflate > bromide > tosylate = chloride.[80, 104] The oxidative addition process is often the rate determining step in the Heck reaction, especially in the case of aryl-bromide and aryl-chlorides. Ligands to stabilise and activate the Pd(0) complex are added to decrease the activation energy and therefore increase the rate of this oxidative addition step.[104] Aryl-chlorides are typically the most sluggish coupling partners (due to the relative strength of the C-Cl bond).[168-169] However, the recent development of an air-stable tri-*tert*-butyl phosphonium tetrafluoroborate salt by the group of Fu, where the active ligand is formed *in situ* during the reaction, has allowed aryl-chlorides to be used as Heck substrates.[170-171]

Migratory Insertion

The migratory insertion process is the step of the catalytic cycle in which the new C-C bond is formed.[148] Following oxidative addition, a ligand of the electrophilic Pd(II) complex **69** is replaced by the olefinic coupling partner **71**.[80, 103, 148, 172] The π-coordinated alkene **72** then rotates to the in-plane position resulting in a four membered 'square-shaped' transition state that allows *syn*-insertion to occur forming a new σ-bond in a concerted fashion. This

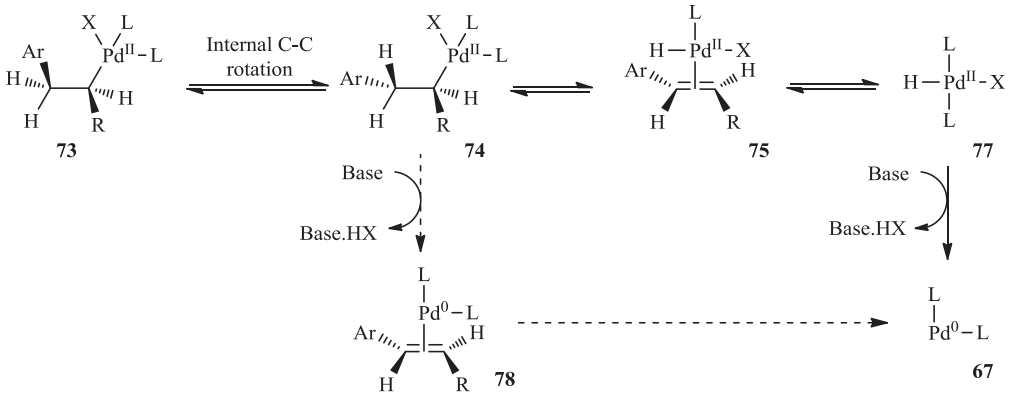
insertion is also rate-determining in the Heck-catalytic cycle. This *syn*-insertion is the key step that determines both the regiochemistry[173-174] and stereochemistry[175-176] of the Heck reaction, with steric and electronic properties of the coupling partners playing significant roles. The regioselectivity of the Heck reaction is discussed in more detail on the following page.

β-Hydride Elimination

The formation of the final olefinic product **76** is a result of the *β*-hydride elimination step of the catalytic cycle. As elimination can only occur in a *syn*-fashion, internal rotation of the new C-C bond formed takes place following the insertion of the olefin into the palladium(II) complex. This rotation allows the Pd(II)-halide complex to align *syn* to the *β*-hydrogen. The elimination of the Pd(II) species **77** to afford the olefin product is a reversible process, with the formation of the more thermodynamically stable *trans* isomer is favoured.[80] However, if dissociation of the Pd(II)-hydride complex to the olefin is slow, re-addition to the double bond can occur, resulting in the formation of double bond regioisomers.[177-178]

Reductive Elimination

The final step in the Heck catalytic cycle is reductive elimination to regenerate the palladium complex to its active Pd(0) species. This process generally involves a base removing the HX from the palladium(II)-complex **77**, producing the $Pd(0)L_2$ species **67** that is required for the next catalytic cycle. The exact mechanism of the reduction of Pd(II) to Pd(0) remains unknown, however a recently published mechanism suggests a base-promoted elimination of Pd(II) to Pd(0) (Scheme 1.20, dotted line), proposed to be more energetically favoured than the traditional *β*-elimination pathway (Scheme 1.20, solid line).[179]

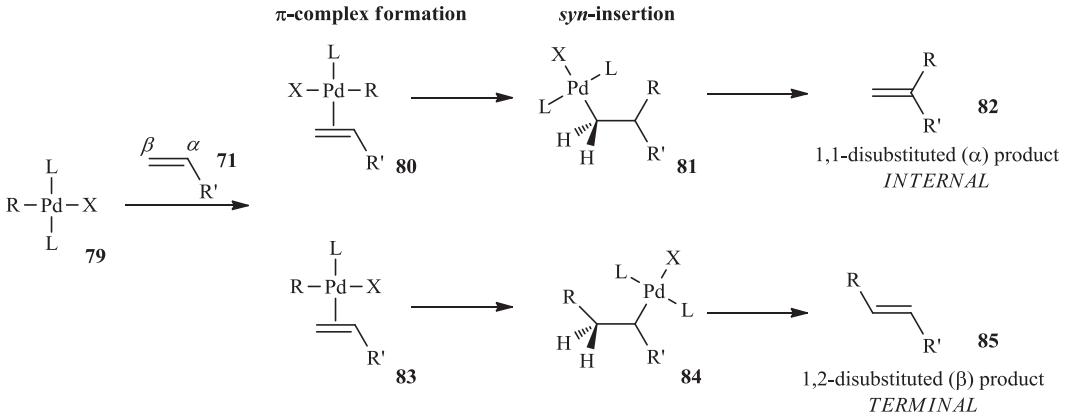


73 **74** **75** **77** **78** **67**

Scheme 1.20 The base-promoted *vs.* the traditional elimination mechanism

Regioselectivity

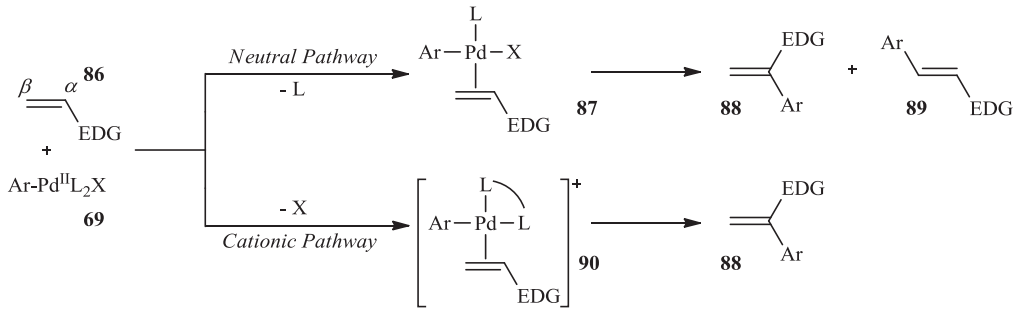
The regiochemical[173-174] and stereochemical[175-176] outcomes of the Heck reaction are defined during the migratory insertion step (Scheme 1.21). This regioselectivity is controlled by two major factors, namely the electronic and steric properties associated with the cross-coupling partners.[103, 148]



Scheme 1.21 The two possible regiochemical outcomes of the Heck reaction

The use of electron-deficient alkenes (for example butyl acrylate) is favoured both sterically and electronically and therefore only results in the terminal *β*-product **85** (Scheme 1.21). However, the use of electron-rich alkenes (for example heteroatom or alkyl substituted alkenes) under classical Heck conditions often results in a mixture of both internal **82** and terminal products **85** (Scheme 1.21).[103] The regioselectivity of the Heck reaction with electron-rich alkenes can be guided by controlling the π-complex formation and insertion steps of the catalytic cycle.

There are two slightly different mechanisms proposed for the Heck reaction (Scheme 1.22), depending on the leaving group present; the neutral pathway (if the leaving group is a tightly coordinating halide e.g. bromide) and the cationic pathway (if the leaving group is weakly coordinating such as a pseudohalide like triflate).[104]



Scheme 1.22 The Heck reaction with an electron-rich alkene can proceed *via* a neutral or cationic mechanism

A number of reaction parameters can be manipulated so that one pathway is favoured. These include judicious choice of the aryl-halide substrate and reaction conditions, however if no precautions are taken the two pathways occur simultaneously, often resulting in a mixture of internal **88** (α-substituted) and terminal **89** (*β*-substituted) products.

The *neutral pathway* predominates when an aryl- or vinyl-halide is used as the Heck substrate, which results in the formation of a neutral oxidative addition complex. When ligation of the olefin to the electrophilic palladium(II) complex takes place, immediately prior to migratory insertion, a phosphine ligand is substituted for the alkene, preferentially to the halide, maintaining the neutrality of the Pd(II) species **87** (Scheme 1.22). In order to favour the neutral pathway, monodentate neutral donor ligands are often employed as they coordinate more weakly to palladium than the bidentate ligands.[148]

The regiochemistry of the Heck reaction proceeding *via* the neutral pathway is largely dependent on the steric properties of the related substrates. With electron-deficient olefins, insertion at the least substituted and most electron-deficient carbon takes place resulting in the terminal *β*-substituted product **89**. For electron-rich alkenes, the electronic factors favour insertion at the carbon with the greatest electron density, which in the case of electron-rich terminal alkenes results in the formation of the internal α-substituted product **88**. However, in these cases the steric factors favour insertion at the least substituted carbon, resulting in formation of the terminal *β*-substituted product **89**. As such, a mixture of regioisomers is often observed from the reaction of an electron-rich alkene when the Heck reaction follows the neutral pathway.[103-104, 180] The neutral pathway typically performs better for the electron-deficient alkenes, where the regiochemistry is much more predictable.

If the *cationic pathway* is followed, many of the regiochemical problems associated with electron-rich terminal alkenes under classic Heck conditions are overcome, as it provides access predominantly to the internal α-substituted Heck adduct **88** (Scheme 1.22). The

cationic pathway was originally proposed by Cabri (and independently by Hayashi[181]) in the early 1990's, after the discovery that a bidentate phosphine ligand controlled regioselectivity in the arylation of vinyl ethers with aryl triflates.[182-183] Dissociation of the weakly coordinating triflate anion, which readily occurs in polar solvents, leads to the formation of a cationic palladium-alkene π-complex **90**.[184] An alternative method to initiate a Pd-cationic pathway is through the use of silver[185-186] or thallium salts.[187-188] The general mechanism for the shift to this pathway is through the abstraction of a halide from the oxidative elimination product ($ArPdL_2X$ **69** – Scheme 1.22) to form the cationic palladium(II) species **90**. This halide dissociation can also be promoted using metal scavengers (typically Ag and Tl), highly polar solvents and aryldiazonium tetrafluoroborate salts.[189-191]

If the cationic pathway dominates electronic factors are favoured over steric factors in determining the regiochemical outcome of the Heck reaction. Following coordination of the alkene to the Pd(II) complex, the polarisation of the olefinic π-system is enhanced. This increase in polarisation facilitates insertion of the aryl group onto the α-carbon of the double bond, due to its associated charge density being less than that of the terminal carbon, resulting in formation of the 1,1-disubstituted product (Scheme 1.22).[188] The role of steric properties in the cationic Heck-reaction, although not as important as electronic properties, cannot be ignored. As in the case of the neutral pathway, there appears to be a fine balance between both of these factors that plays a role in determining the regioselectivity of the Heck reaction. The cationic pathway typically performs better for electron-rich olefins than electron-poor alkenes due to an unfavourable interaction between the latter and the cationic Pd(II) complex, resulting in a slow rate of migratory insertion.[180]

1.3.2 Reaction Conditions

In addition to the mechanistic pathway, there are many other important factors that play a role in determining both the rate and outcome of the Heck reaction. A recent review by Beletskaya[148] has highlighted the fact that even small variations in the conditions surrounding the Heck reaction can have considerable effects on the overall result.

Selection of the *halide* in the Heck substrate is an important consideration. Oxidative addition of the Pd(0) to the aryl-halide or pseudohalide is a key rate determining step of the Heck catalytic cycle. For example, addition of Pd(0) to an aryl-iodide is much faster than that for an aryl-chloride. However, reductive elimination to regenerate the Pd(0) species occurs much faster for the corresponding Pd(II)-chloride complex than for the Pd(II)-iodide, so what is gained in one step of the catalytic cycle is often lost in another.[104] The aryl-iodides are typically much more expensive to prepare than the bromide and chloride

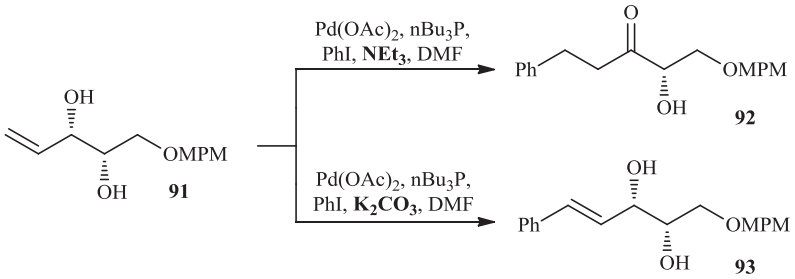
counterparts. The Heck reaction of the widely available aryl-chlorides often requires the use of bulky electron rich phosphine ligands.[171] The development of several Heck reactions that employ C-H activation, where no halide or pseudohalide is required has also been reported in recent years.[192-194] These findings have resulted in the reduction of cost and labour in the preparation of suitable Heck precursors, however the catalytic conditions facilitating the Heck reaction need to be highly reactive and selective to achieve the desired transformation.

A wide range of *palladium complexes* are currently available as sources of Pd(0), including $Pd_2(dba)_3$ and those that require reduction such as palladacycles and *N*-heterocyclic carbene complexes. However, the first choice of a palladium source is often $Pd(OAc)_2$ or $Pd(PPh_3)_4$ because of their reduced cost and applicability in industry. It is difficult to predict how particular catalytic systems will perform in the Heck reaction, and as such, the screening of a range of Pd/Ligand combinations and additives is commonly reported.[80]

The selection of a *ligand* can have a dramatic effect on both the selectivity and reactivity of the Heck reaction. Ligands play a role in all stages of the Heck catalytic cycle, including preactivation of the catalyst, oxidative addition and reductive elimination. In terms of regiochemistry, formation of the terminal *β*-substituted product is promoted in the presence of monodentate phosphine ligands (for example PPh_3) and the internal α-substituted product can be favoured when using strongly chelating, bulky bidentate phosphine ligands.[148, 180] There are a plethora of ligands to choose from including monodentate phosphines (PPh_3, Sphos, XPhos etc.), bidentate phosphines (dppf, BINAP etc.) and *N*-heterocyclic carbenes, many of which are commercially available.[148, 195-197] Phosphine ligands are still the most commonly used as they stabilise the reactive intermediates through both electronic and steric effects.[148] Phosphine ligands have the added advantage of both increasing the rate of dissociation and reducing the rate of readdition of the Pd(II)-hydride complex during the *β*-hydride elimination phase of the catalytic cycle, limiting the formation of double-bond isomers and additional by-products.[148, 198-199] Chiral ligands to impart stereochemistry during the catalytic cycle (for example BINAP and phosphinooxazolines) have also been employed to great effect in the Heck reaction.[200-201] In these instances, the introduction of a new stereogenic centre is only observed through accompanying double bond migration.

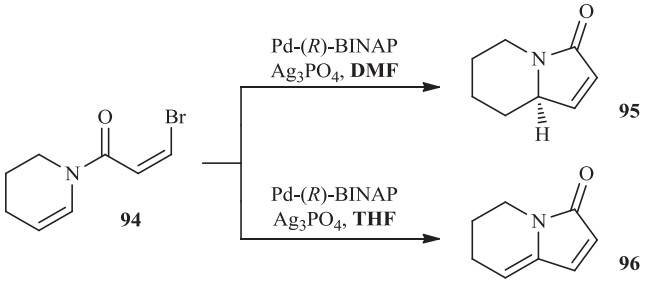
The role of the *base* in the Heck catalytic cycle is still not entirely understood. The main role of the base is to facilitate the reduction of the Pd(II)-halide complex to the catalytically active Pd(0).[148, 202] The most commonly used bases in the Heck reaction are tertiary amines (NEt_3 or Cy_2NMe) or inorganic bases (K_2CO_3 or Cs_2CO_3).[80] In some cases, evidence also exists that the base may play additional roles in the catalytic cycle, including the neutralisation of HBr[203] and as a hydride source in the deoxygenation of triflates.[151 182, 204]

The choice of base used in the Heck reaction can have a significant effect on the product formed during the Heck reaction, as reported by Kang *et al*. where exchanging NEt_3 with K_2CO_3 resulted in the formation of the conjugated diol **93** instead of the saturated ketone **92** (Scheme 1.23).[205]



Scheme 1.23 Changing base from NEt_3 to K_2CO_3 resulted in formation of the diol **93** instead of the ketone **92**

Several different *solvents* have been employed in the Heck reaction, with DMF, MeCN, 1,4-dioxane and THF proving to be the most useful as they are able to weakly coordinate with the palladium complex, increasing its stability.[80] DMSO, benzene and toluene have also been used to great effect in controlling both the regioselectivity and stereoselectivity in a number of processes.[103, 201] The importance of solvent choice in enantioselective palladium-catalysed transformations was demonstrated by Sulikowski *et al*. where the use of THF afforded the indolizidine **96**, however when the reaction was carried out in DMF, the desired asymmetric enamide **95** was the major product (Scheme 1.24).[206]



Scheme 1.24 Changing solvent from THF to DMF resulted in formation of the enamide **95** instead of the indolizidine **96**

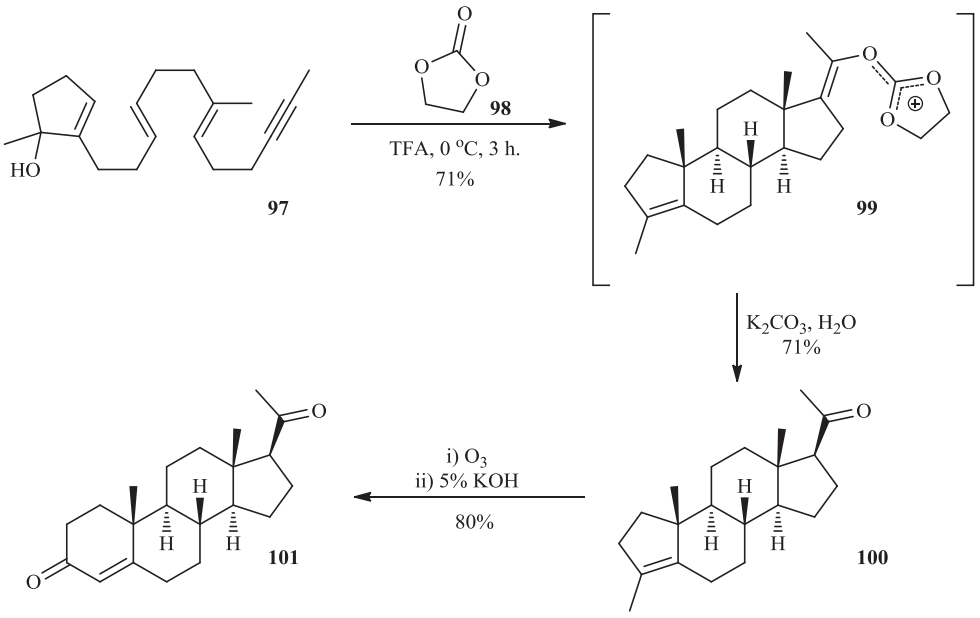
1.4 Palladium-Catalysed Domino Reactions

Many of the transformations carried out in modern organic syntheses involve the use of reagents and solvents that are known to be flammable and/or toxic and can therefore negatively affect both human health and the environment.[207] As such, it is highly desirable

that synthetic processes are developed that produce only the desired compound, in high yields, whilst minimising both reagent consumption and the subsequent generation of waste.

Several of the methodologies investigated during this research project for the synthesis of *N*-heterocycles were domino processes. Domino reactions have emerged as a powerful tool for the modern synthetic chemist, generating a high level of molecular complexity in one efficient step.[208] Domino reactions are attractive to research laboratories because of their potential to minimise the use of solvents, reagents, time and energy.[208] Moreover, in an industrial environment, a process that saves on labour costs is also considered advantageous. A domino reaction is defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation."[208-209]

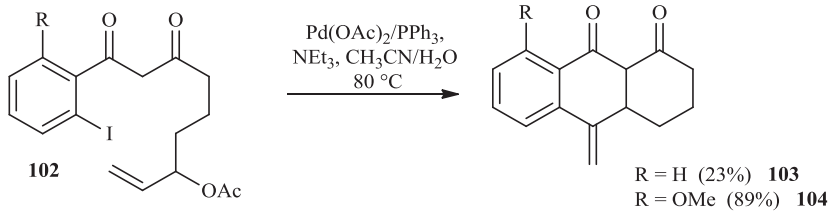
One early example of a domino reaction was the acid-catalysed polycyclisation of the tertiary and allylic alcohol **97** in the presence of ethylene carbonate **98** (Scheme 1.25).[210] During this domino process, four new ring systems were formed, with each corresponding reaction taking place at the functional group introduced by the previous reaction in the sequence. The resulting cyclopentene **100** was then readily converted to the cyclohexanone in progesterone **101**.



Scheme 1.25 An early example of a domino reaction used in the synthesis of progesterone[210]

As domino processes require two or more reactions to take place under the same conditions, the substrate must be controlled in such a way so that each individual reaction occurs in the desired order. This control can often be achieved through steric or electronic differentiation;

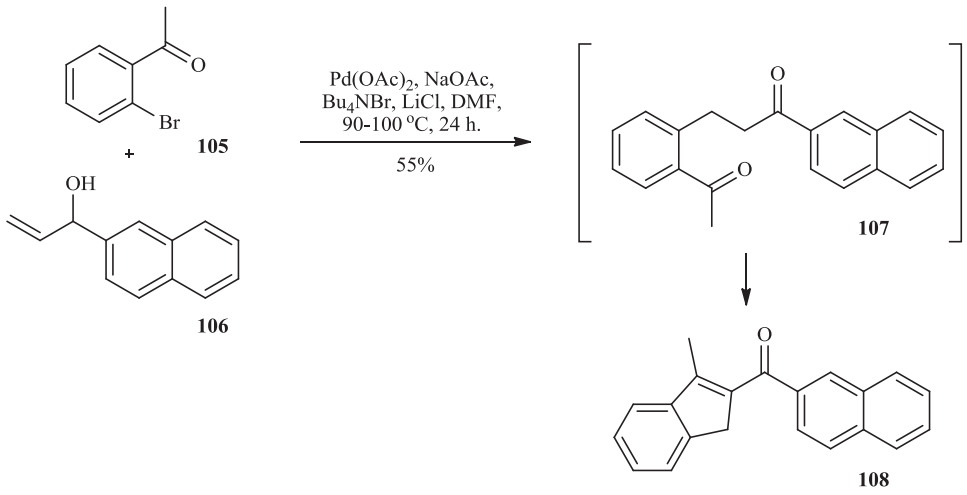
an elegant example of the latter was reported by Tietze *et al*. in the domino Tsuji-Trost/Heck reaction (Scheme 1.26).[211]



Scheme 1.26 A palladium-mediated domino process displaying substrate control

The introduction of the electron-donating methoxy group slowed down the rate of oxidative addition of the aryl-iodide and therefore the Heck reaction, allowing the Tsuji-Trost allylation to occur preferentially, significantly enhancing the yield of the overall domino process (Scheme 1.26).

The range of single-step reactions involving palladium catalysis has grown to the extent where palladium-mediated reactions are commonplace in most synthetic laboratories. Consequently, the number of palladium-mediated domino reactions reported has also increased over the last decade.[212-216] The more feasible domino reactions are those where all transformations occur under similar reaction conditions, for example, where each of the reaction steps is palladium-catalysed (Scheme 1.26).[137, 209, 214, 217] Likewise, because of the reliance of base in many Pd-cross coupling reactions, domino reactions involving both a Pd-catalysed and a base initiated synthetic step (for example Aldol condensation - Scheme 1.27 - or aza-Michael addition) are also plausible.[218-219] ‡



Scheme 1.27 A domino Heck/Aldol process where the first step is palladium-catalysed

‡ An comprehensive review of domino reactions can be found in *Domino Reactions in Organic Synthesis* (Tietze, L. F.; Brasche, G.; Gericke, K., 1 ed.; Wiley-VCH: Weinheim, 2006).[209]

The major focus of the research presented in this thesis was the development of new methodology (including domino reactions) for the synthesis of indole-based *N*-heterocycles from tryptamine. A second project, investigating the synthesis of indole-based PPARγ agonists for the treatment of type-2-diabetes, was also initiated.

1.5 Indole-Based PPARγ Agonists

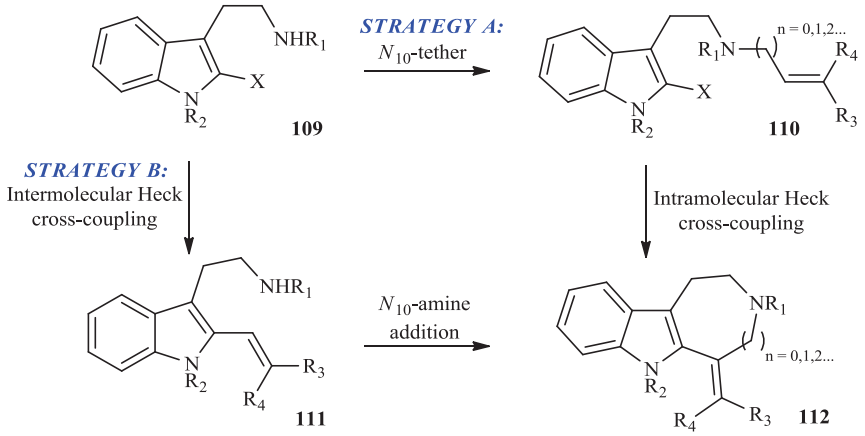
In 2005, over 1.1 million people worldwide died from diabetes.[220] However, this number is more likely closer to 3 million, as many deaths where diabetes was a predominant factor were attributed to heart disease or kidney failure.[220] Currently, over 180 million people worldwide have been diagnosed with diabetes. Alarmingly, the number of sufferers is expected to more than double by the year 2030, as this chronic disease achieves epidemic status.[220]

A large range of antidiabetic drugs are currently available, however there is still no ideal treatment or cure for type 2 diabetes.[221] As such, there remains a great need for the development of new or improved treatments with much better safety profiles. This research project focused on the synthesis of new antidiabetic agents that act at the same biological target as the commercially available thiazolidinedione antidiabetic agents (the Peroxisome Proliferator-Activated Receptor γ or PPARγ), with the aim of developing safer pharmaceutical agents with limited side effects.

1.6 Project Aims

New Palladium-Catalysed Methodology

To complement existing methodology, it was envisaged that a new palladium-catalysed approach, involving either an intermolecular or intramolecular Heck reaction at the indole-2-position, could be developed for the preparation of indole-based *N*-heterocycles from tryptamine.



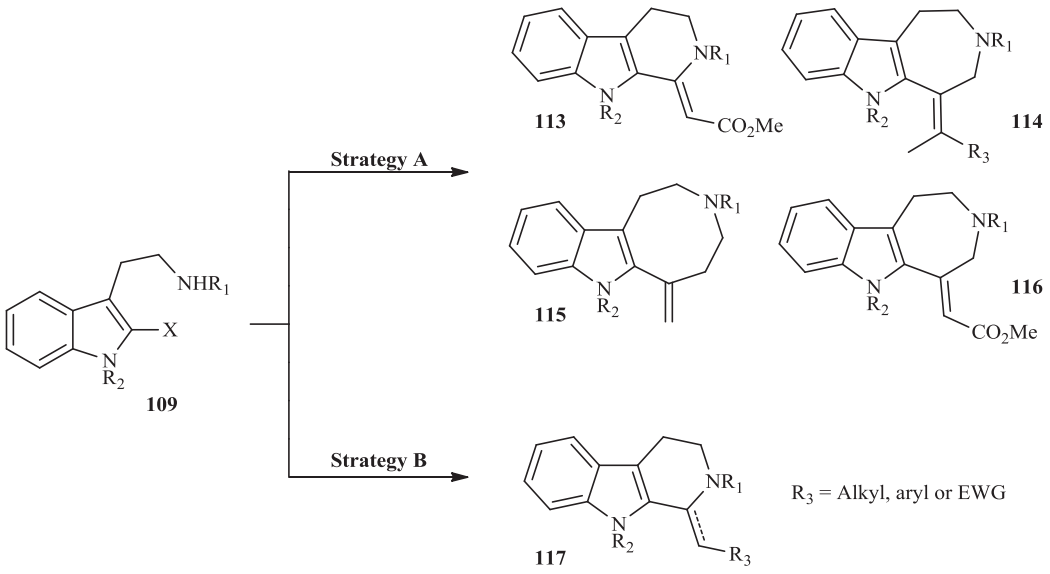
Scheme 1.28 Two alternative strategies identified for the formation of indole-based *N*-heterocycles

Two approaches were initially considered for *N*-heterocycle synthesis, either by the tethering an olefin from the N_{10}-amine of tryptamine followed by intramolecular Heck reaction (Scheme 1.28, Strategy A), or an initial cross-coupling at the indole-2-position followed by nucleophilic amine addition to form the new heterocycle (Scheme 1.28, Strategy B). At the time of design, only one palladium-catalysed cyclisation involving a Heck reaction at the indole-2-position to form an indole-based *N*-heterocyclic scaffold from tryptamine had been reported,[137] and as such, further investigation into this approach was warranted.

As palladium chemistry is well known at the indole-2-position,[§] a Heck reaction was seen as a plausible key step in the formation of indole-based *N*-heterocycles. As numerous functionalised alkenes and alkynes are commercially available, this approach would allow access, from a common 2-haloindole precursor to a diverse range of indole-based heterocyclic scaffolds, differing in both ring size and the functionality introduced by the

[§] The indole-2-position has been functionalised using a range of palladium-mediated transformations including the Kumada,[222-224] Negishi,[225-228] Suzuki,[229-232] Stille,[136, 233-234] Sonogashira,[235-237] and Heck reaction.[238-241] For a comprehensive review of palladium-catalysed reactions involving indoles refer to Chapter 3 of *Palladium in Heterocyclic Chemistry. A Guide for the Synthetic Chemist* (Li, J. J.; Gribble, G. W. Elsevier Science Ltd., 2000)[9]

olefin (Scheme 1.29). A similar approach to a diverse series of benzofused sultams from α-haloarylsulfonamides was recently been reported by Hanson *et al.*[242]

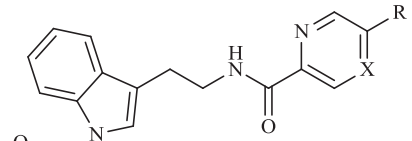


Scheme 1.29 A novel palladium-catalysed approach to functionalised indole-based *N*-heterocycles

Domino reactions are an efficient way to rapidly introduce molecular complexity, and as such a number of the methodologies investigated during this research project for the synthesis of indole-based *N*-heterocycles were domino processes. This includes domino reactions where both of the steps are palladium-catalysed (Tsuji-Trost/Heck domino reactions), in addition to domino processes where only one step is palladium-mediated (the Heck reaction) and the other step is base initiated (alkylation or aza-Michael addition).

Indole-Based PPARγ Agonists

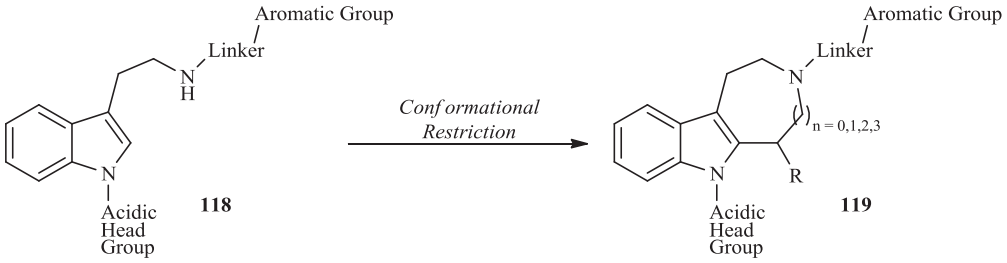
The synthesis of PPARγ agonists from tryptamine employing selected indole-based *N*-heterocyclic scaffolds was also investigated. Recent work within the Pfeffer group focused on the design and synthesis of indole-based PPARγ agonists from tryptamine.[2-3] Two indole-based compounds synthesised from tryptamine and substituted on both nitrogens exhibited a moderate insulin-sensitising effect (Figure 1.6), when compared to the commercially available treatment Rosiglitazone. These compounds were identified as lead compounds in the development of new potential PPARγ agonists for the treatment of type 2 diabetes



DLP-15 X = N, R = CH_3 **109**
DLP-39 X = CH, R = H **110**

Figure 1.6 Two lead compounds that exhibited a moderate insulin-sensitising ability

This medicinal chemistry project involves the synthesis of conformationally rigid analogues of flexible lead compounds previously investigated. This approach is often used in the determination of pharmacophoric conformation, as key functional groups are constrained in the one position.[243] The potential pharmacophore can be locked into various configurations through the incorporation of cyclic or unsaturated functionality into the existing molecule.[243] As a range of methods are currently available for the synthesis of indole-based *N*-heterocycles (see section 1.2), there are many possible variations in both the ring size and functionality introduced onto the indole scaffold during *N*-heterocycle formation.



Scheme 1.30 The proposed modification to improve the biological activity of the PPARγ agonists

A simple modification to the indole-based aromatic scaffold was proposed through the introduction of a second *N*-heterocyclic ring system (Scheme 1.30), whilst keeping the acidic head group and aromatic tail group relatively similar to those previously reported.[2-3] Furthermore, the introduction of key characteristics identified from naturally occurring PPARγ agonists may improve biological activity as well as the safety profile of the potential PPARγ agonists synthesised during this project.

Chapter Two

Indole-Based N-Heterocycles: Intramolecular Heck Reactions

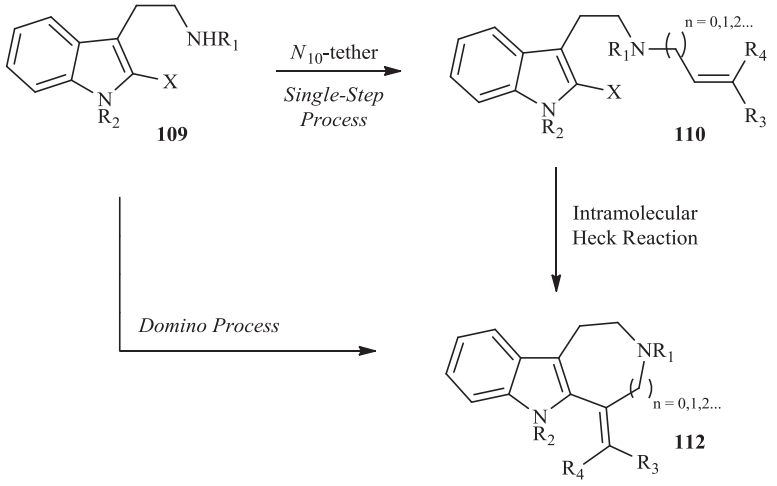
2.1 Chapter Overview

To further exploit the intramolecular Heck reaction at the indole-2-position, a number of new methodologies to access indole-based *N*-heterocyclic scaffolds were investigated using single-step or domino processes. This approach involved the tethering of an appropriate olefin to the N_{10}-amine of tryptamine followed by intramolecular Heck reaction at the indole-2-position to form the new *N*-heterocycle. Although a range of olefinic tethers were installed at the N_{10}-position, the intramolecular Heck reaction to form the new heterocycle could not be completed, and as such at this point in time this approach to indole-based *N*-heterocycles proved unsuccessful.

2.2 The Synthesis of Indole-Based *N*-heterocycles: Intramolecular Heck Reactions

The indole-2-position can be readily halogenated in high yields, using a range of methodologies.[9, 13, 134, 137, 232, 244-248] These indole-2-halogenated precursors are amenable to further functionalisation using a range of synthetic transformations, in particular palladium-mediated cross-coupling reactions.

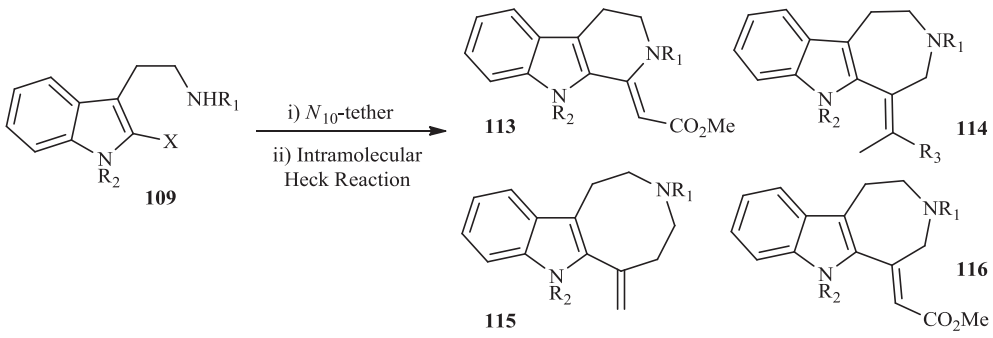
One plausible strategy for heterocycle formation was envisaged by first tethering a suitable group from the amine which could then undergo intramolecular cross-coupling reaction with the halogenated indole-2-position of tryptamine to form the new *N*-heterocycle (Scheme 2.1). As a wide range of substituted alkenes suitable for tethering off the N_{10}-amine are commercially available, the synthesis of numerous *N*-heterocycles of differing size and functionality was envisaged.



Scheme 2.1 The intramolecular Heck reaction strategy the formation of indole-base *N*-heterocycles

Before an investigation into a number of these cyclisation pathways was undertaken, several parameters were considered. The type of halogen to be inserted at the indole-2-position required careful selection. Although aryl-chlorides have recently been shown to partake in the Heck cross coupling reaction,[169, 249-250] they are often sluggish and require the use of more highly active and often very air-sensitive palladium-catalysts (the oxidative-addition step of the catalytic cycle is much slower than for aryl bromides and aryl iodides).[170, 251] As the indole ring system is naturally very electron-rich, a greater degree of electrophilicity would be induced at this position through bromination or iodination, allowing the Heck reaction to proceed at a much faster rate. Iodination at the indole-2-position would be ideal for facilitating a rapid Heck reaction, however the conditions required to iodinate this position are harsh and expensive (traditionally employing metal-halogen exchange with lithium or mercury salts),[13, 134] and do not always tolerate a number of the functional groups expected to be present during this investigation. Previous research has shown the Heck reaction is readily accomplished using 2-bromoindoles.[137] As the synthesis of 2-bromoindoles is readily achieved in high yields using mild reagents (NBS or pyridinium tribromide) [137, 232, 247, 252] 2-bromoindole substrates were used throughout the remainder of this investigation.

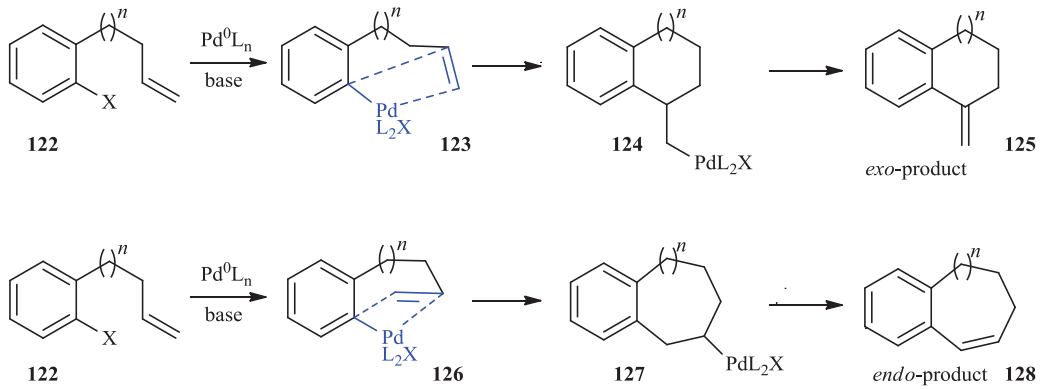
The size of the heterocycle ring formed and the functionality introduced during the cyclisation process could be controlled through careful selection of the N_{10}-amine tether. As a base is required to complete the catalytic cycle of the intramolecular Heck reaction, the possibility of functionalising the N_{10}-amine under the same basic conditions exists (for example alkylation or aza-Michael addition). As such, if the base and solvent required can be selectively chosen to facilitate both the amine functionalisation and the palladium-mediated cross-coupling reactions, a domino process is possible.



Scheme 2.2 A range of *N*-heterocycles were to be synthesised using the intramolecular Heck reaction

For the intramolecular Heck reaction with alkenes following the neutral pathway, the possibility exists for the formation of regioisomers during heterocycle synthesis (for

example the formation of both a 7-membered ring with the double bond external to the ring and an 8-membered ring with the double bond internal to the new ring formed are possible).[253-258] Furthermore, all possible products from the cyclisations proposed during this research project were favoured under Baldwin's rules (5-7-*exo-trig* are favoured as are 6-7-*endo-trig*, however the rules don't cover the formation of 8-membered heterocycles). As such, the outcome of each cyclisation process depends solely on the regioselectivity of the palladium-catalysed cross-coupling reaction. It was considered that the cyclisations investigated during this study would lead predominantly to the *exo-trig* product **125**, where the olefin lies external to the new *N*-heterocyclic ring as it is much less sterically demanding on the "square-like" palladium-alkene π-complex **123** formed during the intramolecular Heck reaction (Scheme 2.3).

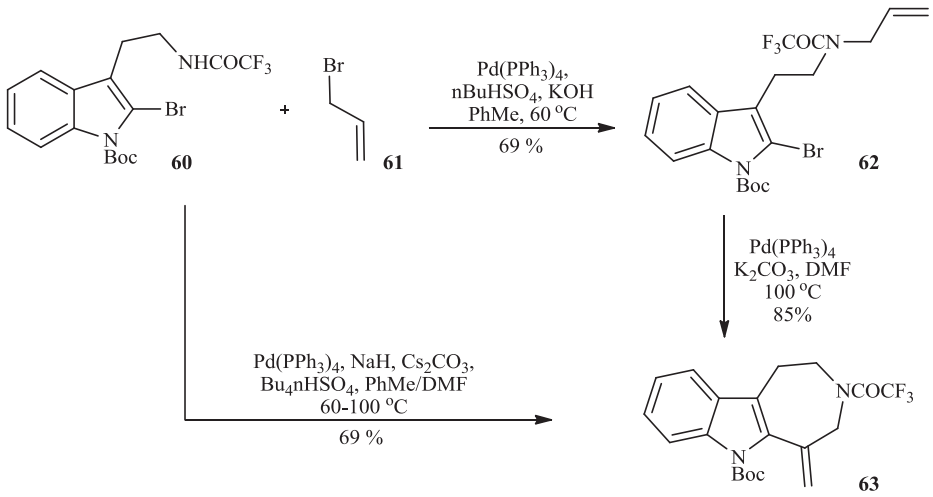


Scheme 2.3 The *exo-trig* cyclisation is favoured for the intramolecular Heck reaction as it is much less sterically demanding

The following section details the investigation into the intramolecular Heck reaction in a number of both single-step and domino processes for the synthesis of 6, 7, and 8-membered indole-based *N*-heterocycles. The syntheses attempted are described in the following section and include a domino Tsuji-Trost/Heck reaction sequence, an aza-Michael/Heck domino process and single-step alkylation/Heck reactions.

2.3 Domino Tsuji-Trost/Heck Reactions

The synthesis of an azepino[4,5-*b*]indole **63** using a palladium-mediated single-step or domino Tsuji-Trost/Heck reaction sequence was recently reported by Stewart *et al.* (Scheme 2.4. See also Section 1.2.6).[137]

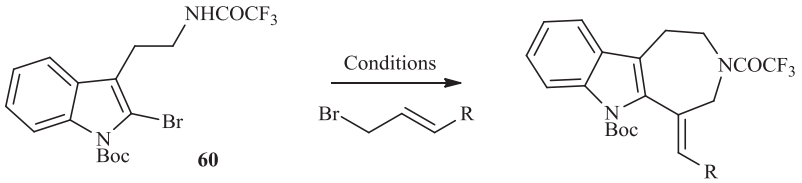


Scheme 2.4 The synthesis of azepino[4,5-*b*]indoles using a Tsuji-Trost/Heck reaction sequence

To date this domino Tsuji-Trost/Heck reaction sequence (Scheme 2.4) had only proved successful using the unsubstituted allyl bromide **61**. The aim of this project was to further develop this methodology to allow access to substituted azepino[4,5-*b*]indoles. As such, it was envisaged that access to more highly functionalised indole scaffolds could be realised by applying a similar domino process to substituted allyl bromides (for example crotyl bromide, dimethylallyl bromide and methyl-4-bromocrotonate).

The domino precursor for the first series of reactions (Table 2.1) was prepared in accordance to the method recently published by Stewart *et al* (Scheme 2.4).[137] The 2-bromoindole domino precursor **60** was then subject to the previously identified domino conditions using crotyl bromide (Table 2.1, entry 1) or methyl-4-bromocrotonate (Table 2.1, entry 2).

Table 2.1 Extension of the domino Tsuji-Trost/Heck reaction to access azepino[4,5-*b*]indoles



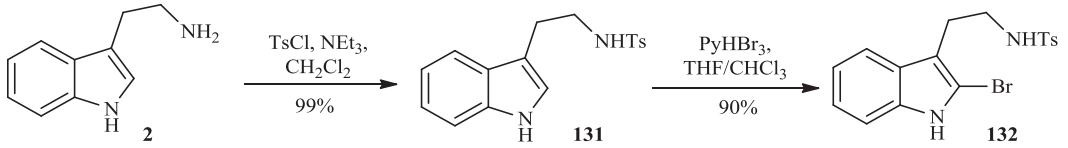
Entry	R	Conditions	Yield (%)
1	Me (**129**)	$Pd(PPh_3)_4$, NaH, Cs_2CO_3, $Bu_4^nHSO_4$, PhMe/DMF	Trace [a]
2	CO_2Me (**130**)	$Pd(PPh_3)_4$, NaH, Cs_2CO_3, $Bu_4^nHSO_4$, PhMe/DMF	NR

c Trace is less than 10% yield as identified by NMR spectroscopy
Reaction was performed by adding NaH (1.6 eq) to a solution containing the aryl-halide (1.0 eq.), Cs_2CO_3 (3.0 eq.), Bu_4nHSO_4 (0.3 eq) in PhMe:DMF (4 mL, 9:1) in a sealed tube. After stirring for 10 min, $Pd(PPh_3)_4$ (10 mol%) and allyl bromide (2.0 eq) were added and the reaction mixture heated to 60 °C for 30 mins. After this time additional NaH (0.6 eq) was added and the reaction mixture heated to 100 °C for 16 h.

Unfortunately, the use of the more highly functionalised allyl bromides using the previously identified domino conditions failed to furnish the desired azepino[4,5-*b*]indoles. A trace

amount of the azepinoindole **129** was identified following the reaction with crotyl bromide (Table 2.1, entry 1), identified through the absence of the resonance previously attributed to the amide proton in the ^{1}H NMR spectrum as well as the presence of the resonances assigned to the additional aliphatic peaks. However, when the ally bromide methyl ester (entry 2) was trialled, the reaction completely failed. It was proposed that under these conditions, which use simple palladium-catalysts and relatively mild bases and non-polar solvents, the complexation of the palladium (oxidative addition) to the more highly substituted allyl bromides does not occur as readily as for allyl bromide. As such, the likelihood of side reactions occurring before allylation can take place is greatly increased.

It was thus envisaged that a more nucleophilic amine would allow allylation to proceed more quickly, avoiding the possibility of side reactions. A substrate was prepared using the *p*-toluenesulfonyl protecting group which is known to be more readily alkylated than the trifluoroacetate amine protecting group under mild basic conditions (Scheme 2.5).[259-262]

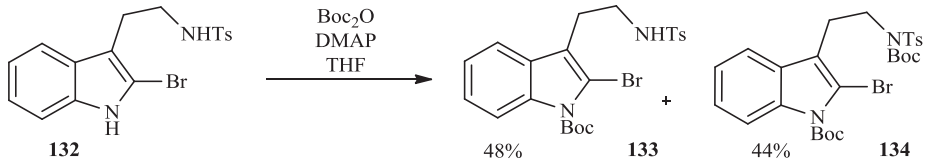


Scheme 2.5 Preparation of the sulfonamide substrate

The tosylation of the N_{10}-amine of tryptamine (**2**) was achieved in quantitative yields, following literature protocol (Scheme 2.5).[263-265] The presence of the desired sulfonamide **131** was identified using NMR spectroscopy through the introduction of the resonance attributed to the methyl group (δ 2.32 ppm), the resonance attributed to the sulfonamide NH proton (δ 4.53 ppm), as well as a downfield shift and additional splitting patterns observed for the resonances attributed to the ethylene chain of tryptamine, following the reaction with the sulfonyl chloride.

Initial attempts to brominate the indole-C2-position using *N*-bromosuccinimide (NBS) in CH_2Cl_2 as described by Jain *et al.*[252] furnished the desired product **132** in a yield of 56%. However, a by-product resulting from the proposed bromination of the sulfonamide was also observed following analysis of the reaction mixture by NMR spectroscopy. The formation of similar complexes has been reported numerous times in the literature, in particular for the aminobromination of olefins.[266-267] To overcome the formation of this by-product, pyridinium tribromide was employed to afford the 2-bromoindole sulfonamide **132** in 90% yield (Scheme 2.5). Following purification by column chromatography, the structure of 2-bromoindole **132** was immediately confirmed by NMR spectrometry and mass spectrometry.

The indole-nitrogen served as a potential competitive nucleophile in the domino process, therefore the final step in the preparation of the domino precursor involved the protection of the indole nitrogen with a *tert*-butoxycarbonyl (Boc) group. The Boc group was installed under standard conditions, by reacting the 2-bromosulfonamide **132** with di-*tert*-butoxycarbonyl dicarbonate in the presence of a catalytic amount of DMAP (Scheme 2.6).[264]

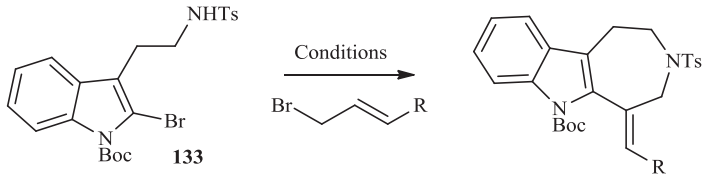


Scheme 2.6 Indole protection of the 2-bromosulfonamide derivative

Unfortunately, the Boc protection of the indole-nitrogen did not proceed as cleanly as desired due to the enhanced nucleophilicity of the sulfonamide. The desired mono-Boc compound **133** was isolated in an unoptimised yield of 48% with the ^{1}H NMR spectrum revealing the presence of the resonance attributed to the *tert*-butyl group (δ 1.68 ppm), as well as the absence of the indole-NH resonance (approximately δ 8.30 ppm) and the downfield shift of the indole-C7-aromatic proton (indole-NH δ 7.33 ppm to indole-*N*-Boc δ 8.00 ppm). The major by-product observed in this reaction was the di-Boc compound **134** (isolated in 44% yield), formed by reaction of both the indole-nitrogen and the sulfonamide. Although this indole protection step did not provide the desired domino precursor in high yields, enough product was isolated to carry out preliminary investigations into the Tsuji-Trost/Heck reaction using the tosyl 2-bromoindole substrate (a more detailed investigation into optimisation of this indole-nitrogen protection is discussed in Section 3.2.4).

The more nucleophilic 2-bromosulfonamide domino precursor **133** was then subjected to the domino process using the same palladium catalyst ($Pd(PPh_3)_4$) that was previously shown to facilitate the Heck reaction at the indole-2-position (Table 2.2).[137, 252] As the first step of this proposed domino sequence occurs in the presence of the palladium-catalyst and base and nucleophilic amine, both an S_N2 alkylation and a Tsuji-Trost allylation are possible to install the necessary olefin.

Table 2.2 The domino Tsuji-Trost/Heck reaction using the 2-bromosulfonamide precursor



Entry	R	Pd Catalyst	Base	Solvent	Yield (%)
1	Me (**135**)	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	NR
2	H (**136**)	$Pd(PPh_3)_4$	K_2CO_3	PhMe	NR

Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), and base (3.0 eq.), PhMe (4 mL). After stirring for 10 min, $Pd(PPh_3)_4$ (10 mol%) and allyl bromide (2.0 eq) were added and the reaction mixture heated to 120 ^oC for 16 h.

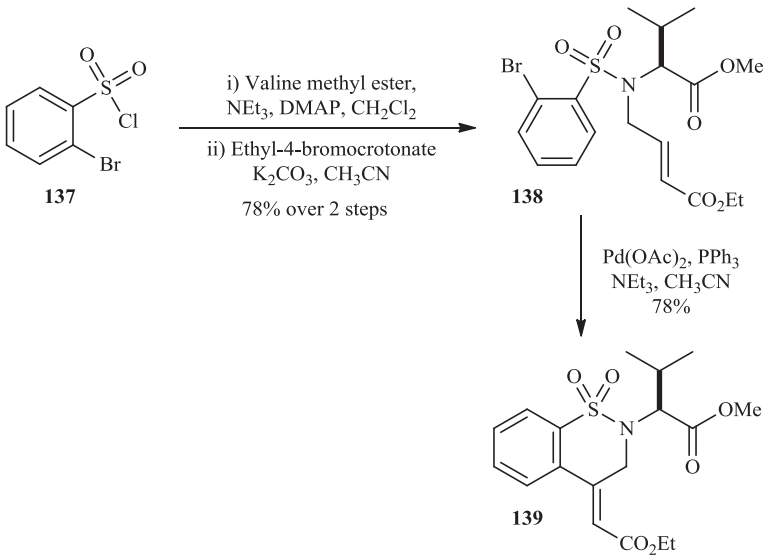
Unfortunately, the use of the 2-bromosulfonamide substrate in this domino process for the formation of azepino[4,5-*b*]indoles, using both allyl bromide and crotyl bromide, proved unsuccessful. Following analysis of the crude reaction mixtures, only starting material was detected in the ^1H NMR spectrum (Table 2.2).

Attempts to further expand the scope of this domino Tsuji-Trost/Heck reaction using more highly substituted allyl bromides and alternative aryl-halide substrates were also unsuccessful. To further pursue the development of new methodology for the synthesis of indole-based *N*-heterocycles attention turned to the single step process involving (i) alkylation of the N_{10}-amine followed by (ii) intramolecular Heck reaction at the indole-2-position.

2.4 Single Step Alkylation/Heck Reactions

Azepino[4,5-b]indoles

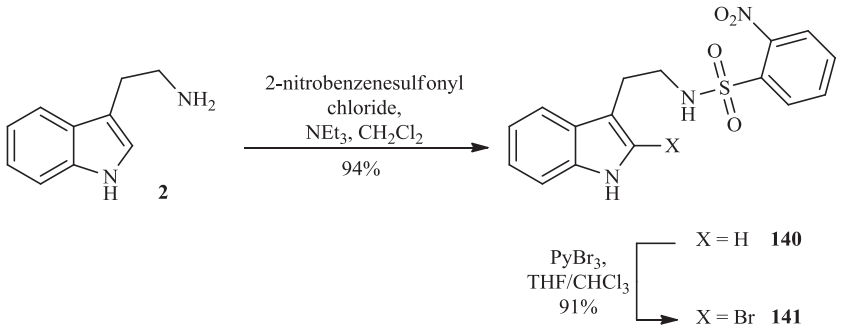
The successful application of a similar single-step methodology was reported in the aforementioned publication by Hanson *et. al.* for the synthesis of benzofused sultams containing both alkene and ester functionality external to the new ring formed (Scheme 2.7).[242]



Scheme 2.7 The alkylation/Heck reaction sequence for the synthesis of benzofused sultam alkenylesters.

Through reaction of the α-haloarylsulfonamide **137** with the ethyl-4-bromocrotonate (Scheme 2.7), an appropriate olefinic partner was installed which then undergoes intramolecular Heck reaction to form the new 6-membered heterocycle **139** in good yield (a favoured *6-exo-trig* cyclisation). As such, it was envisaged that a similar approach could be applied to our 2-bromotryptamine system, using a range of functionalised allyl bromides (see Scheme 2.2) would provide access to azepino[4,5-*b*]indole scaffolds (a 7-*exo-trig* cyclisation).

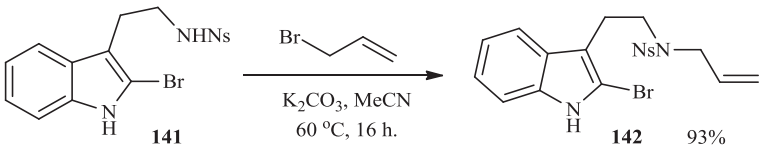
As the starting materials were readily available, initial investigations for this single step process were carried out using the trifluoroacetate **60** and tosyl **133** substrates discussed in the previous section (Section 2.3). Unfortunately, a high yielding, selective, N_{10}-alkylation process for these substrates was not identified following the screening of a range of reaction conditions. It was therefore envisaged that a more acidic amide proton would allow selective functionalisation of the N_{10}-amine. To achieve this selectivity, the more electron withdrawing 2-nitrobenzenesulfonyl (Ns or nosyl) protecting group was installed through reaction of tryptamine (**2**) with 2-nitrobenzenesulfonyl chloride (in 94% yield) following a similar protocol used to introduce the *p*-tosyl group previously (Scheme 2.8).[265]



Scheme 2.8 Preparation of the 2-nosylsulfonamide

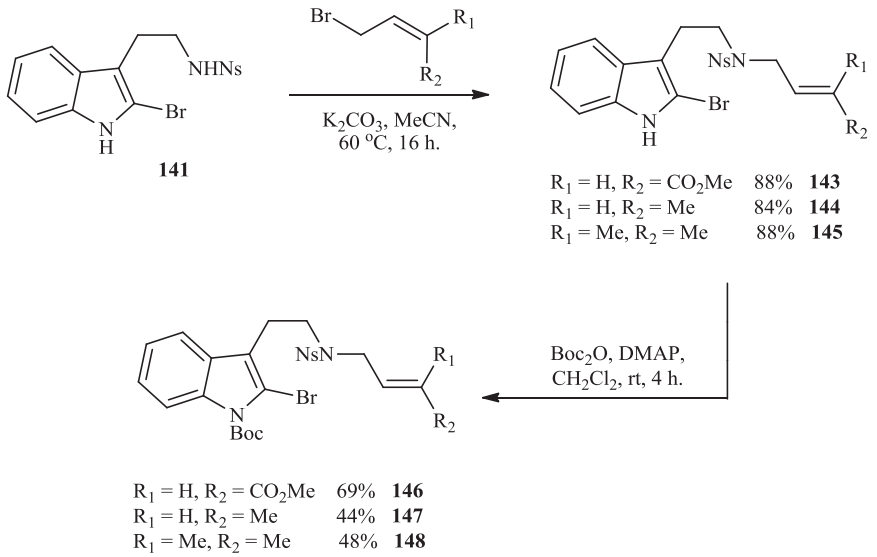
The desired increase in acidity of the sulfonamide proton from tosyl to the nosyl group was readily detected in the ^{1}H NMR spectrum, from the downfield shift of the resonance attributed to the sulfonamide proton (Ts δ 4.45 ppm, Ns δ 5.32 ppm) due to the increased deshielding effect of the aryl-nitro group. Following protection of the N_{10}-amine, the indole-2-position was then brominated using pyridinium tribromide in 91% yield (Scheme 2.8), again confirmed by the absence of the indole-2-proton in the ^{1}H NMR spectrum (δ 7.01 ppm, doublet, indole-2-ArH), in addition to the upfield shift of the indole-C2 resonance in the ^{13}C spectrum (δ 124.4 ppm to δ 109.3 ppm).

The nosyl-2-bromotryptamine **141** was then subjected to alkylation conditions reported in the literature and following a simple work up procedure the desired allylamine product **142** was isolated in an excellent yield of 93% (Scheme 2.9).[261] The identity of this product was confirmed by means of NMR spectroscopy and mass spectrometry, with the characteristic splitting patterns of the allyl group readily observed in the ^{1}H NMR spectrum.



Scheme 2.9 Alkylation of the nosyl sulfonamide with allyl bromide

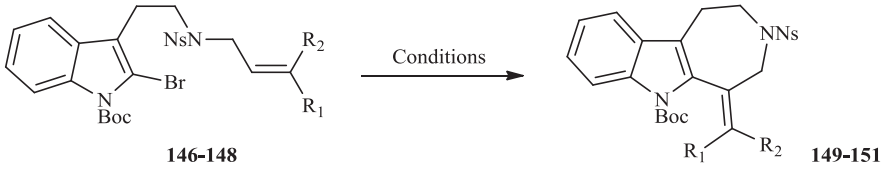
With the installation of the N_{10}-amine olefin tether proceeding in high yields, the requisite Heck cyclisation precursors were prepared through reaction of the 2-bromosulfonamide substrate with three different allyl bromides (crotyl bromide, dimethylallyl bromide and methyl-4-bromocrotonate) in excellent yields (Scheme 2.10). Following this, the indole-nitrogen was protected with the *tert*-butoxycarboyl group (Boc group) in moderate yields to afford the fully functionalised Heck reaction precursors (**146, 147** and **148**).



Scheme 2.10 Preparation of the Heck cyclisation precursors

With the requisite precursors for the formation of azepino[4,5-*b*]indole ring systems synthesised in good yields using a general procedure, attention now turned to the Heck cyclisation reaction. The intramolecular Heck reaction of the 2-bromoindole precursors was investigated by screening a range of palladium catalysts and bases for each of the substrates (Table 2.3).

Table 2.3 Optimisation of the Heck reaction to form functionalised azepino[4,5-*b*]indoles



146-148 **149-151**

Entry	R_1	R_2	Product	Pd Catalyst [a]	Base	Solvent	Yield (%)
1	CO_2Me	H	**149**	$Pd(PPh_3)_4$	K_2CO_3	PhMe	NR
2	CO_2Me	H	**149**	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	NR
3	CO_2Me	H	**149**	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	NR
4	Me	H	**150**	$Pd(PPh_3)_4$	K_2CO_3	PhMe	NR
5	Me	H	**150**	$Pd_2(dba)_3.CHCl_3$	NEt_3	PhMe	NR
6	Me	H	**150**	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	NR
7	Me	H	**150**	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	NR
8	Me	Me	**151**	$Pd(PPh_3)_4$	K_2CO_3	PhMe	NR
9	Me	Me	**151**	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	NR
10	Me	Me	**151**	$Pd_2(dba)_3.CHCl_3$	NEt_3	PhMe	NR
11	Me	Me	**151**	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	NR

[a] Palladium catalyst loading 10 mol%. (where applicable the Pd:Ligand ratio was 1:1).
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), palladium catalyst (10 mol%), and base (3.0 eq.) in PhMe (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

It was known that the Heck reaction at the indole-2-position can be achieved using $Pd(PPh_3)_4$ in reasonable yield in the presence of an inorganic base in toluene or dioxane, and

generally requires reasonable high temperatures to proceed. As such, to form the functionalised azepino[4,5-*b*]indole, initial trials were completed using $Pd(PPh_3)_4$, K_2CO_3, and toluene at 120 ^oC in a sealed tube (Table 2.3, entries 1, 4 and 8). Unfortunately, no trace of the desired product was detected following analysis of the crude reaction mixture by NMR spectroscopy and mass spectrometry.

Formation of the new 7-membered heterocycle using the Heck reaction was then attempted using a range of palladium-catalysts including the highly reactive system pioneered by Fu.[170] Once again, following analysis of the crude reaction mixtures, no trace of the desired azepino[4,5-*b*]indole ring systems was identified (Table 2.3).

The failure of these olefin tethers to cyclise at the indole-2-position and form the new 7-membered heterocycles (**149-151**) was unexpected, as it is known that the Heck reaction does in fact take place at the indole-2-position with electron deficient alkenes (e.g. butyl acrylate). The formation of the 7-membered ring (preferentially to the 8-membered ring also possible during this process) has also proved favourable at this position.[99-100, 137]

Mechanistically, oxidative addition of the palladium(0) species must occur at the halogenated indole-2-position, as highlighted in previous literature examples of a palladium-mediated cross-coupling reactions at this position (see Section 1.2.6).[137, 252] Following oxidative insertion, the palladium forms a complex with the olefin in order to bring it close enough to the indole-2-position for migratory insertion to occur (see Section 1.3 for a discussion on the catalytic cycle of the Heck reaction). From the failure of formation of the new *N*-heterocycle it was proposed that migratory insertion did not take place.

For electron-deficient terminal alkenes (for example butyl acrylate) the σ-alkyl palladium(II) complex is formed α- to the carbonyl, allowing migratory insertion of the R group (the indole attached at the C2-position) to occur at the electron deficient end of the alkene (the β-end). In contrast, if an electron-rich olefin is used, ligation of the olefin by the Pd^{II} species occurs at the β-position, resulting in formation of the α-substituted alkene.

As the more highly substituted allyl bromides contain functionality at this β-position of the alkene, palladium-ligation and therefore migratory insertion would be expected to occur at a much slower rate. The failure of intramolecular Heck reaction is understandable for the case of the dimethylallyl tether as the β-position is disubstituted, however, the fact that the allyl ester and crotyl tethers also did not undergo Heck reaction is surprising (Table 2.3).

A number of reasons were proposed for the failure of the intramolecular Heck reaction, with both the allyl ester and crotyl tethers. In terms of steric properties, the allyl group is much

more crowded in the presence of the 2-nitrobenzenesulfonyl group **152** than it was for the trifluoroacetate group **153** successfully employed in the Tsuji-Trost/Heck reaction sequence discussed earlier (Figure 2.1). Even though free rotation can occur through several of the bonds of this tether, the additional steric bulk may hinder the progress of the migratory insertion process.

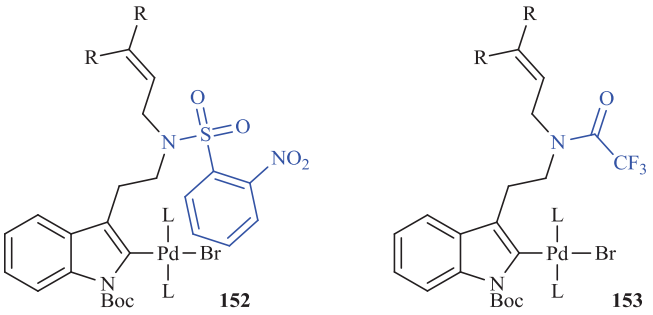


Figure 2.1 The olefin is more sterically hindered in the case of the nosyl sulfonamide when compared with that of the trifluoroacetamide successful in previous cases.

When compared to the reported successful intramolecular Heck reaction of the allyl ester tether **154** for the synthesis of the benzofused sultams (see Scheme 2.6), the tether present in our 2-bromotryptamine derivative **155** also had a much higher degree of free rotation. The conjugation of the sultam system would presumably hold the olefinic tether in much closer proximity to the palladium-halide complex **154**, allowing migratory insertion to occur more readily (Figure 2.2)

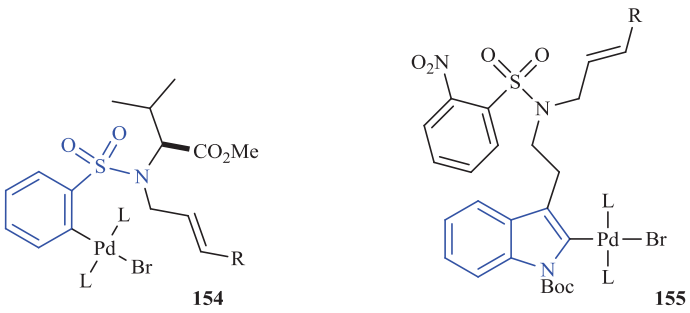
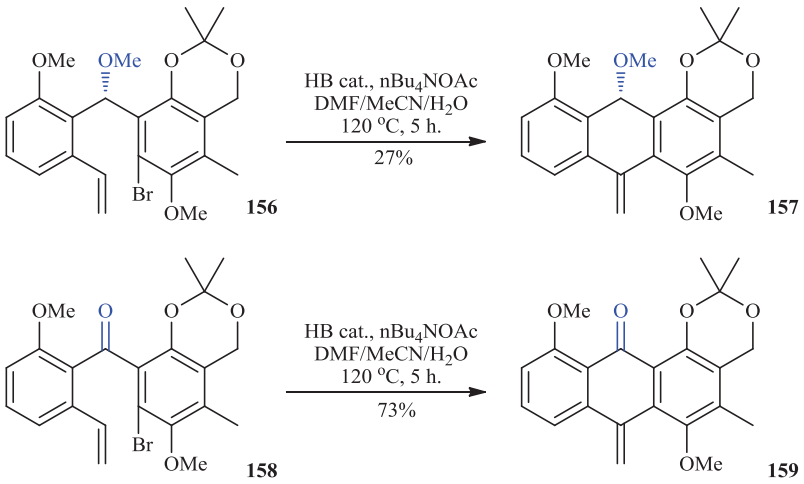


Figure 2.2 Preorganisation in the sultam system means the olefin tether is in much closer proximity to the palladium-halide complex than for the 2-bromotryptamine substrate

Similarly hampered intramolecular Heck reactions have been well reported in the literature, where the addition of even a small amount of flexibility in the molecule can significantly affect the success of the Heck reaction (Scheme 2.11).[268]



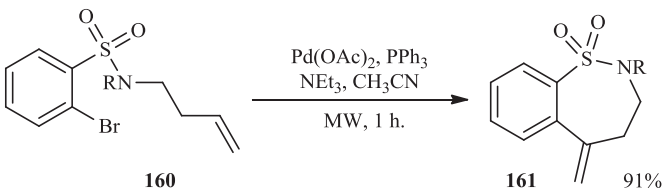
Herrmann-Beller Catalyst (HB cat.) is:
trans-{di(μ-acetato)bis[ortho-(di-ortho-tolylphosphanyl)benzyl]dipalladium(II)}

Scheme 2.11 Flattening of the ring by replacing the central methoxy group with a carbonyl group significantly enhanced the yield of the intramolecular Heck reaction[268]

In conclusion, a combination of favourable steric and electronic properties in the Heck cross-coupling partners were crucial in the facilitation of the intramolecular Heck reaction to form the new *N*-heterocyclic ring. Unfortunately, in our case, the correct combination was not identified and development of new palladium-mediated methodology to access 7-membered indole-based heterocycles was no longer pursued.

Indoloazocines

With the synthesis of azepino[4,5-*b*]indole ring systems unsuccessful using the single-step alkylation/Heck reaction sequence, the synthesis of indoloazocines using this strategy was also briefly investigated. A similar process for the formation of the 7-membered heterocycle **161** was used by the group of Hanson for the synthesis of benzofused sultams (Scheme 2.12).[242]

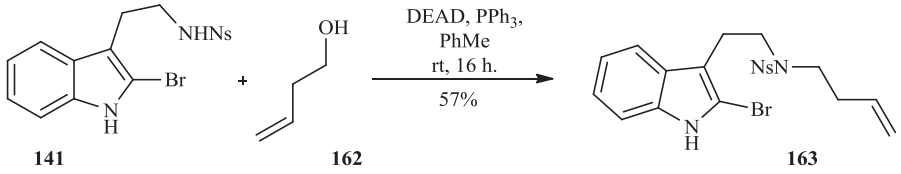


Scheme 2.12 Synthesis of a benzofused sultam containing a 7-membered heterocycle

In a similar fashion, to that discussed for the azepinoindoles, the *σ*-alkyl palladium(II) complex should form at the terminal end of the electron rich alkene, eventually resulting in

the formation of the 8-membered indole-based *N*-heterocyclic ring (the α-substituted product as observed in the synthesis of sultams – Scheme 2.12).

Following a literature protocol for the functionalisation of sulfonamides using the Mitsunobu reaction,[269-270] the nosyl-2-bromotryptamine **141** prepared for the previous study was reacted with 3-buten-1-ol **162** (Scheme 2.13).

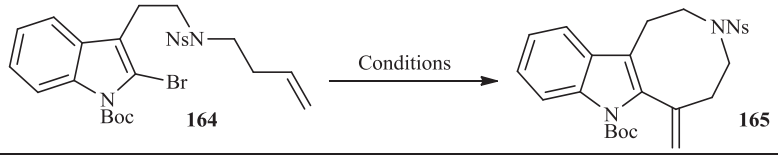


141 **162** **163**

Scheme 2.13 Mitsunobu reaction to prepare the Heck precursor

The highest yield obtained for this Mitsunobu process was 57%, but only when an excess of the azodicarboxylate and triphenylphosphine were used (increasing the chance of forming the activated alcohol species, prior to nucleophilic attack). The immediate success of this reaction was again confirmed by analysis of the ^{1}H NMR spectrum which contained new resonances at δ 5.07 and 5.75 ppm attributed to the olefinic protons within **163**. The absence of the proton resonance that could be assigned to the sulfonamide also confirmed isolation of the desired product. With the 2-bromoindole-alkene in hand, the indole nitrogen was Boc protected as previously (88% yield), and the fully functionalised precursor **164** was subject to Heck conditions to form the indoloazocine **165** (Table 2.4).

Table 2.4 Optimisation of the intramolecular Heck reaction to form the indoloazocine.



164 **165**

Entry	Palladium Catalyst	Base	Solvent	Yield (%)
1	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	NR
2	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	Dioxane	NR
3	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	NR
4	$Pd_2(dba)_3$/DavePhos	Cy_2NMe	PhMe	NR

Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 ^{o}C for 16 h.

The Heck reaction between the indole-2-position and tethered alkene was first trialled using $Pd(PPh_3)_4$ and an inorganic base (Table 2.4, entry 1), as these were previously successful for Heck chemistry at the indole-2-position. However, once again, as in the case of the azepino[4,5-*b*]indole 7-membered ring system, formation of the 8-membered indoloazocine **165** also failed. Screening of several additional catalytic systems did not furnish any of the

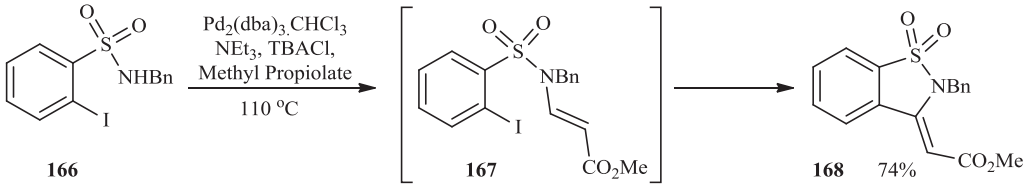
desired *N*-heterocycle. The failure of this approach is also proposed to be due to the palladium-alkene complex not forming as required to facilitate the migratory insertion step as discussed in the previous section.

In summary, investigations were carried out into the development of a general palladium-catalysed approach to functionalised 7- and 8-membered indole-based *N*-heterocycles using an intramolecular Heck cyclisation reaction at the indole-2-position. Attempts to synthesise more highly functionalised indole-based scaffolds than the current methods provide, using various alkene tethers off the N_{10}-amine of tryptamine, proved unsuccessful. As such, this approach was no longer pursued for the synthesis of 7- and 8-membered *N*-heterocycles.

2.5 Domino and Single Step Aza-Michael/Heck Reactions

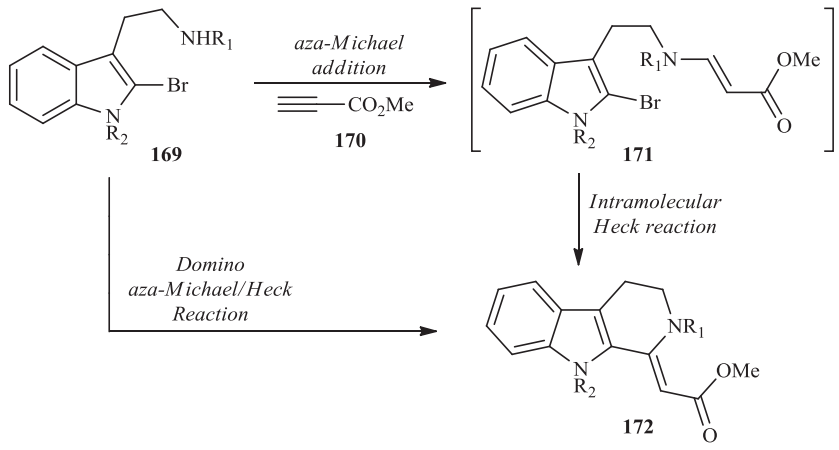
Attempts to improve on existing methodology and develop a new approach to functionalised azepino[4,5-*b*]indoles and indoloazocines to this point had proved unsuccessful. As such, our attention now turned to the synthesis of 6-membered indole-based *N*-heterocycles.

The first approach proposed for the synthesis of C1-substituted tetrahydro-*β*-carbolines was through the use of a domino aza-Michael/Heck reaction sequence. This reaction sequence has been successfully employed by Hanson *et al.*, for the formation of 5-membered heterocycles in the synthesis of benzofused sultams (Scheme 2.14). The domino reaction proceeds under mildly basic conditions for the aza-Michael addition of methyl propiolate, with the resultant alkene **167** undergoing cross-coupling with the aryl-iodide, facilitated by Jeffery conditions (phosphine-free, with the addition of TBACl) to afford the requisite heterocycle **168** in good yield over 2 steps.[261]



Scheme 2.14 A domino aza-Michael/Heck reaction sequence for the synthesis of benzofused sultams

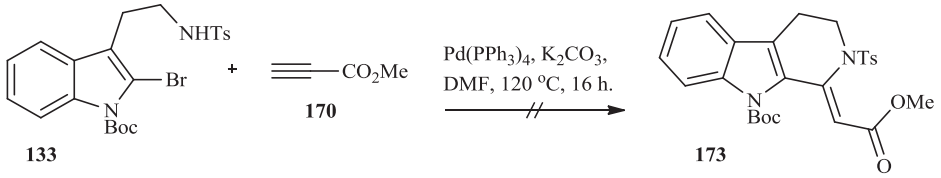
In a similar fashion it was envisaged that a C1-substituted tetrahydro-*β*-carboline **172** could also be formed from reaction of an appropriately functionalised 2-bromotryptamine **169** and methyl propiolate **170** using a domino aza-Michael/Heck reaction (Scheme 2.15, a favoured *6-exo-trig* cyclisation). The formation of the 6-membered ring during this process should result, with migratory insertion of the indole-2-position occurring at the most electron-deficient end of the alkene (the *β*-substituted product).



Scheme 2.15 The proposed domino aza-Michael/Heck reaction for the synthesis of *β*-carbolines

In this system, an appropriate amine protecting group is required that allows aza-Michael addition to proceed rapidly, prior to Heck reaction. As the sulfonamide protecting groups used previously in this investigation (both tosyl and nosyl) are known to be readily functionalised under mildly basic conditions,[242, 260, 265, 270-271] they were considered ideal for this domino process.

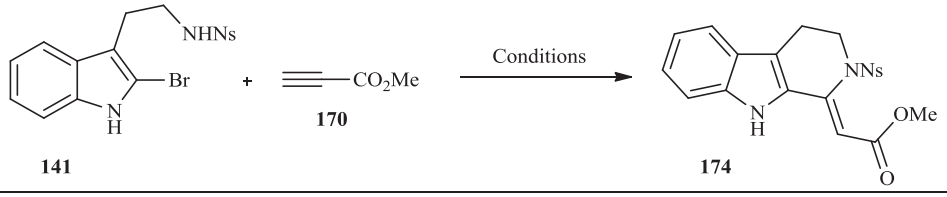
The first domino reaction was attempted with the tosyl-2-bromotryptamine substrate **133**. The reaction was carried out with potassium carbonate and DMF to promote initial intermolecular aza-Michael addition to the alkyne, with $Pd(PPh_3)_4$ present to facilitate the subsequent cross-coupling reaction (Scheme 2.16).



Scheme 2.16 Attempted aza-Michael/Heck domino reaction to form the 6-membered *N*-heterocycle

Following a simple work up, analysis of the crude reaction mixture by NMR spectroscopy revealed a complex mixture of products. As the Heck reaction of similar alkenes is known at the indole-2-position, it was presumed that aza-Michael addition did not take place readily enough to allow sufficient time for Heck reaction to occur. As such, the nosyl-2-bromotryptamine substrate **141**, was then subjected to this domino process (Table 2.5).

Table 2.5 Optimisation of the domino aza-Michael/Heck reaction



141 **170** **174**

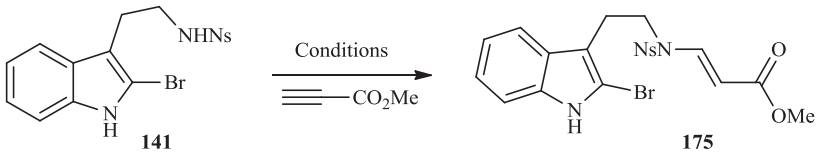
Entry	Pd Catalyst	Base	Additive	Solvent	Yield (%)
1	$Pd(PPh_3)_4$	K_2CO_3	TBACl	PhMe	Trace [a]
2	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	TBACl	Dioxane	Trace [a]
3	$Pd(PPh_3)_4$	Cy_2NMe	TBACl	DMF	NR

a Trace is <10% as determined by ^{1}H NMR
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), palladium catalyst (10 mol%), and base (3.0 eq.) additive (1.0 eq) in solvent (4 mL). The reaction mixture was then heated to 120 ^oC for 16 h.

The domino process was attempted using a range of palladium catalysts, bases, solvents and additives (Table 2.5). The phase transfer agent TBACl was also added in an attempt to improve both the solubility of the reagents and the intermediates in Heck catalytic cycle. Following analysis of the crude reaction mixture by NMR spectroscopy, trace amounts of the desired product **174** were identified in two of the domino reactions (Table 2.5 entries 1 and 2), however, attempts to purify this compound by column chromatography proved unsuccessful.

As this domino process did not provide high yields of the newly formed 6-membered *N*-heterocycle, the domino approach was abandoned and the aza-Michael/Heck reaction sequence investigated in a single step fashion using the nosyl-2-bromotryptamine substrate **141**. Following literature procedures, the aza-Michael addition step with methyl propiolate **170** was investigated first (Table 2.6).[272-273]

Table 2.6 Optimisation of the aza-Michael addition



141 **175**

Entry	Additive	Base	Solvent	Temperature (^oC)	Yield (%)
1	PPh_3 (10 mol%)	-	CH_2Cl_2	25 (16 h.)	NR [a]
2	-	Cy_2NMe	MeCN	0 (2 h.)	86%

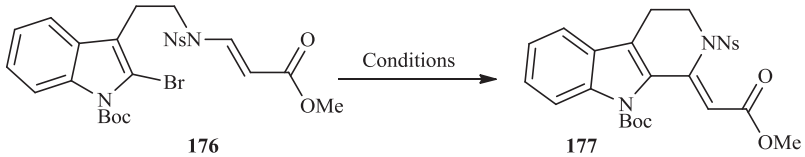
a The major product isolated from this reaction was due to aza-Michael addition of the indole-nitrogen to methyl propiolate

The first method attempted for the aza-Michael addition employed a triphenylphosphine catalyst in CH_2Cl_2 as reported to facilitate aza-Michael addition of sulfonamides to propiolates in high yields with only formation of the (*E*)-isomer (Table 2.6, entry 1).[273] Attempts to functionalise the sulfonamide with methyl propiolate using these conditions lead

exclusively to the aza-Michael addition product from the indole-nitrogen, indicating this PPh_3-catalysed process is selective for aryl amines over alkyl amines.

A second literature procedure reported the aza-Michael addition of sulfonamides to methyl propiolate promoted by *N*-methylmorpholine at 0 °C for two hours in acetonitrile.[272] As *N*-methylmorpholine was not readily available in our laboratory, a similarly hindered amine base *N,N*-dicyclohexylmethylamine (Cy_2NMe) was trialled instead (Table 2.6, entry 2). Following a simple work up the desired product **175** was isolated in 86% yield (as a 9:1 mixture of (*E*):(*Z*) isomers as determined by ^{1}H NMR spectroscopy). The absence of a resonance that could be attributed to a sulfonamide proton was evident. Additionally, the presence of the olefinic proton resonances (δ 5.52 and 8.10 ppm) confirmed that aza-Michael addition to the sulfonamide was successful. Following isolation of the desired alkenyl-ester **175**, the indole nitrogen was protected as the *N*-Boc derivative **176** in a good yield of 66%. With the 2-bromotryptamine-alkenyl ester in hand, the intramolecular Heck reaction to form the new 6-membered *N*-heterocycle was trialled (Table 2.7).

Table 2.7 Optimisation of the Heck reaction for formation of the 6-membered *N*-heterocycle



176 **177**

Entry	Palladium Catalyst [a]	Base	Solvent	Temperature (°C)	Yield (%)
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	120 (16 h.)	Trace [b]
2	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	120 (16 h.)	Trace [b]
3	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	Dioxane	120 (16 h.)	NR

a Palladium catalyst loading 10 mol%. Palladium and ligand used in a 1:1 ratio where applicable.
b Trace is less than 10% as determined by ^{1}H NMR.
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

Following a simple work-up, analysis of the crude reaction mixtures by NMR spectroscopy and mass spectrometry revealed the presence of the desired product. However, separation of this product was not achieved, due to a number of co-eluting by-products. Analysis of the ^{1}H NMR spectrum indicated that both the (*E*) and (*Z*) geometrical isomers of the 6-membered heterocycle were present, as well as the 7-membered ring from Heck reaction at the α-end of the alkene.

Despite the initial starting material containing a mixture of isomers, addition of the palladium complex to the double bond during the reaction process, followed by internal rotation and *β*-hydride elimination, should lead exclusively to the more thermodynamically stable product where the indole-2-position lies *trans* to the methyl ester (as depicted in, Table 2.7). However, as each of the steps in the Heck catalytic cycle are potentially

reversible,[274] if dissociation of the olefin to the Pd(II)-hydride complex is relatively slow, addition of the Pd back into the double bond can occur, leading to the formation of double bond isomers.[177-178]

The electronic properties of the alkene tether were also considered to hinder the progress of this reaction. Under classical conditions, migratory insertion occurs at the most electron-deficient end of the terminal alkene. However, as the alkene was disubstituted (both sulfonamide and ester functionality), formation of the σ-alkyl palladium(II) complex may occur at either side of the alkene, leading to formation of the 6- or 7-membered heterocycle.

2.6 Conclusion

This chapter detailed the attempts to develop new methodology for the synthesis of functionalised indole-based *N*-heterocycles further exploiting the intramolecular Heck reaction at the indole-2-position. This investigation focussed on the initial tethering of an appropriate olefin from the N_{10}-amine of tryptamine, followed by an intramolecular Heck reaction to form new 6,7 or 8-membered ring systems.

Installation of the olefin tether (using substituted allyl bromides and propiolates) to the N_{10}-amine was completed in high yields, however the intramolecular Heck reaction at the indole-2-position to form the new *N*-heterocycle was unsuccessful for each system, with a trace amount of the desired product detected, at best.

Chapter Three

Indole-Based N-Heterocycles: Intermolecular Heck Reactions

3.1 Chapter Overview

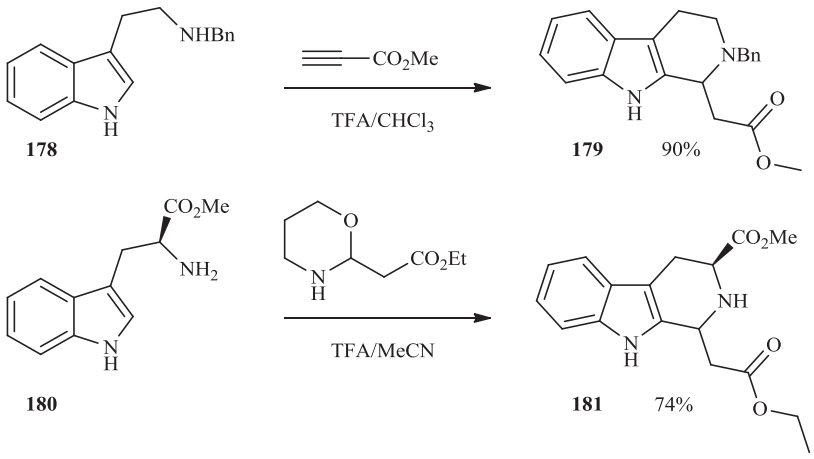
Following the unsuccessful investigations into the construction of indole-based *N*-heterocycles using the *intramolecular* Heck reaction, attention turned to the *intermolecular* Heck cross-coupling reaction at the indole-2-position. The following chapter describes the development a domino Heck-aza-Michael reaction for the synthesis of C1-substituted tetrahydro-*β*-carbolines. Investigations into the optimisation and scope of the domino Heck-aza-Michael process using a variety of commercially available acrylate starting materials are discussed in detail.

3.2 Domino Heck-aza-Michael Reactions

Due to their biological relevance (see Chapter One),[6, 18-25] it is important that tetrahydro-*β*-carbolines (TH*β*Cs) can be easily prepared and contain multiple functional groups for further synthetic manipulation. Traditionally, C1-substituted TH*β*Cs are accessed through the acid-catalysed Pictet-Spengler reaction between tryptamine and an appropriate aldehyde.[35-36] Alternatively, a four step process involving a Bischler-Napieralski reaction to afford the dihydro-*β*-carboline, and subsequent reduction, is effective in producing specific TH*β*Cs.[65]

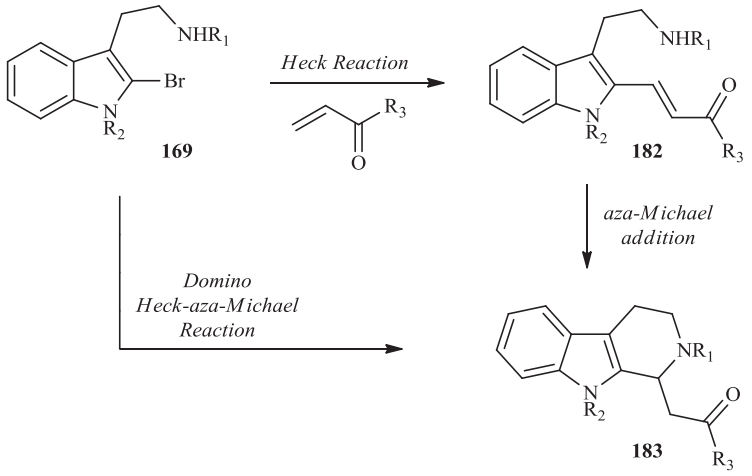
Unfortunately, using these methods specific C1-substituted tetrahydro-*β*-carbolines are not always readily accessible due to the instability of a number of substituted aldehydes, and the requisite reaction conditions required to effect these types of cyclisations (for example the acid-catalyst in the case of the Pictet-Spengler reaction, and $POCl_3$, as well as high temperatures in the Bischler-Napieralski reaction).

One specific example of the limitations of these traditional methods is when access to acetate substituted *β*-carbolines is required. As synthesis of the requisite *β*-formyl ester reagent for the Pictet-Spengler reaction is difficult and the reagent is relatively unstable (it can only be handled at low temperatures, typically -78 ^{o}C),[275] limits are placed on their use in certain types of syntheses. Efforts to overcome the limitations have focused on a modified Pictet-Spengler reaction to access the equivalent tetrahydro-*β*-carboline (**179** and **181**) using alkynoates[22, 276] or perhydro-1,3-heterocycles[25] (instead of the *β*-formyl ester - Scheme 3.1).



Scheme 3.1 Current syntheses of specific 1-substituted TH*β*Cs.

Even with these modified approaches, access to a range of functionalities at the tetrahydro-*β*-carboline C1-position is limited, as the range of commercially available alkynoates are few and the conditions required to prepare the perhydro-1,3-heterocycle starting materials are not trivial. As such, an alternative synthesis to this specific TH*β*C scaffold was sought that would allow access to a series of *β*-carbolines, where the functionality introduced at the C1-position could be readily varied. A domino Heck-aza-Michael reaction of tryptamine **169** (Scheme 3.2), was foreseen as an efficient method for introducing molecular diversity at C1 of the TH*β*C scaffold **183**.



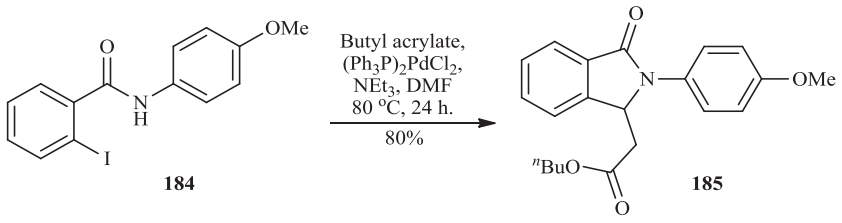
Scheme 3.2 The proposed domino Heck-aza-Michael process to access functionalised tetrahydro-*β*-carbolines

Previous research determined that a Heck reaction between 2-bromotryptamine and electron deficient terminal alkenes takes place using a catalytic amount of $Pd(PPh_3)_4$ in toluene in the presence of K_2CO_3. As the Heck reaction regenerates the olefin functionality following *syn*-

elimination, and is reliably efficient with electron deficient terminal alkenes, the potential exists for a second nucleophilic addition reaction, in this case, a 1,4-Michael addition, depending on the nature of the tethered amine and if it reacts before or after the Heck reaction (an intra *vs.* intermolecular aza-Michael reaction).

As both the Heck reaction[148-149] and aza-Michael additions[261, 277-278] are known to proceed under mildly basic conditions, a domino Heck-aza-Michael reaction to access the TH*β*C scaffold appeared plausible. In this proposed reaction, a new C-C and C-N bond would be created in sequence, at the same carbon atom. Using cheap and readily available acrylates under mild conditions, an orthogonally protected TH*β*C scaffold containing multiple sites for further functionalisation would be produced. Unlike propiolates, a wide range of suitable acrylates (such as butyl acrylate, acrolein, acrylonitrile and acrylic acid) are cheap and commercially available, allowing C1 functionality of the new *N*-heterocycle to be customised *via* appropriate alkene selection.

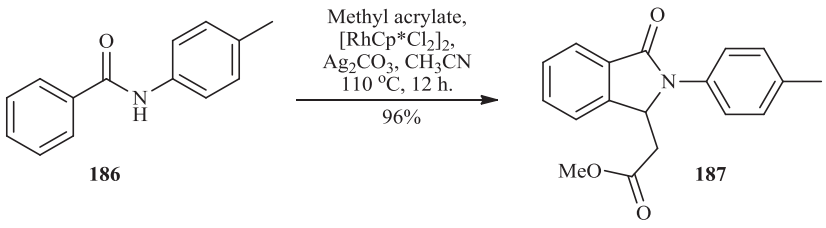
Domino Heck-Michael methodology for the formation of heterocycles has not been widely reported.[218, 279-281] Early examples of this methodology included the synthesis of pthalimidines[281] and tetrahydronapthalenes.[218] Unfortunately these methods suffered from low yields, long reaction times and limited substrate scope. More recently in 2005, the synthesis of isoindolinones **185** using a domino Heck-aza-Michael reaction was reported by the group of Wahab Khan (Scheme 3.3).[280] Although this reaction sequence allowed for the synthesis of a series of isoindolinones where the amide substituent could be readily varied, attempts to use electron deficient alkenes other than acrylates (for example acrylonitrile and acrolein) failed.[280]



Scheme 3.3 The synthesis of isoindolinones using a domino Heck-aza-Michael reaction

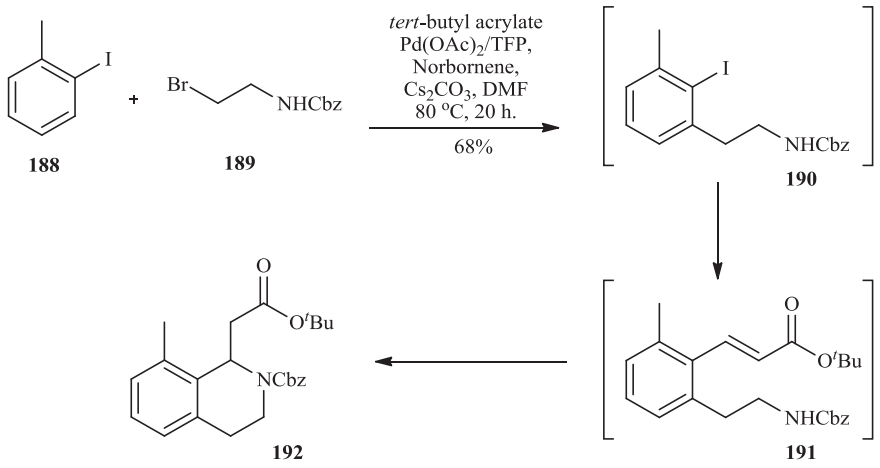
A rhodium-catalysed olefination-aza-Michael process was recently reported for the synthesis of similar isoindolinone systems (Scheme 3.4).[282] Following C-H activation, the rhodium-catalysed cross-coupling of the electron deficient terminal alkene occurs, installing the conjugated Michael acceptor. A 1,4-addition of the benzamide then takes place to form the new *N*-heterocycle **187** in good yields. This process proved successful when using acrylates,

ethyl vinyl ketone and acrylonitrile, allowing access to a greater range of C1-substituted isoindolinones than the aforementioned domino Heck-aza-Michael process.[280]



Scheme 3.4 The rhodium-catalysed olefination/aza-Michael domino process for the synthesis of functionalised isoindolinones[282]

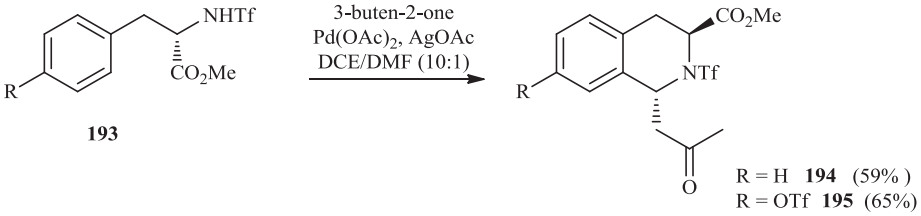
The synthesis of tetrahydroisoquinolines employing a domino Heck-aza-Michael process was published in 2004 by Ferraccioli *et al*.[283] The first step in this multicomponent reaction was the *ortho*-alkylation of an aryl iodide **188** with bromoethylcarbamate **189** to form the corresponding phenethylamine **190** (Scheme 3.5) through a C-H activation process involving norbornene.



Scheme 3.5 A three-component process for the synthesis of tetrahydroisoquinolines employing a domino Heck-aza-Michael reaction

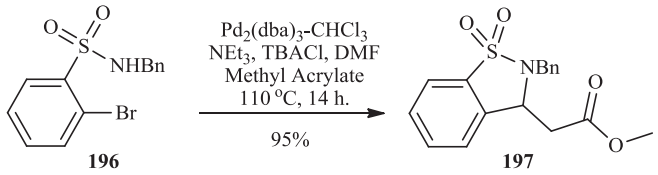
The Heck reaction between the aryl-iodide **190** and *tert*-butylacrylate afforded the conjugated Michael acceptor **191**. Finally, formation of the *N*-heterocycle through 1,4-addition of the carbamate furnishes the new ring system **192** in an excellent yield of 68% for the three step process. Using the bromopropylcarbamate substrate, this reaction sequence was also successfully applied to the synthesis of C1-substituted tetrahydro-2-benzazepines.[283]

A palladium(II) mediated domino C-H olefination/aza-Michael addition was developed for the synthesis of the tetrahydroisoquinoline ketone derivatives **194** and **195** (Scheme 3.6). This process tolerated the presence of electron-withdrawing substituents on the aromatic ring, however when methyl acrylate was employed, only the Heck adduct was isolated.[284]



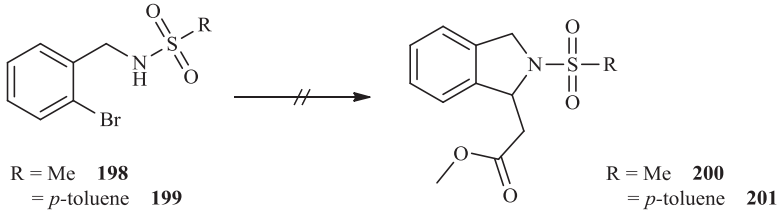
Scheme 3.6 A tandem C-H alkenylation/aza-Michael addition reaction sequence for the synthesis of the tetrahydroisoquinoline ketone

A recent report by Hanson *et al.* detailed the application of a domino Heck-aza-Michael process to the synthesis of a series of unique benzofused sultams (Scheme 3.7).[279] In this case, the initial cross-coupling took place under Jeffery's phosphine-free conditions,[285-287] with the subsequent aza-Michael addition of the sulfonamide forming the new *N*-heterocycle **197** in exceptional yields over a two-step process.



Scheme 3.7 A domino Heck-aza-Michael reaction to access benzofused sultams[279]

Once again, this methodology allowed variation of the sulfonamide substituent, and proved successful for several acrylates including methyl vinyl ketone and acrylic acid. However, attempts by this same group to expand the scope of this domino Heck-aza-Michael methodology to substrates where the sulfonyl group lay *external* to the new heterocycle failed (Scheme 3.8).[279]



Scheme 3.8 Attempts by the group of Hanson to expand the scope of the domino Heck-aza-Michael reaction to include other heterocyclic systems proved unsuccessful[279]

Despite the 'mixed success', the development of a domino Heck-aza-Michael reaction for the synthesis of tetrahydro-β-carbolines using a range of electron deficient terminal alkenes was seen as an efficient way of introducing functionality during the formation of the tetrahydro-β-carboline scaffold. The following section describes our preliminary investigations into such a system using a single-step process and the eventual development of a domino Heck-aza-Michael reaction for the synthesis of C1-substituted tetrahydro-β-carbolines.

3.2.1 Initial Investigations

When assessing this Heck-aza-Michael reaction sequence retrosynthetically (Figure 3.1), a number of parameters were identified that required consideration for the development of the domino process.

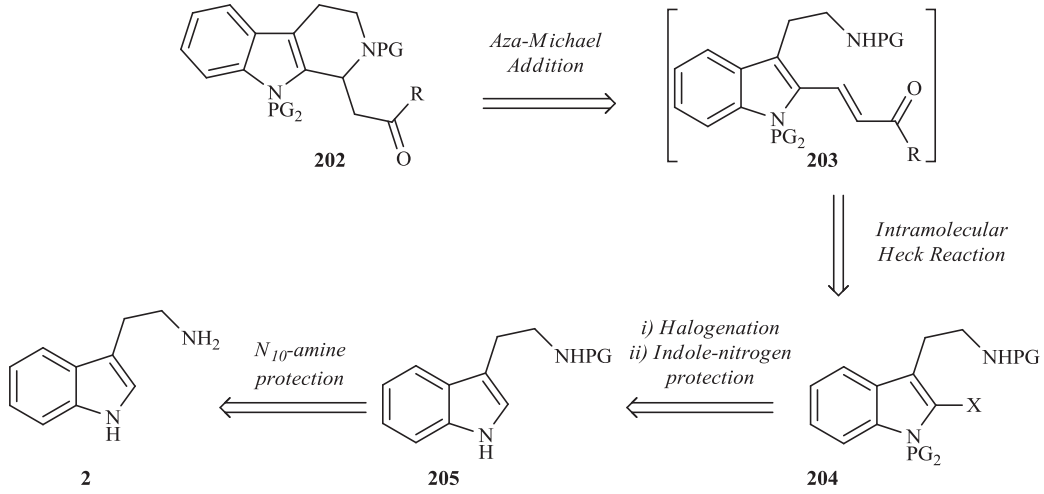


Figure 3.1 Retrosynthetic analysis of the domino Heck-aza-Michael reaction for the synthesis of C1-substituted THβCs

The first consideration was the primary amine of tryptamine (**2**). As this amine is very nucleophilic, it required protection before bromination of the indole-2-position could be attempted. A suitable protecting group was therefore required to prevent this amine from interfering with bromination of the indole-2-postion. However, as this amine was also required to take part in the 1,4-addition process following the Heck reaction, the protecting group needed to allow the N_{10}-amine to retain a certain degree of nucleophilicity. In addition, this nucleophilicity had to be suitably tuned so that aza-Michael addition of the alkene did not occur prior to Heck reaction.

The second consideration for this domino process was the intermolecular Heck reaction. Suitable catalytic conditions were required that would facilitate a swift Heck reaction to

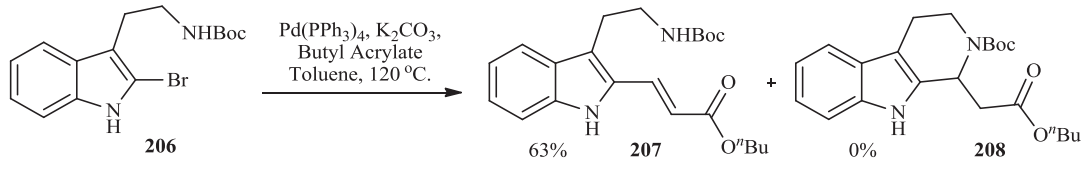
rapidly consume the alkene, negating the possibility of intermolecular aza-Michael addition. In addition to the palladium catalyst, a base and solvent also needed to be identified that were universal to rapid Heck reaction and aza-Michael addition. The Heck reaction between aryl-halides and electron-deficient terminal alkenes results in cross-coupling to the *β*-position of the alkene.[104] Aza-Michael addition at the same *β*-position of the attached alkene can result in only formation of the 6-membered *N*-heterocycle **202**.

The third consideration was the indole-nitrogen. Following halogenation of the indole-2-position, the nucleophilicity of this amine is enhanced.[288] Therefore, protection of this indole-nitrogen may be required so that either complexation with the palladium-catalyst and/or 1,4-addition to the conjugated alkene from this amine did not take place. Protection of this nitrogen with an electron withdrawing group would have the added advantage of increasing the electrophilicity at the indole-2-position, increasing the rate of oxidative addition of the palladium, and hence the rate of the early stages of the Heck reaction. It was also envisaged that through protection of the indole-nitrogen, electron density would be withdrawn from the *β*-carbon of the Michael acceptor installed during the first step of the domino process, promoting conjugate addition under mildly basic conditions.

As the Heck reaction was known to occur at the indole-2-position using *tert*-butoxycarbonyl-2-bromotryptamine and the trifluoroacetamide-2-bromotryptamine **60**, these systems were investigated first.[2, 137]

Tert-butoxycarbonyl Protected Tryptamine

The first system examined was *tert*-butoxycarbonyl (Boc) protected 2-bromotryptamine **206**. The requisite functionalised tryptamine was prepared by Boc-protection at the N_{10}-amine, followed by bromination of the indole-2-position using pyridinium tribromide.[2] This substrate was then subjected to the previously identified conditions for the intermolecular Heck reaction with butyl acrylate (Scheme 3.9).

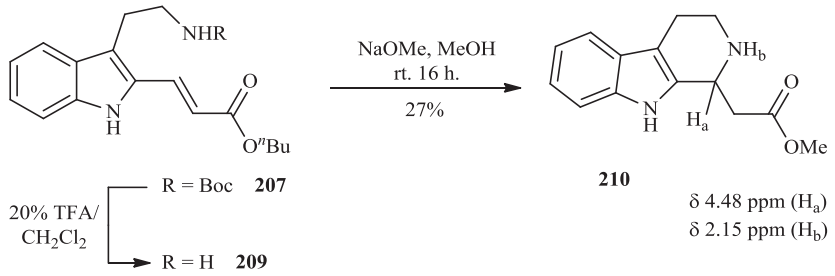


Scheme 3.9 The Heck reaction between Boc-2-bromotryptamine and butyl acrylate

This reaction lead exclusively to the formation of the Heck adduct **207**, with none of the domino product **208** identified *via* initial analysis of the crude reaction mixture by ^{1}H NMR

spectroscopy. Isolation of the Heck adduct (63% yield) was readily confirmed by the presence of the olefinic resonances in the ^{1}H NMR spectrum at δ 6.20 and 7.74 ppm. Although the N_{10}-amine was sufficiently protected to allow Heck reaction to occur, the carbamate was not nucleophilic enough to undergo aza-Michael addition. As such, the Boc protecting group was not considered ideal for the *domino* process. However, further investigations into this system were carried out in a *single-step* fashion following isolation of the Heck adduct (Scheme 2.35).

Following deprotection of the Boc group from amine **207** (20% TFA in CH_2Cl_2), the indole ester **209** was subject to conditions known to promote Michael addition, [242, 277-278, 280-281, 289-293] i.e. potassium carbonate in refluxing THF for 16 hours. After this time, the solvent was removed and analysis of the crude product was performed by ^{1}H NMR spectroscopy. Surprisingly, under these reaction conditions none of the desired *β*-carboline **210** was observed. Using the recovered starting material, formation of the *N*-heterocycle was then attempted using a stronger base and more polar solvent combination. To this end, the tryptamine ester **209** was stirred with sodium methoxide in methanol at room temperature overnight (Scheme 3.10).[294]



Scheme 3.10 Following Boc deprotection aza-Michael addition occurred to form the TH*β*C.

Following workup, analysis of the crude mixture by ^{1}H NMR spectroscopy revealed that the aza-Michael addition to form the 6-membered *N*-heterocycle had been successful, though in a low yield. Formation of the tetrahydro-*β*-carboline **210** was readily observed in the ^{1}H NMR spectrum by the new resonance at δ 4.48 ppm (triplet) assigned to the proton at the C1-position where the two new bonds were formed. In the presence of methanol, transesterification from the butyl ester to the methyl ester also occurred.

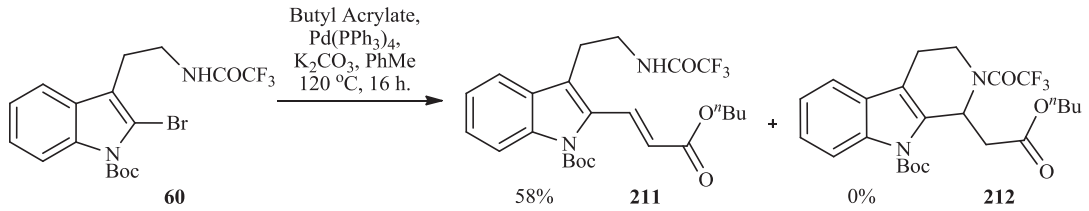
Although several steps were required to prepare the C1-substituted TH*β*C scaffold **210** using the *N*-Boc tryptamine **206**, this positive result proved that a Heck-aza-Michael reaction sequence for the formation of a new 6-membered heterocycle using tryptamine was

plausible. As such, subsequent tuning of the nucleophilicity of the N_{10}-amine was undertaken.

Trifluoroacetate Protected Tryptamine

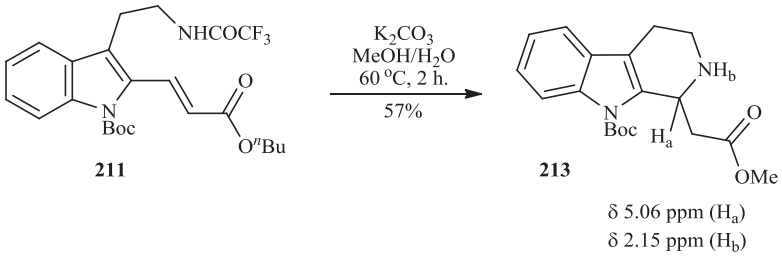
The next N_{10}-amine protecting group investigated for this domino process was trifluoroacetate. The pKa of the trifluoroacetamide (typically 17.2 in DMSO)[295] is much less than that of the *tert*-butyl carbamate (typically 24.2 in DMSO)[295], and from the previous domino Heck-aza-Michael processes investigated it is known that functionalised amides are able to undergo aza-Michael addition subsequent to the intermolecular Heck reaction to form the new *N*-heterocycle (see Schemes 3.3-3.4). As such, it was expected that the trifluoroacetate amine protecting group was well suited to the domino process.

The preparation of the requisite starting material has previously been completed, thus the Heck precursor was readily available. The domino Heck-aza-Michael process with trifluoroacetate-2-bromotryptamine **60** and butyl acrylate (1.2 equivalents) was attempted using the previously identified conditions for the Heck reaction ($Pd(PPh_3)_4$, and K_2CO_3 in toluene at 120 ^oC) (Scheme 3.11).



Scheme 3.11 Attempted domino Heck-aza-Michael process with the trifluoroacetate-2-bromotryptamine lead only to formation of the Heck adduct

Once again, formation of the desired THβC **212** was not observed, however the Heck adduct **211** was isolated in an unoptimised yield of 58%. Intramolecular aza-Michael addition of the isolated conjugated ester to form the THβC **212** was then attempted by stirring the Heck adduct **211** with 1.5 equivalents of NaH in THF at room temperature overnight. Unfortunately, cyclisation to form the desired THβC scaffold did not occur. However, the mildly basic conditions often used to promote aza-Michael addition can also be employed in the cleavage of the trifluoroacetamide protecting group.[264, 296-297] Therefore, a one-pot deprotection and subsequent aza-Michael addition was attempted using K_2CO_3 in methanol/H_2O (Scheme 3.12).



Scheme 3.12 One-pot trifluoroacetate-deprotection and subsequent aza-Michael addition

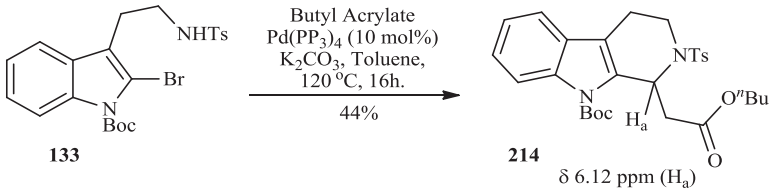
Following purification by column chromatography the desired C1-substituted TH*β*C **213** was isolated in a yield of 57%. The presence of the TH*β*C scaffold was confirmed by a resonance at δ 5.06 ppm in the ^{1}H NMR spectrum assigned to the C1-proton, the presence of a resonance at δ 3.75 ppm assigned to the methyl group as well as the downfield shift and the additional splitting patterns induced by the ring strain on the tryptamine ethylene CH_2 proton resonances following cyclisation. Transesterification from the butyl to methyl ester was again observed.

When the trifluoroacetate protecting group was used, the desired tetrahydro-*β*-carboline **213** was synthesised in fewer steps in comparison with the Boc-protecting group reaction sequence (Scheme 3.10). Unfortunately, both approaches required deprotection of the N_{10}-amine prior to aza-Michael addition and as such, a more efficient domino process was sought. The conditions necessary to promote aza-Michael addition to this point also required optimisation so that transesterification did not take place.

Sulfonyl Protected Tryptamine

Alkyl-sulfonamides have been shown to be readily functionalised using a range of methods including allylation, Mitsunobu reactions and more importantly aza-Michael addition.[259-262] Due to its ready availability, the *p*-toluenesulfonyl (tosyl) protecting group for the N_{10}-amine of tryptamine was investigated first.

To investigate the likelihood of a domino process occurring with the sulfonamide system, 2-bromosulfonamide **133** and butyl acrylate (1.2 equivalents) were subjected to the conditions previously identified for Heck reaction at the indole-2-position (Scheme 3.13).



Scheme 3.13 The domino Heck-aza-Michael reaction with the tosyl-2-bromotryptamine

The first reaction attempted with this tosyl-2-bromosulfonamide **133** afforded the domino Heck-aza-Michael adduct **214** as the major product in a yield of 44%. This domino product was readily detected in the ^{1}H NMR spectrum with the presence of a new resonance at δ 6.12 ppm assigned to the C1-proton (Figure 3.2). The absence of the resonance assigned to the sulfonamide, in addition to the resonances assigned to the butyl ester protons confirmed the identity of the desired tetrahydro-*β*-carboline **214** (Figure 3.2).

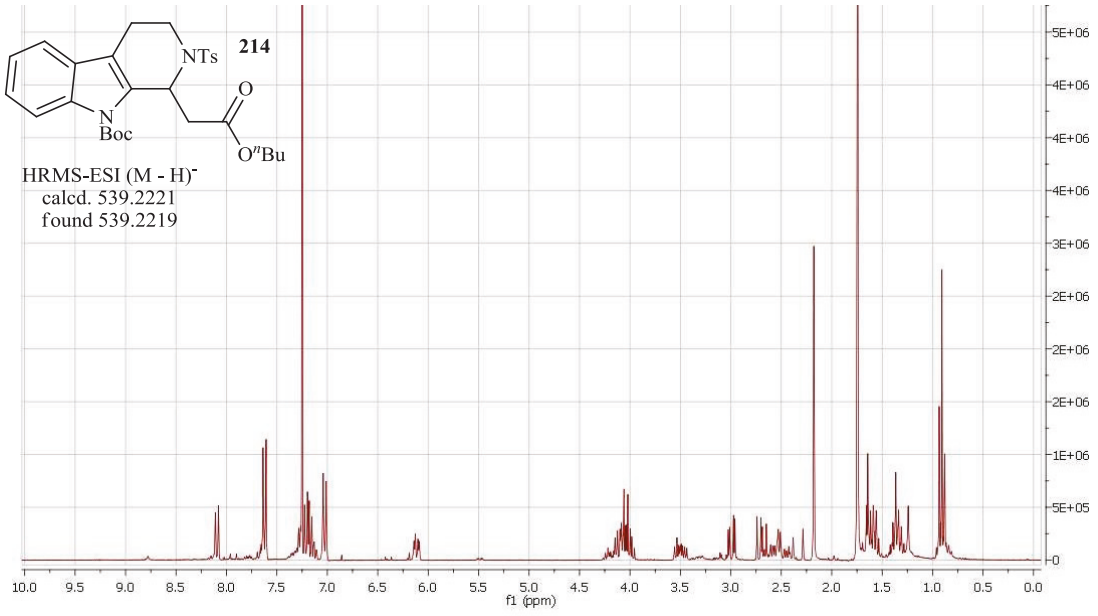
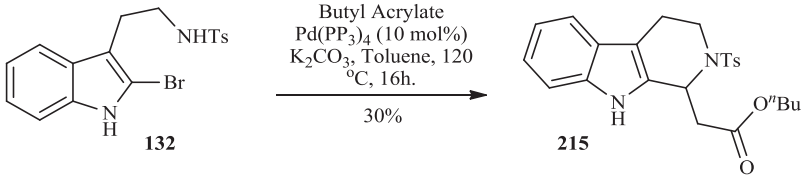


Figure 3.2 The ^{1}H NMR spectrum of the tetrahydro-*β*-carboline butyl ester

This promising result confirmed that the use of a sulfonyl protecting group was suited for aza-Michael addition to occur, under mildly basic conditions and without the need for deprotection of the N_{10}-amine. The isolation of the desired TH*β*C also established that both the Heck and aza-Michael reactions would proceed under the same mildly basic conditions ($Pd(PPh_3)_4$, K_2CO_3, PhMe). With the knowledge that a domino Heck-aza-Michael process was possible, our attention now turned to increasing the yields of each step in the reaction sequence to afford the desired *N*-heterocycle in synthetically useful amounts.

As protection of the indole nitrogen was proceeding with less than satisfactory yields (< 50%, Scheme 2.6) the domino Heck-aza-Michael reaction was attempted with the indole unprotected using the previously identified domino conditions (Scheme 3.14).



Scheme 3.14 The domino Heck-aza-Michael reaction with the indole-nitrogen unprotected

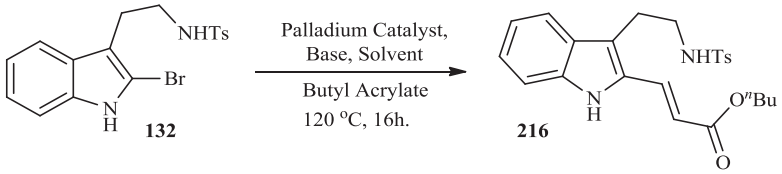
The domino process, this time with the indole nitrogen unprotected, once again proved successful affording the C1-substituted tetrahydro-*β*-carboline **215** as the major product in a modest yield of 30% (Scheme 3.14).

To further improve the yield of this domino process, without protection of the indole-nitrogen, three features of were identified for optimisation; namely, the Heck reaction conditions, the nucleophilicity of the sulfonamide, and the degree of electron deficiency of the Michael acceptor.

3.2.2 Optimisation of the Intermolecular Heck Reaction

The initial step of this domino process, the Heck reaction with N_{10}-tosyl-2-bromotryptamine **132** where the indole-nitrogen remained unfunctionalised, was optimised first. An ideal palladium catalyst was required that was active in the presence of a mild base and relatively non-polar solvent so that intermolecular aza-Michael addition did not occur prior to the Heck reaction. A range of catalysts, mild bases and solvents were trialled in the attempt to couple the tosyl-2-bromotryptamine **132** with butyl acrylate (Table 3.1).

Table 3.1 Optimisation of the catalytic conditions for the intermolecular Heck reaction at the indole-2-position.



Entry	Palladium Catalyst (10 mol%)	Base	Solvent	Yield (%)
1	$Pd(OAc)_2/PPh_3$ [a]	NEt_3	Toluene	22
2	$Pd_2(dba)_3/P(tBu)_3$ [a]	NEt_3	Toluene	43
3	$Pd_2(dba)_3/P(tBu)_3$ [a]	Cy_2NMe	Toluene	65
4	$Pd(PPh_3)_4$	NEt_3	Toluene	39
5	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	99
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	Trace [b]
7	$Pd(PPh_3)_4$	K_2CO_3	MeCN	Trace [b]
8	$Pd(PPh_3)_4$	K_2CO_3	Dioxane	32
9	$Pd(PPh_3)_4$	CH_3CO_2Na	Toluene	75

[a] Catalyst and ligand used in a 1:1 ratio.
[b] Trace is < 10% as determined by ^{1}H NMR.
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), acrylate (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

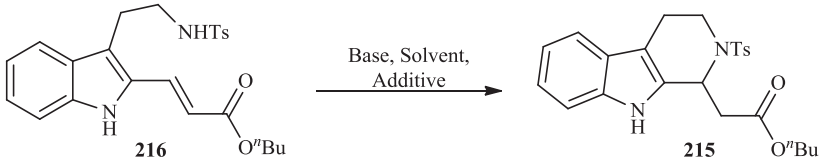
The results from this investigation were consistent with previous reports of the Heck reaction at the indole-2-position,[137, 252] with $Pd(PPh_3)_4$ (10 mol%) generating the highest yields (entries 5 and 9, Table 3.1). An interesting phenomenon was observed when looking at the carbonate counter-ions; the use of Na_2CO_3 produced only the Heck adduct **216** (Table 3.1, entry 5), whereas K_2CO_3 facilitated the formation of the desired tetrahydro-*β*-carboline **215** (Scheme 3.14). Unfortunately, the highly reactive catalytic system pioneered by Fu, afforded only a moderate amount of the Heck product (Table 3.1, entry 3).[170] As $Pd(PPh_3)_4$ produced the highest yield of the Heck adduct **216**, this catalyst was used for the remainder of this study.

With the indole nitrogen unprotected, the Heck reaction was occurring in very high yields, ruling out this step as the cause for the overall low yield observed in the domino process (Scheme 3.14). From this study, it was identified that the aza-Michael addition step to form the new *N*-heterocycle must be limiting and as such was investigated next.

3.2.3 Optimisation of aza-Michael addition

Initial investigations involved identifying the conditions required to promote aza-Michael addition in a single-step fashion. The Heck adduct **216** was treated with a range of bases, solvents and additives known to promote aza-Michael addition at varying temperatures (Table 3.2).[242, 277-278, 280-281, 289-293, 298]

Table 3.2 Attempts to promote aza-Michael addition in a single step fashion



216 **215**

Entry	Base	Solvent	Additive	Temperature (^{o}C)	% Conversion [a]
1	K_2CO_3	Toluene	-	110	0
2	K_2CO_3	DMF	-	110	0
3	K_2CO_3	Methanol/H_2O	-	60	0
4	K_2CO_3	H_2O	-	100	0
5	KO^{t}Bu	Toluene	-	25	0
6	DBU	Toluene	-	25	0
7	NEt_3	Toluene	-	110	0
8	NEt_3	DMF	-	120	0
9	Na_2CO_3	DMF	-	100	0
10	-	Toluene	TBACl	100	0
11	K_2CO_3	Toluene	$Pd(PPh_3)_4$	100	0
12	K_2CO_3	Toluene	$Pd(OAc)_2$	110	0

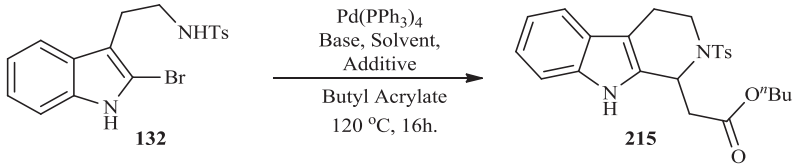
a As determined by ^{1}H NMR Spectroscopy.
Reaction was performed in a sealed tube containing Heck adduct **216** (1.0 eq.), base (3.0 eq.) and additive in solvent (4 mL). The reaction mixture was then heated to temperature for 16 h.

Unfortunately, aza-Michael addition to form the desired THβC **215** was not achieved in a single step reaction sequence from the Heck adduct **216** (Table 3.2). Initial trials involved the use of potassium carbonate in various solvents at elevated temperatures (Table 3.2, entries 1-4). Analysis of each crude mixture through ^{1}H NMR spectroscopic analysis revealed no trace of the desired aza-Michael product. A range of bases were then trialled in either toluene or DMF (Table 3.2, entries 5-9). The use of amine bases (DBU and NEt_3) and a stronger *tert*-butoxide base (KO^{t}Bu) failed to promote aza-Michael, with not even a trace of the desired product detected in any of the ^{1}H NMR spectra. The role of tetra-*n*-butylammonium chloride (TBACl) was also investigated as it had been used as an additive in previous reports of domino Heck-aza-Michael reactions.[279] The Heck adduct was stirred with TBACl in toluene at 100 ^{o}C (Table 3.2, entry 10), but as in previous cases, analysis by NMR spectroscopy revealed only starting material.

As the aza-Michael addition was observed in the preliminary domino process previously investigated (Scheme 3.14), but not promoted in a single step fashion, it was considered that the palladium catalyst could be playing a role in facilitating aza-Michael addition (through an aminopalladation pathway either with Pd^0 or Pd^{II}).[299] This was investigated by stirring the Heck adduct with $Pd(PPh_3)_4$ or $Pd(OAc)_2$ and K_2CO_3 in toluene again at elevated temperatures (Table 3.2, entries 11-12). Once more, these reactions did not produce the aza-Michael product **215**.

The failure of a range of bases, solvents and additives to induce aza-Michael addition to form the THβC scaffold in a *single-step* fashion was unexpected. In the continued attempts to increase the yields of this domino process above 30% (Scheme 3.14), without protection of the indole-nitrogen, attention turned to the optimisation of the base and solvent employed in the *domino* Heck-aza-Michael reaction. With the Heck reaction optimised, and single step aza-Michael cyclisation of the Heck adduct unsuccessful, optimisation of this domino process by its very nature would optimise the aza-Michael process. To investigate this parameter of the domino reaction, 2-bromoindole **132**, in the presence of butyl acrylate and $Pd(PPh_3)_4$, was reacted with a range of bases, solvents and additives (Table 3.3).

Table 3.3 Optimisation of the domino Heck-aza-Michael process



Entry	Base	Solvent	Additive	Yield (%)
1	K_2CO_3	Toluene	-	30
2	Na_2CO_3	Toluene	-	Trace
3	Cs_2CO_3	Toluene	-	0
4	CH_3CO_2Na	Toluene	-	0
5	NEt_3	Toluene	-	Trace
6	DBU	Toluene	-	Trace
7	KO*t*Bu	Toluene	-	0
8	K_2CO_3	MeCN	-	Trace
9	K_2CO_3	DMF	-	Trace
10	K_2CO_3	Dioxane	-	0
11	K_2CO_3	Toluene/DMF (9:1)	-	0
12	K_2CO_3	Toluene	TBACl (1 eq.)	Trace
13	Na_2CO_3	Toluene	TBACl (1 eq.)	Trace
14	Na_2CO_3	Toluene	TBACl [a] (1 eq.)	17
15	Na_2CO_3	Toluene	TBACl [a] (3 eq.)	Trace

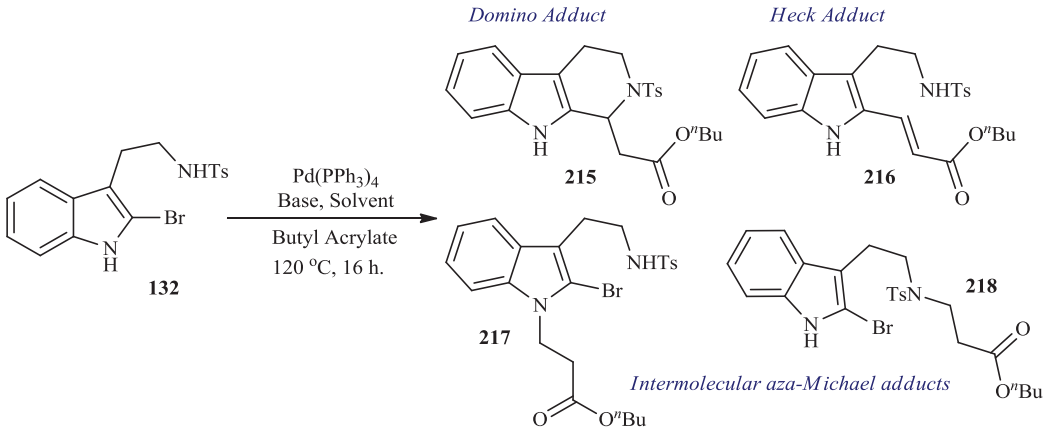
[a] Additive added after stirring for 12 hrs and stirring continued for 4 hrs.
Trace is <10% as determined by ^{1}H NMR
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), acrylate (1.2 eq), palladium catalyst (10 mol%),additive (1.0 eq) and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

Both inorganic and organic bases of varying strength were trialled in the domino process, using $Pd(PPh_3)_4$ and butyl acrylate in toluene (Table 3.3, entries 1-7). The best results obtained were using potassium carbonate (Table 3.3, entry 1), as in the initial combination used (Scheme 3.14). A variety of more polar solvents were used in an attempt to improve the domino process (Table 3.3, entries 8-11). Unfortunately these did not enhance formation of the β-carboline scaffold **215** using the domino process, and intermolecular aza-Michael reaction was observed at either the sulfonamide or indole-nitrogen.

The use of the additive tetra-*n*-butylammonium chloride (TBACl) was also investigated. The TBACl can play several roles: as a source of Cl^- improving the Heck catalytic cycle

(increasing the rate of reductive elimination following halogen exchange and catalyst regeneration),[104] as a phase transfer agent improving solubility of the inorganic base and intermediates in the catalytic cycle, and also as a base promoting aza-Michael addition of the sulfonamide.[279] This reaction was carried out where in one-pot, the TBACl was added after 16 hours (to allow sufficient time for Heck reaction to take place), and stirring continued at 120 °C for an additional 4 hours. Although this approach proved slightly more effective than when polar solvents or stronger bases were used, the desired TH*β*C scaffold **215** was still only isolated in a low yield of 17% (Table 3.3, entry 14).

Unfortunately, the use of varying combinations of bases, solvents and additives, failed to improve the overall yield of the domino process from the initial 30% (Scheme 3.14). Predominantly, the use of stronger bases and more polar solvents resulted in aza-Michael addition occurring at the sulfonamide or indole nitrogen *before* the Heck reaction had taken place at the indole-2-position. This often resulted in a complex mixture of inseparable compounds (including the desired compound **215** and several by-products - Scheme 3.15).



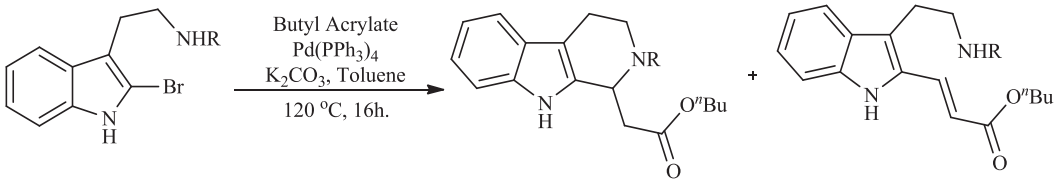
Scheme 3.15 The desired product and by-products formed during the domino process

To minimise side reactions, the domino Heck-aza-Michael process for this *N*-sulfonyl-2-bromotryptamine system was confined to the use of mild bases and relatively non-polar solvents, allowing sufficient time for the Heck reaction to take place before aza-Michael addition occurred.

To this point it had been identified that the *p*-tosyl-2-bromotryptamine substrate **132** underwent a domino Heck-aza-Michael reaction to form the new *N*-heterocycle **215** in 30% yield (Scheme 3.14). However, it was considered that the nucleophilicity of this sulfonamide may not be ideal for this cyclisation step. In a further attempt to increase the yields of the domino process, with the indole-nitrogen remaining unprotected, alternative sulfonyl

protecting groups were also trialled (in order to tune the nucleophilicity of the sulfonamide proton at the N_{10}-position of tryptamine). The 2-bromotryptamine substrates were prepared as before, by reacting tryptamine with the appropriate sulfonyl chloride, followed by bromination of the indole-2-position using pyridinium tribromide. These substrates were then subjected to the previously identified domino conditions (Table 3.4).

Table 3.4 The role of the sulfonyl protecting group amine for the N_{10}-amine



Domino Heck-aza-Michael Adduct *Heck Adduct*

Entry	R	Major Product	Conversion (%)
1	*p*-toluenesulfonyl	Heck-aza-Michael (**215**)	30
2	benzenesulfonyl	Heck-aza-Michael (**219**)	36
3	2-nitrobenzenesulfonyl	Heck (**220**)	50

Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), acrylate (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

Alternative sulfonyl groups for the N_{10}-amine of tryptamine did not significantly increase the yield of the domino Heck-aza-Michael process. The use of 2-nitrobenzenesulfonamide (Table 3.4, entry 3) increased the acidity of the sulfonamide proton (as observed by the downfield shift of the resonance attributed to the amide in the ^{1}H NMR spectrum when compared to that of the *p*-tosyl sulfonamide), however it only resulted in formation of the Heck adduct **220** in 50% yield; no aza-Michael addition was observed. The benzenesulfonyl group (Table 3.4, entry 2) performed similarly to the *p*-toluenesulfonyl group (Table 3.4, entry 1) in terms of yields for the domino process; however, it proved more difficult to handle in terms of solubility and purification following bromination. For this reason, along with a useful spectroscopic 'handle' provided by the methyl group present, the *p*-toluenesulfonyl group was used for the remainder of this investigation.

Thus far, several approaches to increasing the yield of the domino Heck-aza-Michael process without protecting the indole-nitrogen had proved unsuccessful. With the N_{10}-amine protecting group, palladium catalyst, base and solvent all investigated for the optimisation of the domino process, the only avenue left to pursue was the protection of the indole-nitrogen.

3.2.4 The Role of the Indole Protecting Group

The indole moiety is known to be extremely electron rich, and this has been exploited in a number of the cyclisations discussed in Chapter One. As such, it was considered that the

indole ring system may be donating electron density into the *β*-position of the Michael acceptor following Heck reaction, deactivating this carbon for the required 1,4-addition. It was therefore envisaged that aza-Michael addition could be improved by drawing electron density away from this Michael acceptor through protection of the indole nitrogen (Figure 3.5). It was also proposed that protection of the indole-nitrogen would also increase the electrophilic nature of the initial aryl-halide, increasing the rate of the Heck reaction by speeding up the oxidative addition step.

A molecular model of the Heck adduct **216** with the indole-nitrogen unprotected was compared to one in which the indole-nitrogen was protected with the *tert*-butoxycarbonyl (Boc) group **221** (Figure 3.3). It was clear, even at this simple level of theory,[**] that the electrophilic nature of the Michael acceptor could be enhanced through the protection of the indole-nitrogen (with a Boc group in this case). With the indole-nitrogen unprotected the Michael acceptor appears to be quite electron-rich (Figure 3.4 – red region). However, following protection, the *β*-position of the Michael acceptor becomes much more electron-deficient (Figure 3.3 – blue region).

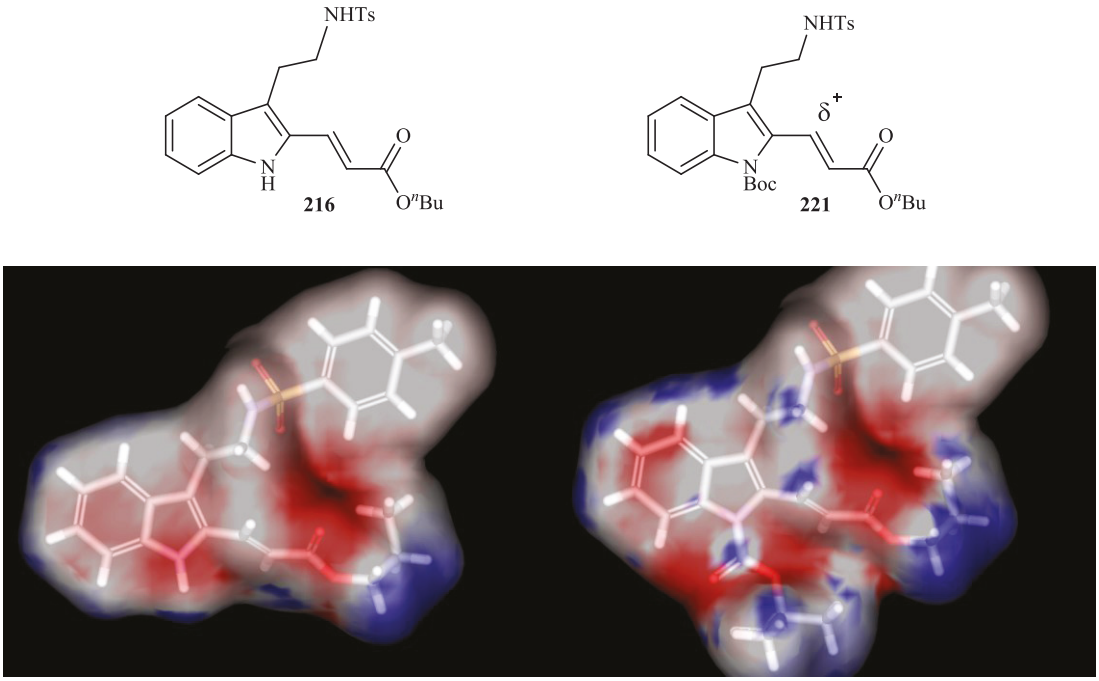


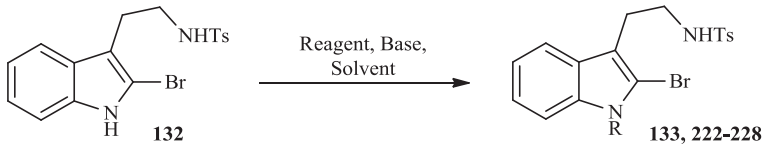
Figure 3.3 The electrophilicity of the Michael acceptor could be increased through protection of the indole nitrogen
(Red = electron-rich, Blue = electron-deficient)

[**] Molecular modelling was performed using *Discovery Studio 2.1* (Accelrys). It uses the DelPhi to calculate the spatial distribution of electrostatic potential and the potential on atoms. It uses a two-dielectric implicit solvent model and a finite difference method to solve the Poisson-Boltzmann equation. The structure geometry was minimised with CHARMm. 159 iterations were carried out.

The first domino process trialled with the indole-protected domino precursor **133** produced the desired THβC **214** in an unoptimised yield of 44%, indicating that indole protection had the potential to significantly increase the yield for the domino process (Scheme 3.13). It was proposed that the greater the electron withdrawing effect of the indole protecting group would enhance 1,4-addition *via* electrophilic enhancement of the Michael acceptor.

Unfortunately, initial attempts to protect the indole nitrogen by reaction with Boc_2O had afforded the desired mono-protected compound **133** in a moderate yield of 48% (Scheme 2.6). The installation of the indole protecting group in good yield was now crucial to the overall synthesis of the desired tetrahydro-β-carboline from tryptamine. To further investigate the protection of the indole-nitrogen of the tosyl-2-bromotryptamine, a number of parameters were evaluated including the protecting group itself, the base, solvent, and the reaction temperature (Table 3.5).

Table 3.5 Optimisation of the protection of tosyl-2-bromotryptamine indole-nitrogen



Entry	Reagent	Base (Equivalents)	Solvent	Temp (^oC)	R	Yield (%)
1	Boc_2O	DMAP (0.05)	THF	40	Boc (**133**)	48
2	Boc_2O	DMAP (0.10)	THF	60	Boc (**133**)	47
3	Boc_2O	DMAP (0.10)	Dioxane	100	Boc (**133**)	33
4	Boc_2O	DMAP (0.10)	MeCN	60	Boc (**133**)	50
5	Boc_2O	DMAP (0.05)	MeCN	60	Boc (**133**)	44
6	Boc_2O	DMAP (0.05)	DCM	30	Boc (**133**)	**56**
7	Boc_2O	DMAP (0.05)	DCM	40	Boc (**133**)	50
8	Boc_2O	DMAP (0.10)	DCM	40	Boc (**133**)	50
9	Boc_2O	DMAP (0.10)	DMF	50	Boc (**133**)	35
10	Boc_2O	DMAP/NEt_3	DCM	40	Boc (**133**)	45
11	Boc_2O	-	THF	60	Boc (**133**)	0
12	Boc_2O	NEt_3	Dioxane	25	Boc (**133**)	0
13	Boc_2O	NaH (2)	THF	25	Boc (**133**)	0
14	Boc_2O	KO*t*Bu (1.5)	THF	25	Boc (**133**)	**55**
15	Boc_2O	KO*t*Bu (2)	THF	25	Boc (**133**)	43
16	Boc_2O	$NaHCO_3$ (3)	DMF	25	Boc (**133**)	0
17	Boc_2O	Na_2CO_3 (3)	DMF	25	Boc (**133**)	**52**
18	Boc_2O	K_2CO_3 (3)	DMF	40	Boc (**133**)	47
19	Boc_2O	K_2CO_3 (3)	MeCN	50	Boc (**133**)	36
20	Bn Bromide	NaH (2)	DMF	25	Bn (**222**)	35
21	Bn Bromide	NaH (3)	THF	25	Bn (**222**)	39
22	Ns Chloride	DMAP (0.2)/ DIPEA(1.5)	DCM	25	Ns (**223**)	30
23	Ts Chloride	DMAP (0.2)/ DIPEA (1.2)	DCM	25	Ts (**224**)	32
24	Ac Chloride	NaH (2)	THF	25	Ac (**225**)	Trace
25	Bz Chloride	Na_2CO_3 (2)	DMF	25	Bz (**226**)	0
26	Bz Chloride	K_2CO_3 (2)	DMF	25	Bz (**226**)	0
27	Bz Chloride	KOtBu (2)	DMF	25	Bz (**226**)	Trace
28	Bz Chloride	NaH (2)	DMF	25	Bz (**226**)	Trace
29	Bz Chloride	NaH (4)	DMF	25	Bz (**226**)	0
30	Bz Chloride	DMAP (0.2)/ DIPEA (1.2)	DCM	25	Bz (**226**)	Trace
31	Benzyl Chloroformate	NaH (3.5)	DMF	25	Cbz (**227**)	Trace
32	DNBz Chloride	DMAP (0.2)/NEt_3	CH_2Cl_2	25	DNBz (**228**)	0

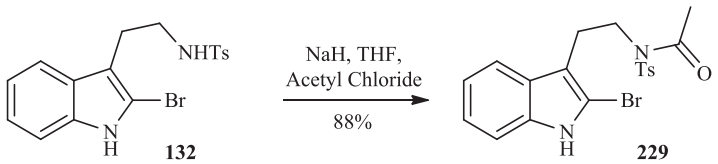
Trace is <10% as determined by ^1H NMR

The *tert*-butoxycarbonyl (or Boc) protecting group was the most extensively investigated (Table 3.5, entries 1-19), with reactions carried out where the base, catalyst, solvent and reaction temperature were varied. The success of this reaction process was determined by analysis of the crude product by NMR spectroscopy with the ^1H NMR spectrum revealing the absence of the resonance typically attributed to the indole-nitrogen proton (δ 8.30 ppm),

the downfield shift of the indole-C7-aromatic proton resonance and the addition of the proton resonances due to the new functional group installed.

Despite the range of conditions trialled, the desired *tert*-butoxycarbonylindole **133** was at best isolated in yield of 56% (Table 3.5, entry 6). The major by-product from this reaction was the aforementioned di-Boc indole **134**. The best yields for this reaction were obtained using a catalytic amount of DMAP (0.05 equivalents) in DCM at 30 ^{o}C. A range of alternative protecting groups were investigated through reaction with the appropriate sulfonyl chlorides, acid chlorides, alkyl halides and chloroformates. The indole nitrogen was successfully protected using the benzyl, 2-nitrobenzenesulfonyl and *p*-toluenesulfonyl protecting groups (Table 3.5, entries 20-23), in yields ranging from 32-39%.[13, 300-302] Further attempts to protect the indole amine using acetyl chloride, benzoyl chloride, benzyl chloroformate and 3,5-dinitrobenzoyl chloride also failed, as these groups showed a much greater affinity for the sulfonamide over the indole nitrogen.[13, 302-308]

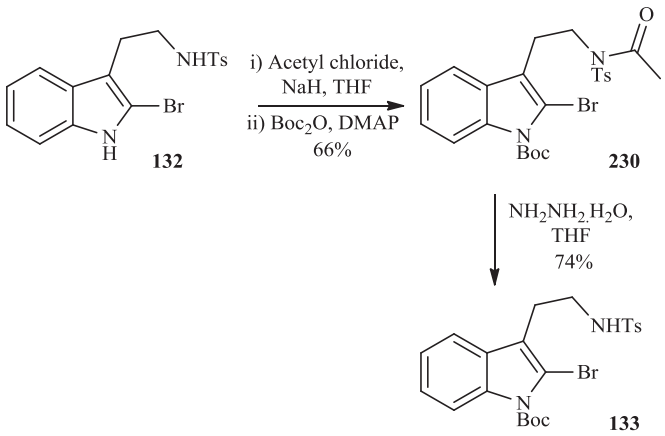
During attempts to selectively protect the indole nitrogen using acetyl chloride (Table 3.5, entry 24), it was observed that stirring 2-bromoindole **132** with one equivalent of sodium hydride followed by the addition of acetyl chloride, lead almost exclusively to the acetylated sulfonamide **229** (Scheme 3.16).



Scheme 3.16 Selective protection of the sulfonamide over the indole nitrogen

The selective deprotection of an acetyl group in the presence of an indole-Boc group has been reported to occur in the presence of one equivalent of hydrazine monohydrate.[309] In an attempt to further exploit this selectivity, an alternative approach to the protection of the indole nitrogen was investigated. This approach involved the initial protection of sulfonamide with the acetyl group, followed by functionalisation of the indole nitrogen as required, and subsequent removal of the acetyl protecting group.

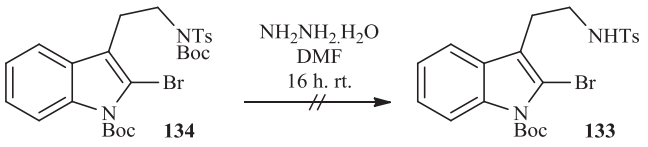
To carry out this investigation, acetyl protection of the *p*-toluenesulfonamide to afford the disubstituted-sulfonamide **229** was followed by reaction with Boc_2O under standard conditions to afford the fully functionalised 2-bromoindole **230** in 66% yield over 2 steps (Scheme 3.17). The Boc-acetyl substrate was then treated with one equivalent of hydrazine-monohydrate in THF at room temperature for 3 hours.



Scheme 3.17 An alternative approach for preparation of the domino precursor

Following a simple work up, the desired tosyl-2-bromotryptamine **133** was isolated in 74% yield. Unfortunately, the overall yield for this three-step process (48%) was no better than that achieved using standard Boc protection conditions (56%, Table 3.5, entry 6). Although this approach showed promise for improving the overall yield of the synthesis of the domino precursor, it was no longer pursued at this point. The introduction of additional steps in the pathway to access the domino precursor was not ideal, as the purification and isolation of the corresponding intermediates negated the positive effects of the domino process.

As some of the di-Boc-2-bromotryptamine **134** was on hand from previous investigations (Scheme 2.6), the selective deprotection of the Boc group from the sulfonamide using hydrazine monohydrate was also briefly investigated. The di-Boc-2-bromotryptamine **134** was subjected to the same conditions that had previously proved successful in acetyl cleavage (Scheme 3.18).

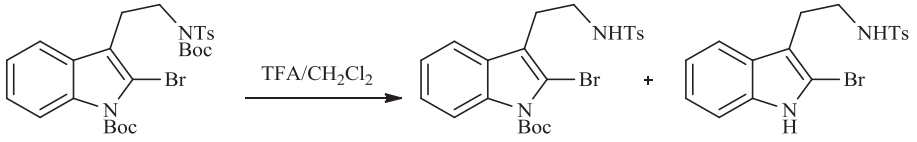


Scheme 3.18 Attempted selective deprotection of the Boc-sulfonamide

Analysis of the crude reaction mixture by NMR spectroscopy revealed that both of the Boc groups remained intact. A further survey of the literature revealed that selective deprotection of secondary amine-Boc group in the presence of an indole-Boc group could be achieved using low concentrations of TFA in CH_2Cl_2.[310-311] As such, the di-Boc-2-bromotryptamine **134** was treated with increasing concentrations of TFA in CH_2Cl_2 and the reactions were

monitored over several hours. After 16 hours, the reaction mixtures were analysed by ^{1}H NMR spectroscopy with the results shown in Table 3.6.

Table 3.6 Attempted selective Boc deprotection of the N_{10}-sulfonamide



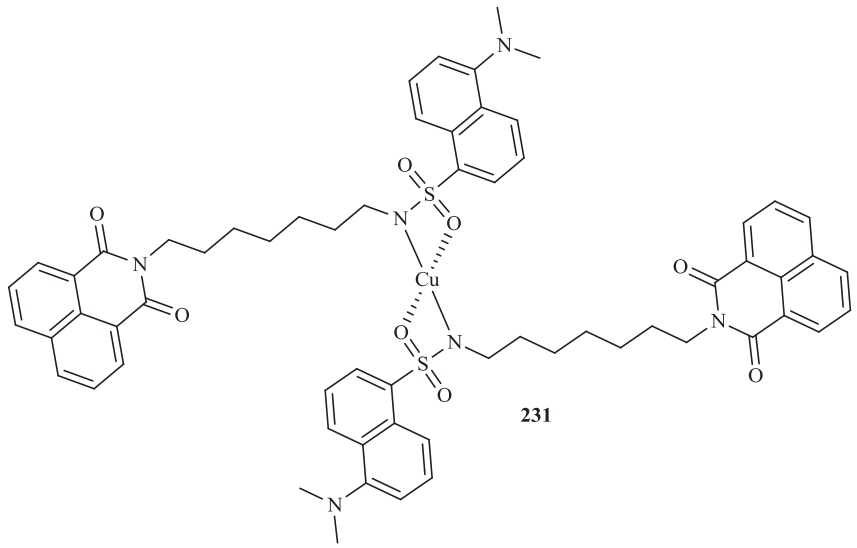
134 **133** **132**

Entry	% TFA in CH_2Cl_2	Major Product [a]
1	1%	**134**, **133** (trace)
2	2%	**134**: **133** (2:1)
3	3%	**134**: **133**: **132** (mixture)
4	4%	**132**
5	5%	**132**

a As determined by ^{1}H NMR spectroscopy

The attempts to selectively cleave the Boc group from the sulfonamide failed, as at concentrations of TFA sufficient to cleave the sulfonamide Boc group (>2% TFA in CH_2Cl_2), the indole-Boc group was also removed. This approach to selective deprotection of the sulfonamide was therefore no longer pursued.

An alternative strategy to selectively protecting the indole nitrogen was devised involving the use of copper salts. A report by Jisha *et al.* in 2009 detailed the selective recognition of Cu^{2+} ions using Dansyl-Naphthalimide dyads as fluorescent hosts (Figure 3.4).[312]



231

Figure 3.4 Selective recognition of copper(II) ions by Dansyl-Naphthalimide dyads

A number of other reports also described the isolation of compounds with sulfonamide moieties complexed to copper(II) ions.[313-317] Applying this theory to our system, selective protection of the indole nitrogen seemed plausible given that the copper(II) ion could exclusively complex to the sulfonamide. The copper could then be readily removed during workup, affording the desired 2-bromoindole domino precursor **133**.[††]

As Cu^{2+} can associate with four ligands, there were two different ways this complexation could occur, either in a 1:2 copper:sulfonamide complex **232** (Figure 3.5 A) or in a 1:1:1 copper:sulfonamide:ligand complex **233** (Figure 3.5 B – Where the ligand is *N,N*-tetramethylethylenediamine (TMEDA)).

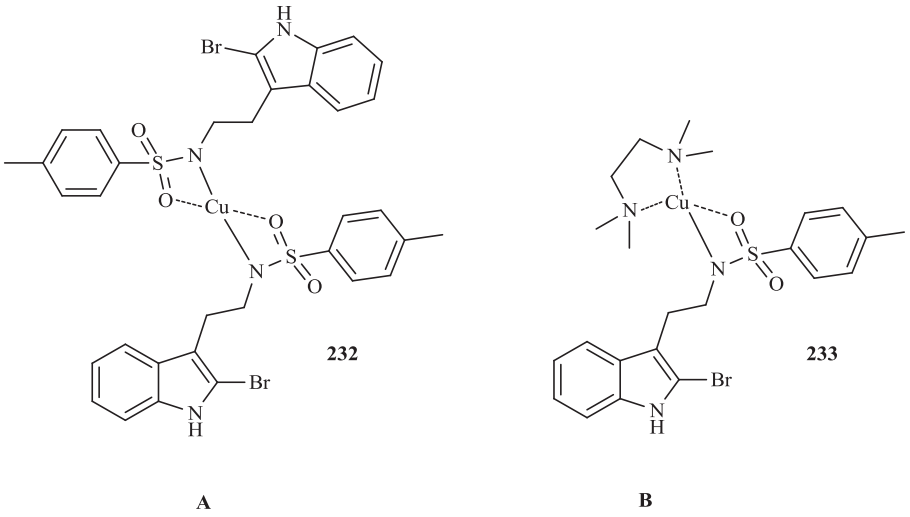
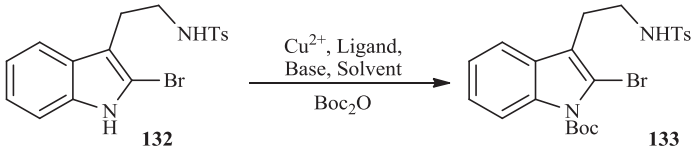


Figure 3.5 The possible 1:2 copper-sulfonamide complex (A) or the 1:1:1 TMEDA-copper-sulfonamide complex (B)

The reaction was carried out by stirring the copper(II) salt (and ligand where applicable) with the sulfonamide. After a few hours, allowing time for the copper-sulfonamide complex to form, a base was added to the reaction mixture followed by the Boc_2O to protect the indole nitrogen. This reaction was carried out a number of times using a range of Cu^{2+} sources, bases, solvents, and also ligands (Table 3.7).

[††] A similar strategy has been employed using boron and copper chelates for the selective protection of the side chain of specific amino acid residues.[318-321]

Table 3.7 Protection of the indole nitrogen using copper(II) to protect the sulfonamide.



Entry	Copper Source	Ligand	Base (Eq.)	Solvent	Yield (%)
1	$CuBr_2$	-	DMAP (0.2)	THF	0
2	$CuBr_2$	-	KO*t*Bu (1.5)	MeCN	0
3	$CuSO_4$	-	K_2CO_3 (2.0)	DMF	Trace
4	$CuSO_4$	-	K_2CO_3 (2.0)	DMF	0
5	$CuSO_4$	TMEDA	KO*t*Bu (1.0)	THF	39
6	$CuSO_4$	TMEDA	KO*t*Bu (2.0)	THF	43
7	$CuSO_4$	TMEDA	KO*t*Bu (1.5)	THF	58

Trace is <10% as determined by ^{1}H NMR TMEDA = *N,N*-Tetramethylethylenediamine
Reaction performed by stirring 2-bromotryptamine (1.0 eq), the copper salt (1.0 eq), and ligand (1.0 eq) for 1 h. The base was added, and after 30 mins, Boc_2O (1.1 eq) was added and the reaction mixture stirred at room temperature for 16 h.

Following a workup involving several washes of the reaction mixture with a saturated aqueous solution of ammonium chloride to remove the copper(II), analysis of the crude product was carried out by NMR spectroscopy and, where applicable, the mono-Boc indole **133** was isolated by column chromatography. The use of copper salts to temporarily protect the sulfonamide allowed selective protection of the indole-nitrogen, strongly suggesting that the copper(II) was playing a role, but did not significantly increase the reaction yield. The highest yield obtained for the protection step using copper sulfate, TMEDA, and potassium *tert*-butoxide (Table 3.7, entry 7, 58%) was not considerably greater than the use of DMAP in DCM employed previously (Table 3.5, entry 6, 56%). Without confirming the formation of the copper:sulfonamide complex through a crystal structure or by other means, it was not possible to know if the copper (II) was in fact complexing to the sulfonamide moiety, and hence this approach to selectively protecting the indole nitrogen was no longer pursued.

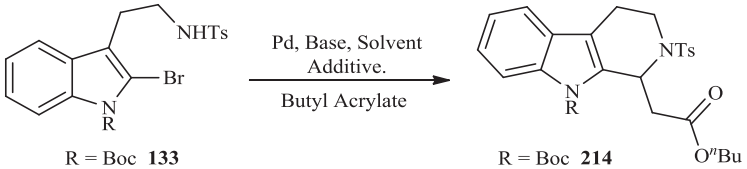
In conclusion, with the indole-2-position brominated, the *p*-toluenesulfonamide and the indole-nitrogen have very similar properties and selective functionalisation of the indole nitrogen could not be accomplished. Resigned to the fact that indole protection would proceed at less than 60% yield, attention now turned to optimising the domino Heck-aza-Michael process.

Optimisation of the Domino Heck-aza-Michael Reaction

With the indole nitrogen protected, the increased electrophilicity (due to the EWG now present on the indole nitrogen) about the conjugated 1,4-system, following the Heck reaction, should allow for aza-Michael addition to proceed much more readily than in

previous cases. The domino process was optimised using varying combinations of bases and additives with $Pd(PPh_3)_4$ and butyl acrylate remaining consistent throughout (Table 3.8).

Table 3.8 Optimisation of the domino Heck-aza-Michael process with the indole-nitrogen protected.



R = Boc **133** = Bn **222** = Ts **224**

R = Boc **214** = Bn **234** = Ts **235**

Entry	R	Palladium Catalyst	Base	Solvent	Additive	Yield (%)
1	Boc	$Pd(PPh_3)_4$	K_2CO_3	Toluene	-	83
2	Boc	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	-	27
3	Boc	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	TBACl [a]	86
4	Boc	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	NaH [a]	0
5	Boc	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	TBAF [a]	0
6	Boc	$Pd(PPh_3)_4$	K_2CO_3	Toluene [b]	-	0
7	Ts	$Pd(PPh_3)_4$	K_2CO_3	Toluene	-	54
8	Ts	$Pd(PPh_3)_4$	K_2CO_3	Toluene	TBACl [c]	0
9	Bn	$Pd(PPh_3)_4$	K_2CO_3	Toluene	-	54

a Added after 16 hrs. Stirring continued at 120 °C for further 4 hrs.
b Reaction performed in microwave at 120 °C, 200W for 90 mins.
c Added to initial reaction mixture
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), acrylate (1.2 eq), palladium catalyst (10 mol%), additive (1.0 eq) and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

The use of the Boc-protected indole-nitrogen (Table 3.8, entry 1) dramatically improved the domino Heck-aza-Michael process and the THβC **214** was produced in an excellent yield of 83% using $Pd(PPh_3)_4$ and K_2CO_3 in toluene. Given that these conditions had previously worked the best with the indole nitrogen unprotected (Scheme 3.14, 30%), this result confirmed the original hypothesis (Figure 3.4) that protection of the indole-nitrogen had the capacity to significantly enhance the yields of this domino process by increasing electrophilicity of the Michael acceptor following the initial Heck reaction.

To confirm the role this indole-protecting group was playing, benzyl and tosyl protecting groups on the indole-nitrogen were also trialled. The domino process performed reasonably well for the benzyl and tosyl protected 2-bromoindoles (Table 3.8, entries 7 and 9, both 54%). From these results it was apparent that a protecting group on the indole-nitrogen enhanced the intramolecular 1,4-conjugate addition required for the domino Heck-aza-Michael process.

It was also determined that a one-pot system (Table 3.8, entry 3) could be employed to access the THβC **214** using butyl acrylate. In this case, the use of Na_2CO_3 and $Pd(PPh_3)_4$, resulted in the Heck adduct undergoing partial aza-Michael addition (up to approximately 30% - Table 3.8, entry 2). After this time, one equivalent of TBACl was added and further

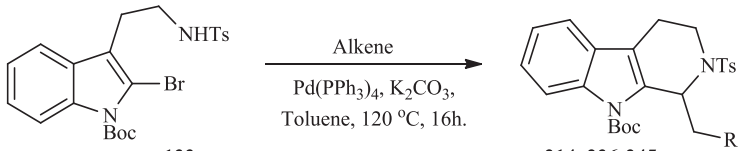
reaction at 120 °C for four hours furnished the tetrahydro-*β*-carboline in an exceptional yield of 86% for the two-step process.

In further reactions, tosyl-2-bromotryptamine **133** was subjected to the previously identified domino conditions, this time however instead of the conventional heating method, microwave irradiation was used (Table 3.8, entry 6). The use of microwave heating in organic synthesis has been shown to reduce reaction times, whilst increasing yields and product purity through the elimination of side reactions often observed when longer conventional heating methods are employed.[322-324] Following a simple workup, analysis of the crude reaction mixture by NMR spectroscopy revealed that the major product from this microwave reaction was in fact the Heck adduct, with only a trace amount of the desired tetrahydro-*β*-carboline detected in the ^{1}H NMR spectrum.

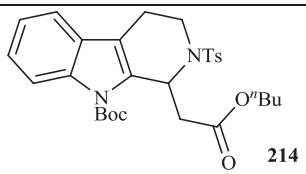
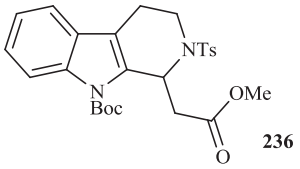
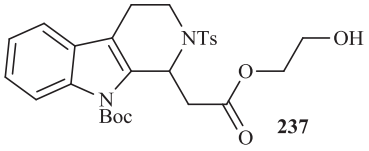
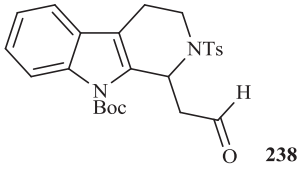
3.2.5 The Scope of the Domino Heck-aza-Michael Methodology

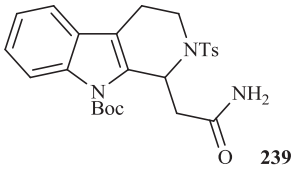
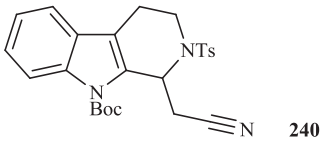
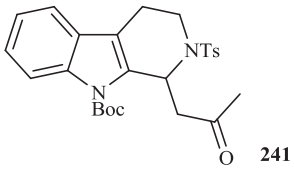
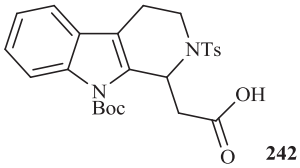
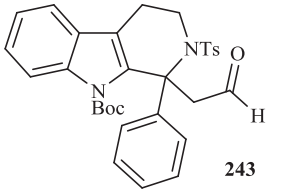
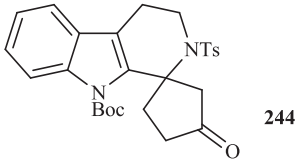
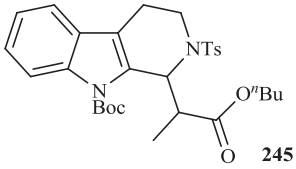
The domino Heck-aza-Michael reaction with butyl acrylate (Table 3.8) proved successful in producing the resultant butyl ester tetrahydro-*β*-carboline **214** in reproducible yields of ≥80%. To establish the versatility of this methodology, the domino process was repeated using a range of suitable alkenes possessing a 1,4-conjugated Michael acceptor (Table 3.9).

Table 3.9 The synthesis of C1-substituted TH*β*Cs using the domino Heck-aza-Michael process.



133 **214, 236-245**

Entry	Alkene	Product [a]	Yield (%)
1	butyl acrylate	 **214**	83
2	methyl acrylate	 **236**	79
3	2-hydroxyethylacrylate	 **237**	64
4	acrolein	 **238**	64

Entry	Alkene	Product [a]	Yield (%)
5	acrylamide	 **239**	80 [b]
6	acrylonitrile	 **240**	67
7	3-buten-2-one	 **241**	78
8	acrylic acid	 **242**	NR
9	cinnamaldehyde	 **243**	NR
10	2-cyclopenten-1-one	 **244**	NR
11	butyl methacrylate	 **245**	NR

a products isolated as a racemic mixture
b Partial Boc deprotection during synthesis resulted in an inseparable mixture of the indole protected and indole unprotected THβC.
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), alkene (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 ^{o}C for 16 h.

The two-step domino process performed well for a number of terminal alkenes with isolated yields ranging from 64-83% (Table 3.9, entries 1-7). The methodology provided access to a series of structurally diverse THβC scaffolds, containing a variety of functional groups readily available for further functionalisation, including esters **214, 236, 237** (Table 3.9, entries 1-3), aldehyde **238** (Table 3.9, entry 4), nitrile **240** (Table 3.9, entry 6) amide **239** (Table 3.9, entry 5), and ketone **241** (Table 3.9, entry 7). The unreactive nature of the acrylic acid (Table 3.9, entry 8) may be explained by the poor solubility of the corresponding carboxylate ion. The one-pot procedure (using Na_2CO_3 and TBACl) developed for the

synthesis of the butyl ester derivative (Table 3.9, entry 3) was also trialled using a range of alkenes, however; for reasons unknown the only other example that proved successful under these conditions was when methyl acrylate was used as a reagent (81%, Table 3.9, entry 2).

The domino process was next trialled with a number of more highly substituted alkenes in an attempt to introduce a greater level of molecular complexity into the newly formed tetrahydro-*β*-carboline scaffold. Unfortunately, no trace of the desired domino product was observed following the attempts with cinnamaldehyde, cyclopenten-2-one and butyl methacrylate (Table 3.9, entries 9-11).

The Heck reaction with these more highly substituted alkenes is not as trivial as the terminal alkenes successfully employed previously largely due to steric effects. During the Heck catalytic cycle, migratory insertion of the substituted alkene into the palladium-complex following oxidative addition does not occur as readily as for the unsubstituted terminal alkenes, and often requires the use of more active palladium-complexes (for example $Pd_2(dba)_3/P(tBu)_3$).[104, 325-328] An additional disadvantage of the Heck reaction using disubstituted alkenes is the lack of regioselectivity during the formation of the double bond product. This low regioselectivity can be explained by a lack of selectivity during the *β*-hydride elimination step of the Heck catalytic cycle. Additionally, as each of the steps of this catalytic cycle are reversible, readdition of the H-Pd-Br complex to the double bond (before being reduced back to the Pd(0) species by the base present) can result in *β*-hydride elimination to different hydrogen atoms resulting in various double bond isomers being formed.[104, 327]

In conclusion, a domino Heck-aza-Michael process, using a number of electron deficient alkenes for the synthesis of a series C1-substituted TH*β*C scaffolds was successfully developed. It was determined that the *p*-toluenesulfonyl protecting group was ideal for the N_{10}-amine, as it did not interfere with bromination of the indole-2-position, and also allowed Heck reaction to take place before aza-Michael addition occurred. It was also found that protection of the indole-nitrogen with a Boc group was essential for obtaining synthetically useful yields of the TH*β*Cs from this domino process.

This new methodology complements existing methods for the synthesis of tetrahydro-*β*-carbolines and provides an alternative strategy when access to specific C1-substituted TH*β*Cs are required.

3.3 Conclusion

Investigation into the synthesis of indole-based *N*-heterocycles employing an intermolecular Heck reaction at the indole-2-position lead to the development of an extremely efficient domino Heck-aza-Michael reaction that furnished C1-substituted tetrahydro-*β*-carbolines in four steps from tryptamine. Through judicious choice of the N_{10}-amine protecting group, it was possible to exclusively access either the Heck adduct or the domino TH*β*C adduct.

This novel methodology, employing cheap and readily available starting materials under mild conditions, afforded a series of functionalised *N*-heterocycles highly amenable to larger total syntheses. This domino Heck-aza-Michael reaction paves the way for the development and application of many more domino reactions of this type. The synthesis of a series of C1-substituted tetrahydro-*β*-carbolines using a domino Heck-aza-Michael reaction resulted in a recent publication (see Appendix One).[329]

Additional investigations into this domino Heck-aza-Michael reaction and attempts to apply this process to the synthesis of additional *N*-heterocycles are described in the following chapter (Chapter Four).

Chapter Four
Extension of the Domino Heck-aza-Michael Methodology

4.1 Chapter Overview

Following the successful development of a domino Heck-aza-Michael process for the synthesis of C1-substituted tetrahydro-*β*-carbolines (Chapter Three), several additional *ortho*-halogenated aryl amines were identified as suitable substrates for this domino process. This chapter details the development of domino Heck-aza-Michael methodology for the synthesis of a number of *N*-heterocyclic systems (Figure 4.1). Further extensions of this domino process, to include a multicomponent version and an asymmetric variant, are also discussed.

4.2 Domino Heck-aza-Michael Reactions: A General Approach to *N*-Heterocycles

In theory, any aryl- or vinyl-halide containing an *ortho*-tethered primary amine group is a potential substrate **246** for this domino reaction; provided the *N*-heterocyclic ring formed is of suitable size (*i.e.* cyclisation of a 2-bromoaniline to produce a 4-membered ring would not be favoured). As such, 2-bromobenzylamine, 2-bromophenethylamine, in addition to appropriately substituted benzofuran and benzothiophene scaffolds were identified as ideal candidates for further investigation into domino Heck-aza-Michael reactions (Figure 4.1).

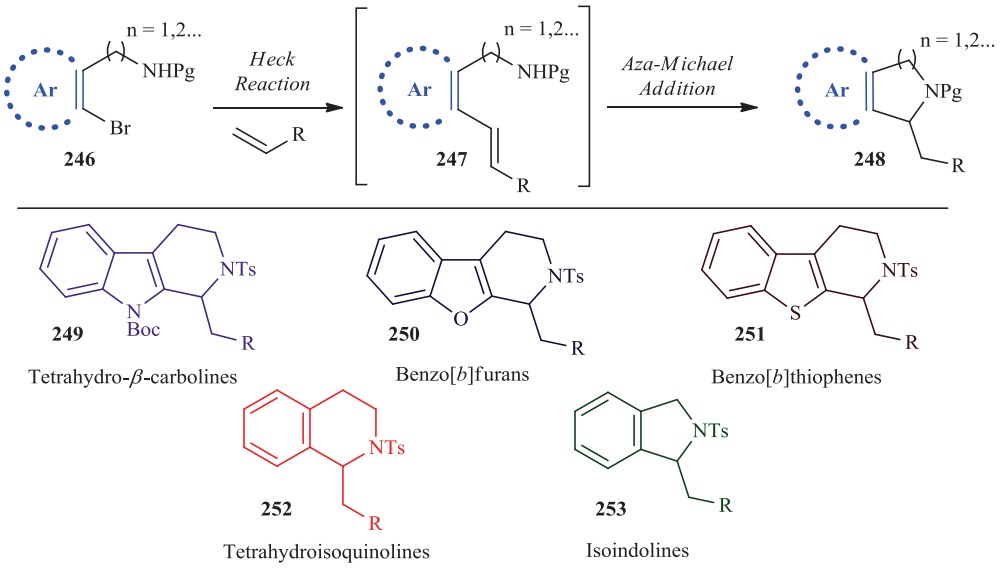


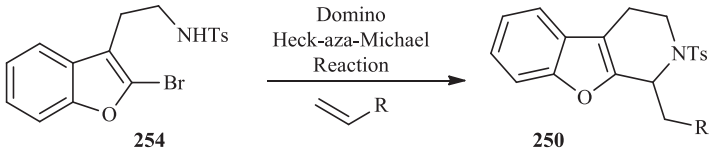
Figure 4.1 A generic domino process potentially applicable to the synthesis of other functionalised *N*-heterocycles

The key considerations for this domino process, as determined during the TH*β*C synthesis, were the need for a relatively fast Heck reaction, whilst controlling the nucleophilicity of the tethered amine through careful selection of the protecting group, base and solvent. Other factors that needed to be taken into account included the size of the *N*-heterocyclic ring

being formed, the differing reactivity of each aryl halide, and the variation of the nucleophilic nature of phenethylamines as compared to benzylamines. The following sections describe attempts to prepare a range of additional *N*-heterocyclic ring systems utilising the domino Heck-aza-Michael reaction.

4.2.1 Domino Heck-aza-Michael Reactions: Benzofurans

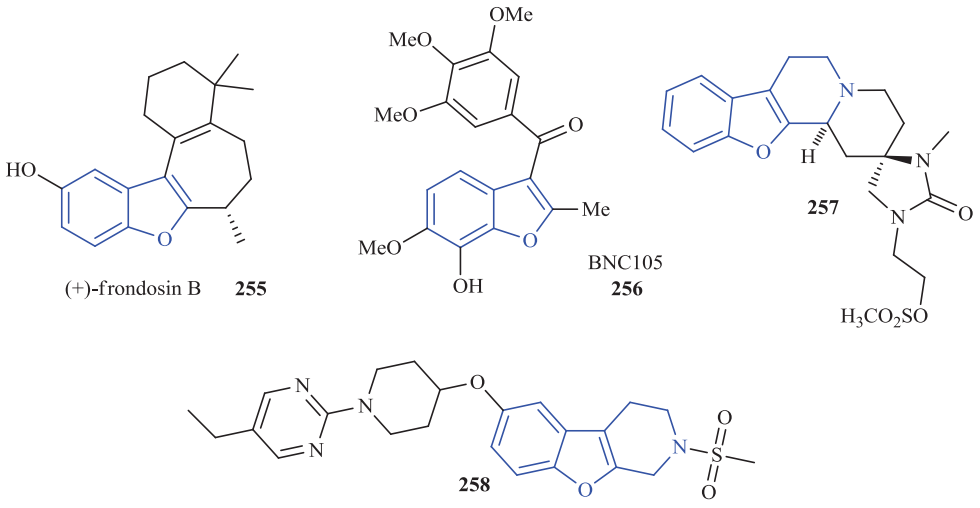
Following the success of the domino Heck-aza-Michael process for the synthesis of the indole-based *N*-heterocycles **249**, it was envisaged that tetrahydro-*β*-carboline analogues **250** where the indole nitrogen is replaced with an oxygen (*i.e.* benzofuran based *N*-heterocycles) could be prepared using a similar strategy. The requisite 2-bromobenzofuran domino precursor **254** containing both the tethered sulfonamide and the *ortho*-halogenated aromatic scaffold is shown below (Scheme 4.1)



254 **250**

Scheme 4.1 The proposed synthesis of benzofuran based *N*-heterocycles using domino Heck-aza-Michael reactions

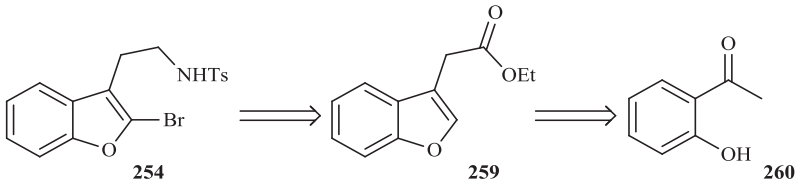
The benzofuran scaffold is found in a number of natural products (Frondosin B, Figure 4.2),[330-335] and medicinal chemistry targets, for example BNC105 which was developed as a vascular disruption agent for the treatment of tumours (Figure 4.2).[336-341] Benzofuran analogues of the tetrahydro-*β*-carboline have also shown potential for the treatment of diabetes (Figure 4.2, benzofuran **257**), asthma, hypertension (Figure 4.2, benzofuran **258**), and depression.[342-343]



(+)-frondosin B **255** BNC105 **256** **257** **258**

Figure 4.2 The benzofuran scaffold is found in natural products and medicinal chemistry agents

Methodology to access the *O*-analogue of the tetrahydro-*β*-carbolines is limited, and these approaches are often based around the acid catalysed Pictet-Spengler reaction.[41, 344-347] Both bromination[348-351] and the Heck reaction at the benzofuran-2-position have been reported using a variety of conditions,[9, 352-356] and as such, the domino Heck-aza-Michael reaction to form the *O*-analogue of tetrahydro-*β*-carbolines was envisaged as a plausible route to benzofuran-based *N*-heterocycles. The benzo[*b*]furan analogue of tryptamine is not readily available and had to be prepared. To achieved this, a multistep synthesis from 2-hydroxyacetophenone was devised, as outlined below (Scheme 4.2).

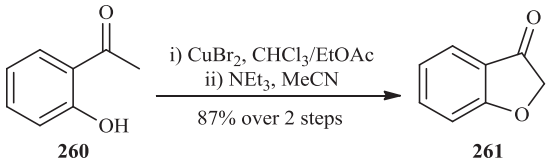


Scheme 4.2 The retrosynthesis of the tosyl-2-bromobenzofuran domino precursor

The first stages of the conceived retrosynthetic analysis involved the synthesis of 3-coumarone from 2-hydroxyacetophenone **260** through bromination of the methyl group, followed by cyclisation (facilitated by nucleophilic attack from the alcohol).[357] A Wadsworth-Horner-Emmons reaction between benzofuranone and an appropriate phosphonate would allow installation of the ethyl acetate and double-bond migration should produce the benzo[*b*]furan scaffold **259** (Scheme 4.2).[358] Reduction of the ester with $LiAlH_4$ to form the corresponding alcohol would follow. A similar approach taken to access the tryptamine analogue in the aforementioned *O*-analogue Pictet-Spengler publication[41] involved activation of the alcohol through reaction with trifluoromethansulfonic anhydride and subsequent nucleophilic displacement by 4-methoxypyridine to afford the substituted tryptamine *O*-analogue. As access to trifluoromethanesulfonic anhydride was limited, we proposed a modified approach to prepare the domino precursor, through reaction of the alcohol with *p*-toluenesulfonyl chloride followed by displacement with *p*-toluenesulfonamide to afford the *O*-analogue of the tosyl-tryptamine. Subsequent bromination of the benzofuran-2-position would provide access to the requisite domino precursor **254**. The following section describes the synthesis of the tosyl-2-bromobenzofuran **254** following the approach outlined above.

The first step in this reaction sequence involved the synthesis of 3-coumarone (**261**) from 2-hydroxyacetophenone (**259) (**Scheme 4.3). The α-bromination of the methyl group was achieved using copper(II) bromide in a refluxing mixture of ethyl acetate and chloroform, according to literature protocol.[359-360] The successful bromination of the methyl ketone was

readily determined by ^{1}H NMR spectroscopy (and confirmed by mass spectrometry), with an upfield shift in the resonance attributed to the hydroxyl group of the phenol (-OH, δ 12.24 ppm to δ 11.72 ppm) and the downfield shift of the resonances assigned to the methyl proton following bromination (-CH_3 δ 2.61 ppm, to -CH_2Br δ 4.44 ppm).

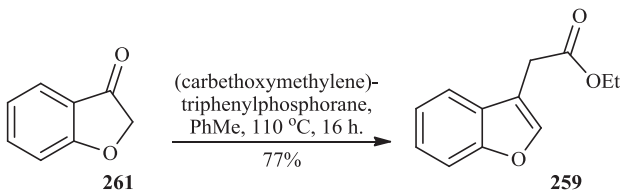


260 **261**

Scheme 4.3 The synthesis of 3-coumarone from 2-hydroxyacetophenone

Initial attempts to cyclise the bromoacetophenone were made using sodium acetate in DMF,[361] with limited success. It was eventually determined that cyclisation in the presence of triethylamine and acetonitrile, afforded 3-coumarone (**261**) in 87% yield over 2 steps (Scheme 4.3). Cyclisation to form the new 5-membered ring was confirmed by NMR spectroscopy, with the absence of the resonance previously attributed to the alcohol proton, and the slight downfield shift of the CH_2 proton resonance (-CH_2Br δ 4.44 ppm, -CH_2-O- δ 4.61 ppm).

The next step in the sequence was the Wadsworth-Horner-Emmons (W-H-E) reaction to install the ethyl acetate functionality, and subsequent internalisation of the double-bond to form the benzofuran aromatic ring (Scheme 4.4).



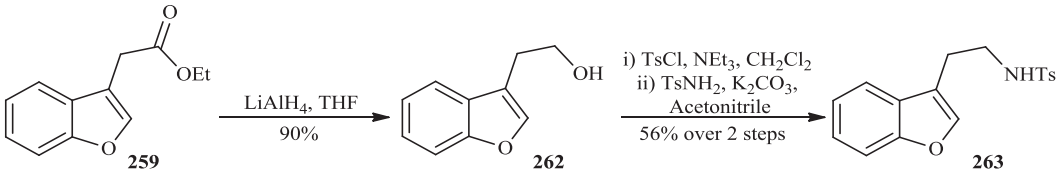
261 **259**

Scheme 4.4 Synthesis of the benzofuran ester from 3-coumarone

A similar reaction pathway employing a nitrile phosphorane followed by reduction of the nitrile to afford the primary amine, has been reported as an efficient means to access tryptamine analogues.[357] However, as the approach using the ester phosphorane is more cost effective, it was used instead. The reaction was carried out by refluxing 3-coumarone (**261**) with 1.5 equivalents of (carbethoxymethylene)triphenylphosphorane in toluene for 16 hours (Scheme 4.4). Following purification by column chromatography the ethyl ester benzofuran **259** was isolated in 77% yield. The identity of this product was confirmed by absence of the

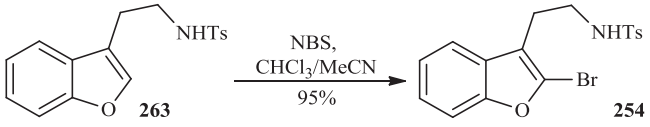
CH_2 resonance of the C2-position once the benzofuran ring system was formed (now an aromatic-CH, δ 7.63 ppm, singlet), and the addition of the ethyl acetate proton resonances.

The ester **259** was reduced to the corresponding alcohol **262** with lithium aluminium hydride (Scheme 4.5, 90% yield). The alcohol product **262** was readily detected in the ^{1}H NMR spectrum by the absence of the ethyl ester proton resonances and the addition of both a CH_2 and an OH proton resonance. Following this, the alcohol **262** was converted to the sulfonate through reaction with *p*-toluenesulfonyl chloride and the activated alcohol (-OTs) displaced by *p*-toluenesulfonamide under basic conditions to afford benzofuran **263** (in 56% yield over 2 steps, Scheme 4.5). [362] The correct identity of the sulfonamide-benzofuran was confirmed by NMR spectroscopy and mass spectrometry.



Scheme 4.5 Synthesis of the benzofuran-sulfonamide from the benzofuran-acetate

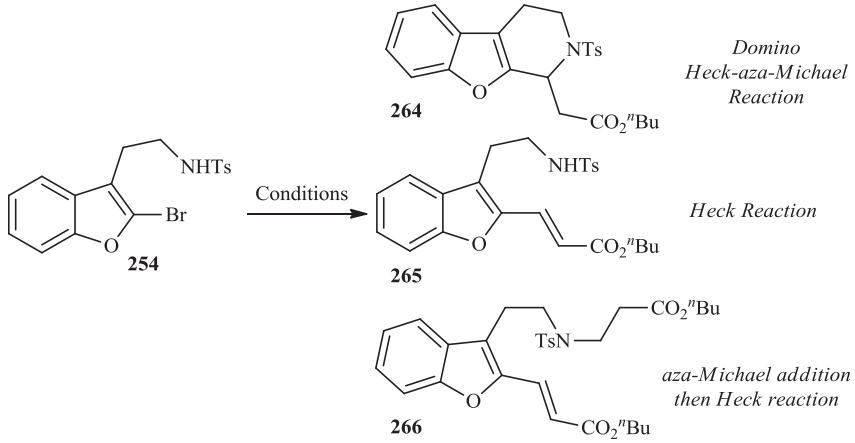
With the tosyl benzofuran **263** in hand, attention turned to the C2-bromination of the benzo[*b*]furan to complete the synthesis of the domino precursor **254**. A number of methods are reported,[350, 352-353] however, in our hands, this bromination was accomplished (Scheme 4.6) using *N*-bromosuccinimide in a solution of chloroform/acetonitrile (95% yield).[350] The identity of this product was confirmed by NMR spectroscopy with the absence of the benzo[*b*]furan-C2-aromatic proton resonance and the upfield shift of the C2 resonance in the ^{13}C NMR spectrum following bromination (-CH δ 142.3 ppm to –CBr δ 128.1 ppm).



Scheme 4.6 Bromination of the benzo[*b*]furan-2-position

The synthesis of the novel domino precursor **254** was achieved in 32% yield over 7 steps from 2-hydroxyacetophenone (**260**), and it was subsequently used as a substrate in the domino Heck-aza-Michael reaction for the synthesis of functionalised benzofuran-based *N*-heterocycles. A range of palladium catalysts, base, and solvents were trialled in the presence of butyl acrylate, and following a simple work up, the crude reaction mixture was analysed by ^{1}H NMR to initially determine the success of the reaction (Table 4.1).

Table 4.1 Domino Heck-aza-Michael reaction to access benzofuran-based *N*-heterocycles



Entry	Palladium Catalyst [a]	Base	Solvent	Major Product [b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	**266** [c]
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	Heck adduct **265** (61%)[d]
3	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	**266** [c]
4	$Pd(OAc)_2$/SPhos	K_2CO_3	PhMe	**266** [c]
5	$Pd_2(dba)_3/P(^tBu)_3$	K_2CO_3	PhMe	**266** [c]
6	$Pd(OAc)_2$/SPhos	NEt_3	DMF	**266** [c]
7	$Pd(OAc)_2$/XPhos	NEt_3	DMF	**266** [c]
8	$Pd(PPh_3)_4$	NEt_3	DMF	**266** [c]

a Palladium catalyst loading 10 mol%, where applicable palladium:ligand ratio used was 1:1
b As determined by ^{1}H NMR spectroscopy
c Trace of the domino adduct detected in the ^{1}H NMR spectrum
d Isolated yield
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), butyl acrylate (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 ^{o}C for 16 h.

The first attempt (Table 4.1, entry 1) was made using $Pd(PPh_3)_4$ and K_2CO_3 in toluene, the conditions previously found optimal for the domino reaction in the synthesis of tetrahydro-*β*-carbolines (see Chapter Three). Unfortunately, the major product identified from this reaction mixture was produced from intermolecular Michael addition, followed by Heck reaction (as indicated by two sets of butyl ester proton resonances and the alkene proton resonances). The result from this first reaction indicated that under these catalytic conditions, intermolecular aza-Michael addition takes place prior to Heck reaction. In an attempt to slow down the rate of aza-Michael addition, Na_2CO_3 was used as base instead of K_2CO_3, in the presence of $Pd(PPh_3)_4$ (Table 4.1, entry 2). The major product from this attempt was the Heck adduct **265**, isolated in a yield of 61%. This result confirms that $Pd(PPh_3)_4$ does in fact promote the Heck reaction at the benzofuran-2-position, however the conditions are not sufficient to promote intramolecular aza-Michael addition.

Further attempts focussed on increasing the rate of the Heck reaction (instead of slowing down the aza-Michael addition) so that a rapid concentration of the Heck adduct was produced prior to aza-Michael addition. These reaction trials (Table 4.1, entries 3-5) were

carried out using more active palladium catalysts in the presence of K_2CO_3 and toluene. Once again, however, the major product identified from these reaction mixtures was due to intermolecular 1,4-addition taking place prior to the Heck reaction. The more active catalytic conditions did not significantly increase the rate of the Heck reaction at the benzofuran-2-position.

Three additional reactions were trialled using DMF and triethylamine (Table 4.1, entries 6-8), with palladium catalysts known to promote Heck reaction at the benzofuran-2-position.[353] Again, the major product identified in each of these cases was the aza-Michael/Heck adduct **266**.

The high yielding synthesis of benzo[*b*]furan-based *N*-heterocycles was not successfully completed. In a number of cases, a trace amount of the desired product **264** was detected in the ^{1}H NMR spectrum of the crude reaction mixture. Although the Heck reaction was completed in some instances, it was not occurring at a fast enough rate, and as such, intermolecular aza-Michael addition was taking place prior to completion of the Heck reaction. Attempts to slow down the rate of aza-Michael addition (Table 4.1, entries 2, 6-8) by altering the base and solvent employed proved unsuccessful, as did attempts to increase the rate of the Heck reaction using palladium catalysts known to be more active (Table 4.1, entries 3-7).[80, 148]

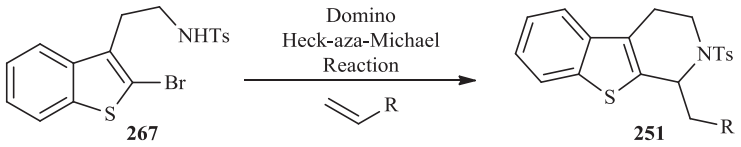
It was proposed that iodination of the benzo[*b*]furan-2-position would facilitate a faster Heck reaction, increasing the chance of the domino process taking place. The literature procedures currently available to iodinate this position require the use of reagents that do not tolerate a number of the functional groups present (for example the use of *n*-BuLi to facilitate lithium-iodine exchange is not ideal in the presence of an ester, alcohol or amide during preparation of the domino precursor), and an efficient route to iodinate this benzofuran-2-position was not identified. Also proposed was the use of an alternative N_{10}-amine protecting group which would not undergo aza-Michael addition as readily as the *p*-toluenesulfonamide (for example the 2-nitrobenzenesulfonyl or trifluoroacetyl protecting groups), however this approach was not investigated.

These results highlight how subtle electronic differences in the aryl-halide substrate can play a significant role in determining the success of *N*-heterocycle formation**.** For the tetrahydro-*β*-carboline synthesis, the yield of the domino process was significantly enhanced through the protection of the indole-nitrogen, drawing electron density away from both the aryl-halide and *β*-position of the Michael acceptor. Unfortunately, the electron rich benzofuran system cannot be optimised using a similar approach. Additional electron withdrawing

groups (e.g. NO_2 or CF_3) could be introduced onto the aromatic scaffold during benzo[*b*]furan synthesis to further modulate electronic properties.

4.2.2 Domino Heck-aza-Michael Reactions: Benzothiophenes

In a similar approach to that just discussed, it was envisaged that the synthesis of benzothiophene analogues of tetrahydro-*β*-carbolines **251** could be accessed using domino Heck-aza-Michael reactions (Scheme 4.7).



Scheme 4.7 The proposed synthesis of benzothiophene-based *N*-heterocycles using domino Heck-aza-Michael reactions.

The benzothiophene analogues of the tetrahydro-*β*-carbolines have been employed in a number of medicinal chemistry projects, for example as antagonists of the H3 histamine receptor (Figure 4.3, benzothiophene **268**) as well as inhibitors of the histone deacetylase (HDAC) enzyme (Figure 4.3, benzothiophene **269**).[363-364]

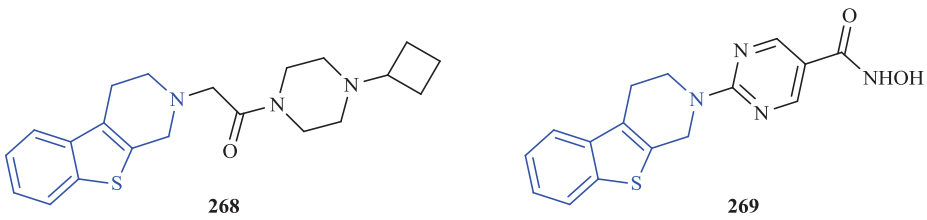
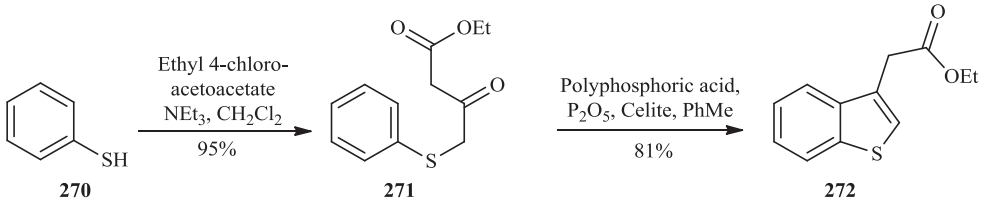


Figure 4.3 Benzothiophene-based *N*-heterocycles have been developed to treat a range of medical conditions

Although the benzothiophene scaffold has been extensively studied, methodology to access the *S*-analogue of the tetrahydro-*β*-carbolines is limited.[344, 365-366] As both bromination[349, 367-369] and the Heck reaction at the benzothiophene-2-position have been reported,[9, 370-371] a domino Heck-aza-Michael reaction was seen as an efficient way to access benzofuran-based *N*-heterocycles, introducing molecular diversity at the C1-position of the newly formed heterocyclic scaffold.

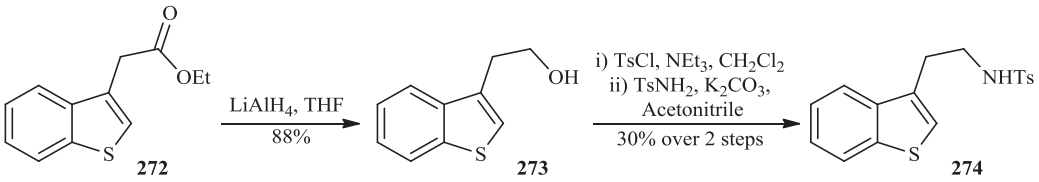
Once again the benzothiophene analogue of tryptamine was not readily available, and a similar approach to that used for the synthesis of the benzofuran domino precursor **267** was employed from thiophenol following literature procedures.[372-373] The first step in the

synthesis of the benzothiophene domino precursor involved the alkylation of thiophenol (**270**) with ethyl-4-chloroacetoacetate under basic conditions to afford the thiophenol ketoester **271** in 95% yield (Scheme 4.8).[374]



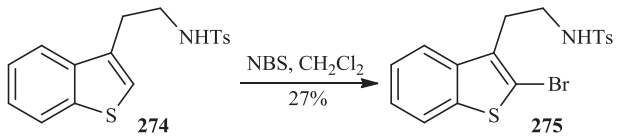
Scheme 4.8 Synthesis of the benzothiophene ester from thiophenol

Cyclodehydration of keto ester **271** in the presence of polyphosphoric acid and phosphorous pentoxide afforded the benzothiophene ester **272** (Scheme 4.8, 81% yield).[373] The successful cyclisation to form the benzothiophene ring system was confirmed by NMR spectroscopy, with the absence of the corresponding CH_2 resonance in the ^{1}H NMR spectrum and the addition of the C2-aromatic proton resonance (δ 7.36 ppm).The ester **272** was then reduced to the corresponding alcohol **273** (Scheme 4.9) upon treatment with $LiAlH_4$ (88%). This result was readily detected through analysis of the ^{1}H NMR spectrum with the addition of the proton resonances assigned to the CH_2 and OH functionality. In similar fashion to the reaction sequence used to prepare the benzo[*b*]furan domino precursor, the alcohol was reacted with *p*-toluenesulfonyl chloride to form an appropriate leaving group, which was then displaced by *p*-toluenesulfonamide in a moderate yield over 2 steps (33%) to afford benzothiophene **274** (Scheme 4.9).



Scheme 4.9 Synthesis of the benzothiophene sulfonamide from the benzothiophene ester

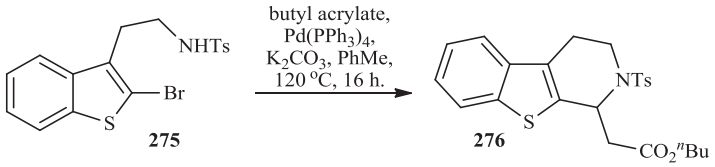
With the requisite sulfonamide **274** accessed in 5 steps from thiophenol (**270**), attention turned to the chemoselective bromination of the benzothiophene-2-position. Several attempts to brominate this benzothiophene-2-position were carried out using a number of the standard procedures employed previously during this research project (pyridinium tribromide, NBS, Br_2).[367]



Scheme 4.10 Bromination of the benzothiophene-2-position

Unfortunately, the highest yield obtained for the bromination of the benzothiophene-2-position was 27%, using NBS in CH_2Cl_2 (Scheme 4.10). The major by-product identified from this reaction was once again the bromo-sulfonamide complex, discussed previously in Chapter 2 (section 2.3.1).[266-267] Further attempts were made to brominate the benzothiophene-2-position earlier in the reaction sequence for the synthesis of the domino precursor (using the ester, alcohol and sulfonate derivatives). However, these bromination attempts also failed to produce the desired 2-bromobenzothiophene **275** and an efficient, high yielding synthesis of the domino precursor from thiophenol (**270**) was not identified.

One attempt at the domino Heck-aza-Michael reaction for the synthesis of benzothiophene-based *N*-heterocycles was carried out using the small amount of domino precursor **275** isolated following the bromination using NBS (Scheme 4.10). The domino reaction was performed using the catalytic conditions that produced the highest yields of the analogous tetrahydro-*β*-carboline (Scheme 4.11).



Scheme 4.11 Attempted domino Heck-aza-Michael reaction for the synthesis of benzothiophene-based *N*-heterocycles

Following analysis of the crude reaction mixture, the major products identified from this attempted domino reaction was the intermolecular aza-Michael product along with the desired product **276** (inseparable by column chromatography). The presence of the benzothiophene-based *N*-heterocycle (<30% conversion by ^{1}H NMR spectroscopy) was identified by the C1-proton resonance at δ 5.69 ppm of the ^{1}H NMR spectrum and also mass spectrometry ($[M + H]^+$ 458.2). This result confirmed that the domino reaction was indeed a plausible pathway to access benzothiophene-based *N*-heterocycles **251**, however a much more efficient synthesis of the domino precursor is required before further optimisation of this reaction sequence can be carried out.

4.2.3 Domino Heck-aza-Michael Reactions: Tetrahydroisoquinolines

In our continuing attempts to expand the scope of this domino Heck-aza-Michael methodology, tetrahydroisoquinolines **252** were the next *N*-heterocyclic scaffold to be investigated. The tetrahydroisoquinoline scaffold forms the central part of a number of naturally occurring alkaloids,[375-381] such as the antitumor natural product quinocarcinol **277** (Figure 4.4).[380-381] A number of potential pharmaceuticals have also been formed around this tetrahydroisoquinoline core.[310, 382]

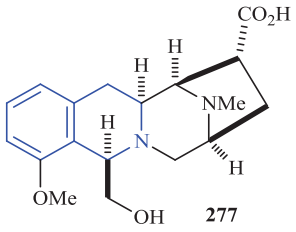
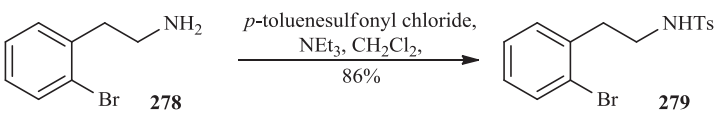


Figure 4.4 The tetrahydroisoquinoline antitumour natural product quinocarcinol

Tetrahydroisoquinolines have traditionally been prepared from phenethylamine based starting materials using the Pictet-Spengler reaction,[35-36, 383-385] or the related Bischler-Napieralski methodology.[66, 384, 386-389] Alternatives to these aforementioned reactions are limited; the Ferracioli synthesis involving a sequential palladium-catalysed *ortho*-alkylation/vinylation combined with aza-Michael addition being one of the most recent (Scheme 3.5).[283]

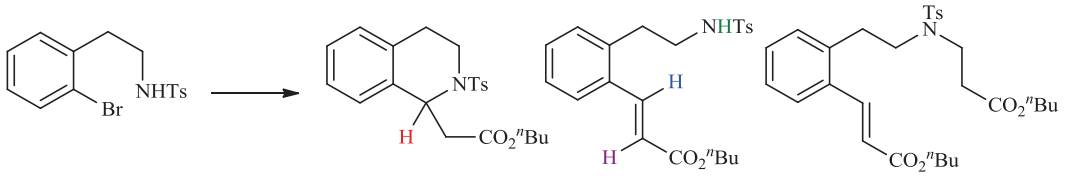
The synthesis of tetrahydroisoquinolines using a four step reaction sequence, through initial intermolecular Heck reaction, amine deprotection, aza-Michael addition and then amine reprotection has been reported.[277] To complement and further investigate the scope of these existing methodologies, the development of the domino Heck-aza-Michael reaction, using cheap and readily available acrylates for the efficient synthesis of a series of substituted tetrahydroisoquinolines **252** was investigated. As in the case of the TH*β*Cs, the tosyl (Ts) protecting group was employed to control amine nucleophilicity through the sulfonamide.[329] The domino substrate **279** was prepared by reacting 2-bromophenethylamine (**278**) with tosyl chloride in 86% yield (Scheme 4.12).



Scheme 4.12 The preparation of the tosyl-2-bromophenethylamine domino precursor

Using this substrate, a series of trial reactions were carried out to determine if a domino Heck-aza-Michael process was feasible. These reactions were initially performed by treating aryl bromide **279** with butyl acrylate, a palladium catalyst, base and solvent in a pressure vessel and heating to 120 °C for 16 hours. Identification of the products was initially performed by means of ^{1}H NMR spectroscopy of the crude reaction mixture (Table 4.2).

Table 4.2 Optimisation of the domino process for tetrahydroisoquinoline formation



279 **280** **281** **282**

Domino Heck-aza-Michael Reaction *Heck Reaction* *Aza-Michael-Heck Reaction*

Entry	Palladium Catalyst [a]	Base	Solvent	Major Product [b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	**282**
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	Heck adduct **281**
3	$Pd_2(dba)_3$/P(*t*Bu)$_3$	Cy_2NMe	PhMe	Heck adduct **281**
4	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	Heck adduct **281**
5	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	Heck adduct **281**
6	$Pd_2(dba)_3.CHCl_3$	K_2CO_3	PhMe	NR
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	Domino adduct **280** (80) [d]
8	$Pd_2(dba)_3$/DavePhos	K_2CO_3	PhMe	Domino adduct **280** (79) [d]
9	Herrmann-Beller palladacycle [e]	Cy_2NMe	DMF/MeCN/H_2O [c]	Domino adduct **280** (67) [d]

a Catalyst loading was 10 mol%, where applicable palladium catalyst and ligand used in a 1:1 molar ratio
b As determined by ^{1}H NMR analysis of crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra *δ*: H = 5.46; H = 4.60, H = 7.84, H = 6.28 ppm
c DMF/MeCN/H_2O (5:5:1)
d Isolated Yield
e Herrmann-Beller catalyst is [*trans*-Di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]-dipalladium (II)].
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), butyl acrylate (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

In the first attempt, the optimum conditions identified for the synthesis of TH*β*Cs ($Pd(PPh_3)_4$, K_2CO_3, PhMe, Table 4.2, entry 1), produced adduct **282** exclusively *i.e.* aza-Michael reaction favoured but Heck reaction slow. A number of alternative Pd-catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3$/P(^{t}Bu)$_3$ and $Pd(OAc)_2/PPh_3$) combined with a range of bases (Table 4.2, entries 2-4) were subsequently trialled, however, only the Heck adduct **281** was produced. It was apparent that whilst the Heck reaction was proceeding, the base used in each of these trials (Na_2CO_3, Cy_2NMe and NEt_3, Table 4.2, entries 2, 3 and 4 respectively) was not strong enough to induce either intra- or intermolecular aza-Michael addition as only traces of these products were observed. From the previous work into TH*β*Cs it was known that the aza-Michael process was sensitive to subtle variations in the base used, and again changing the base (e.g. from K_2CO_3 to Na_2CO_3 Table 4.2, entries 1 and 2) either facilitated or reduced the

likelihood of the aza-Michael reaction. Of the bases trialled to this point (Table 4.2, entries 1-6), only K_2CO_3 was successful in promoting aza-Michael reaction (albeit intermolecularly).

To ensure rapid formation of the Heck intermediate **281**, the highly reactive and electron rich $Pd_2(dba)_3$/DavePhos catalyst system (developed by Buchwald and Hartwig) was used in combination with K_2CO_3.[390] This catalytic system furnished the desired tetrahydroisoquinoline **280** in 80% yield (Entry 8, Table 4.2). Following further trials, other catalytic systems (Entries 7 and 9, Table 4.2) also resulted in clean conversion of the domino precursor to tetrahydroisoquinoline **280**. These additional successes indicate that judicious choice of base and solvent is crucial for promoting the desired aza-Michael cyclisation (compare entries 4 and 8, Table 4.2). In assessing each of these procedures the $Pd(OAc)_2/PPh_3$ and K_2CO_3 in toluene catalytic system was deemed the most attractive due to its availability and relatively low cost.[391]

The identity of the tetrahydroisoquinoline butyl ester **280** was confirmed using mass spectrometry and NMR spectroscopy. The characteristic peaks in the ^{1}H NMR spectrum (Figure 4.5) included the C1-proton resonance (δ 5.46 ppm) and the resonances assigned to the butyl ester.

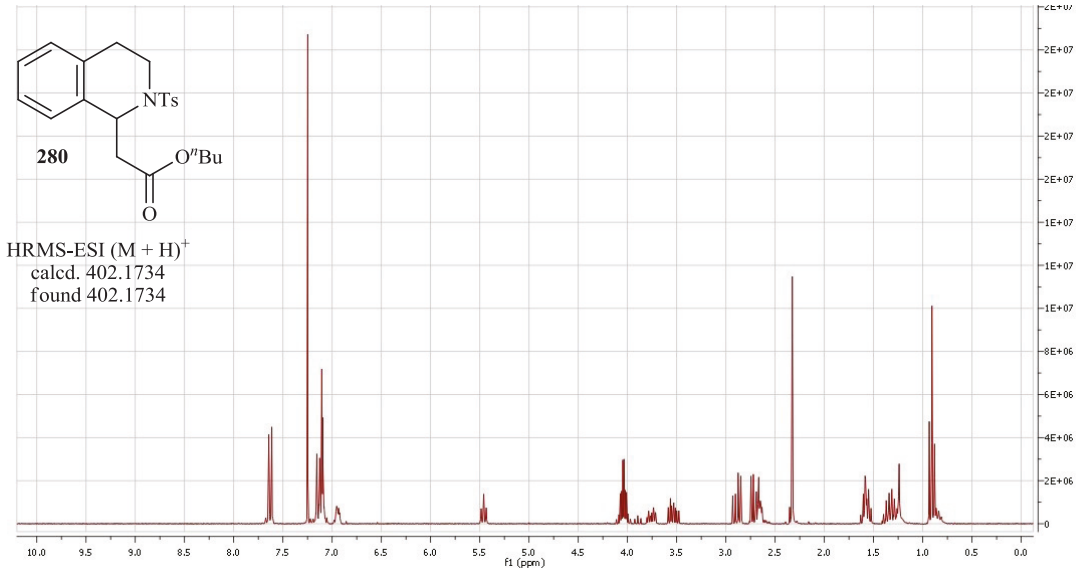
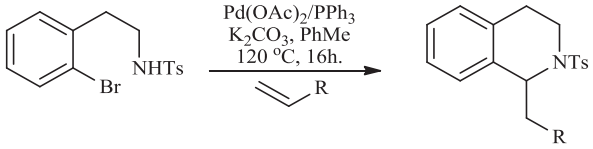


Figure 4.5 The ^{1}H NMR spectrum of the tetrahydroisoquinoline *n*-butyl ester

A range of acrylates were then subjected to this domino process to afford a series of C1-substituted tetrahydroisoquinolines (Table 4.3).

Table 4.3 The formation of C1-substituted tetrahydroisoquinolines



Entry	Alkene	R	Yield (%) [a]
1	butyl acrylate	$CO_2{}^nBu$ (**280**)	80
2	methyl acrylate	CO_2Me (**283**)	83
3	2-hydroxyethyl acrylate	$CO_2(CH_2)_2OH$ (**284**)	76
4	acrylonitrile	CN (**285**)	82
5	3-buten-2-one	$COCH_3$ (**286**)	79
6	acrylamide	$CONH_2$ (**287**)	Trace [b]
7	acrolein	CHO (**288**)	NR [c]
8	acrylic acid	CO_2H (**289**)	NR [c]

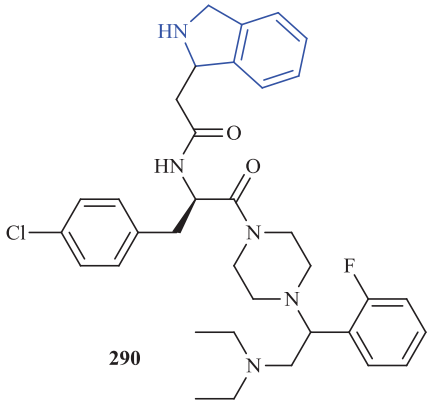
a Products isolated as a racemic mixture
b Trace = less than 10% as determined by ^1H NMR
c NR = No reaction
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), alkene (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

The resulting products contained a range of functionalities including esters **280**, **283** and **284**, ketone **286** and nitrile **285** (Table 4.3, Entries 1-5). Unfortunately, reactions attempted with both acrolein and acrylic acid did not furnish the desired tetrahydroisoquinolines, even though the reaction with acrolein had been successfully employed in the TH*β*C domino Heck-aza-Michael reaction.[329]

4.2.4 Domino Heck-aza-Michael Reactions: Isoindolines

Domino Heck-aza-Michael processes had now been developed for the synthesis of *six* membered *N*-heterocyclic scaffolds in the form of C1-substituted tetrahydro-*β*-carbolines **249** and tetrahydroisoquinolines **252**. The next heterocyclic scaffold to be investigated was the isoindolines **253**, to ascertain if the scope of this methodology could be extended to include *five* membered *N*-heterocycles.

Although not as prevalent in natural products, the isoindoline scaffold has been employed in a number of potential pharmaceutical agents, including isoindoline **290** (Figure 4.6), synthesised as a ligand for the melanocortin subtype-4 receptor (MC4R).[293, 310, 382, 392-393]

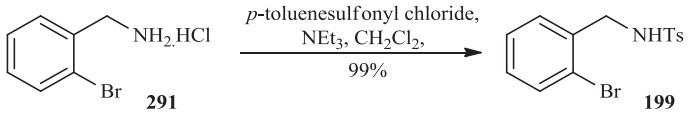


290

Figure 4.6 An isoindoline synthesised as a ligand for the MC4 receptor

Isoindolines substituted at the C1-position have been accessed using a radical cyclisation of *N*-benzylenaminone esters.[394] More recently, 1,3-disubstituted isoindolines have been synthesised using Brønsted acid catalysed 1,2-addition followed by aza-Michael addition.[395]

The synthesis of isoindolines using a four step reaction sequence, through initial Heck reaction, amine deprotection, aza-Michael addition and then amine reprotection has also been reported.[293] To complement these existing methodologies, the development of a domino Heck-aza-Michael reaction, using cheap and readily available acrylates, for the efficient synthesis of a series of substituted isoindolines was investigated. An appropriately substituted benzylamine **199** was prepared in 99% yield as a precursor to C1-substituted isoindolines (Scheme 4.13).

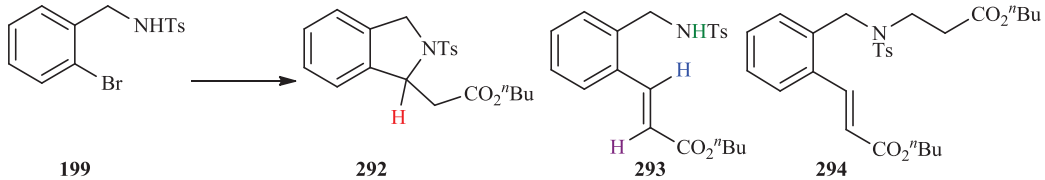


291 **199**

Scheme 4.13 The preparation of the tosyl-2-bromobenzylamine domino precursor

As with both the TH*β*Cs and the tetrahydroisoquinolines, a range of conditions were evaluated in the preparation of the desired isoindoline (Table 3.4). The bromosulfonamide **199**, butyl acrylate, a palladium catalyst, base, and solvent were combined in a pressure vessel and heated to 120 ^{o}C for 16 hours. Following a simple work up, the major product was identified by means of ^{1}H NMR spectroscopy (Table 4.4).

Table 4.4 Optimisation of the domino process for isoindoline formation



199 **292** **293** **294**

Domino Heck-aza-Michael Reaction *Heck Reaction* *Aza-Michael-Heck Reaction*

Entry	Palladium Catalyst [a]	Base	Solvent	Major Product [b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	Mixture
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	Mixture
3	$Pd(PPh_3)_4$	Cs_2CO_3	PhMe	NR [c]
4	$Pd(PPh_3)_4$	K_2CO_3	DMF	NR [c]
5	$Pd_2(dba)_3/P(tBu)_3$	Cy_2NMe	PhMe	**293**/**292**
6	$Pd_2(dba)_3.CHCl_3$	NEt_3	DMF	NR [c]
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	NR [c]
8	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	Isoindoline **292** (74) [d]
9	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	Isoindoline **292** (77) [d]
10	$Pd_2(dba)_3$/DavePhos	Cy_2NMe	DMF	Isoindoline **292** (79) [d]
11	$Pd_2(dba)_3$/XPhos	Cy_2NMe	DMF	Isoindoline **292** (62) [d]
12	$Pd_2(dba)_3$/SPhos	Cy_2NMe	DMF	Isoindoline **292** (48) [d]
13	Herrmann-Beller palladacycle [e]	Cy_2NMe	DMF:MeCN:H2O [f]	Isoindoline **292** (54) [d]

a Palladium and ligand used in a 1:1 molar ratio
b As determined by ^{1}H NMR analysis of crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra *δ*: H = 5.28; H = 5.10, H = 7.62, H = 6.38 ppm
c NR = No reaction
d Isolated yield
e Herrmann-Beller catalyst is [*trans*-Di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]-dipalladium (II)].
f DMF/MeCN/H_2O (5:5:1)
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), butyl acrylate (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 ^oC for 16 h.

The first trial with tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) afforded mixtures of the three predicted products (entry 1, Table 4.4). Repeating the reaction with $Pd(PPh_3)_4$ but changing the base and solvent (entries 2-4, Table 4.4) also proved unsuccessful. The highly active catalytic system of $Pd_2(dba)_3/P(^tBu)_3$ minimised the formation of the aza-Michael-Heck product **294**, however, complete conversion of the Heck adduct **293** to the desired isoindoline **292** did not occur (entry 5, Table 4.4).[170] A high yield of the desired isoindoline **292** was observed when $Pd(OAc)_2/PPh_3$ and triethylamine were used in either toluene or DMF (entries 8 and 9, Table 4.4). The use of other highly active Pd-catalysts also proved successful when combined with an amine base in DMF. Again, it was apparent that a suitable base (in this case an organic base rather than an inorganic base) was crucial to effecting the desired cyclisation following Heck reaction.

Even though the Pd_2dba_3/DavePhos catalytic system (entry 10, Table 4.4) provided the isoindoline **292** in the highest yield, it was not significantly greater than that obtained when

the $Pd(OAc)_2/PPh_3$ system was used (entry 9, Table 4.4). This latter system was subsequently used for the remainder of this investigation due to its low cost and availability.

The identity of the isoindoline butyl ester **292** was confirmed using mass spectrometry and NMR spectroscopy. The characteristic peaks in the ^1H NMR spectrum (Figure 4.7) included the C1-proton resonance (δ 5.27 ppm), the downfield shift and additional splitting patterns of the C3-proton resonances (δ 4.73 and 4.50 ppm), and the resonances assigned to the butyl ester protons.

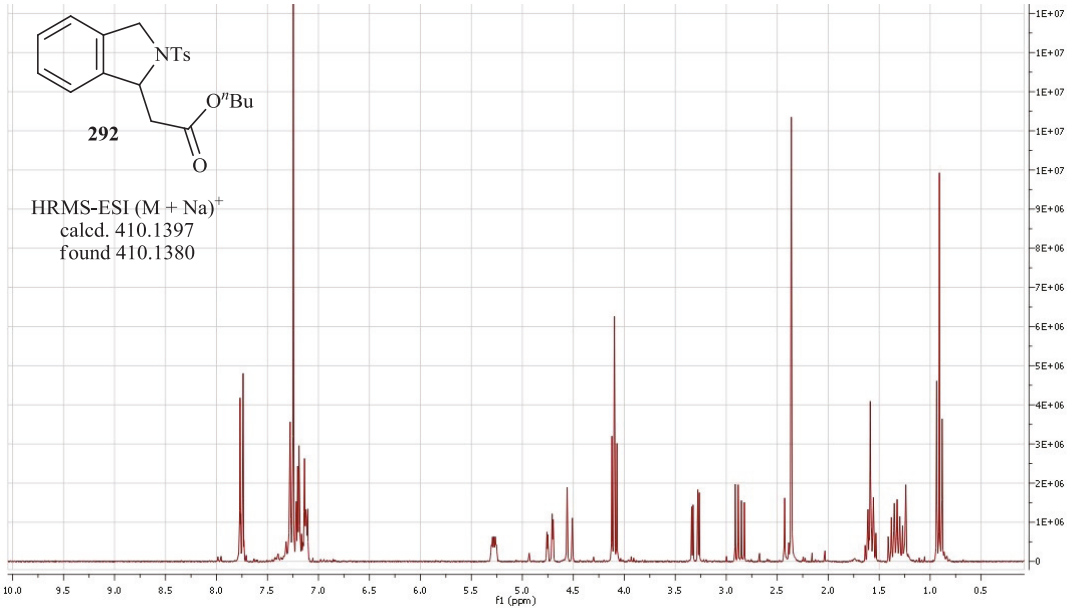
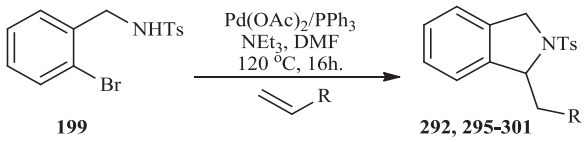


Figure 4.7 The ^1H NMR spectrum of the isoindoline *n*-butyl ester

This optimised domino process was then used with a range of acrylates to afford a series of C1-substituted isoindolines (Table 4.5).

Table 4.5 The formation of C1-substituted isoindolines

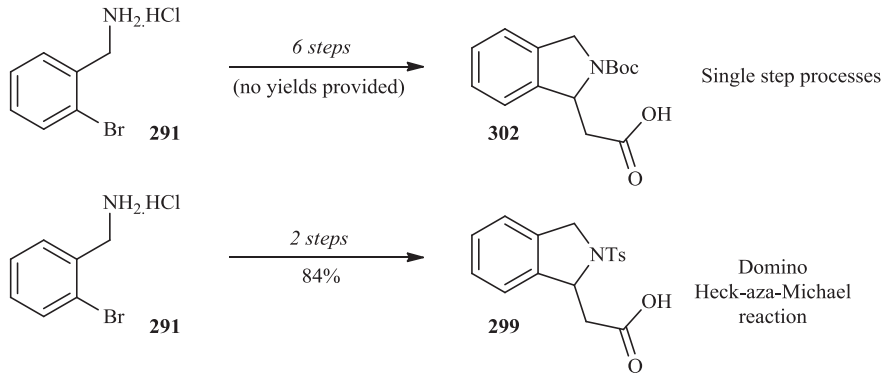


Entry	Alkene	R	Yield (%) [a]
1	butyl acrylate	$CO_2{}^nBu$ (**292**)	77
2	methyl acrylate	CO_2Me (**295**)	Unknown [b]
3	2-hydroxyethyl acrylate	$CO_2(CH_2)_2OH$ (**296**)	84
4	acrylamide	$CONH_2$ (**297**)	71
5	acrylonitrile	CN (**298**)	68
6	acrylic acid	CO_2H (**299**)	85
7	3-buten-2-one	$COCH_3$ (**300**)	86
8	acrolein	CHO (**301**)	NR [c]

a products isolated as a racemic mixture
b This domino process also performed well using methyl acrylate, however the isoindoline product could not be separated from the remaining starting material by column chromatography.
c NR = No reaction
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), alkene (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

The series of products synthesised contain a range of functionalities including a carboxylic acid **299**, esters **292** and **296**, ketone **300**, amide **297** and nitrile **298**. This time the use of acrylic acid resulted in the formation of the isoindoline acetic acid **299**, presumably due to the increased solubility of the resulting carboxylate ion in the triethylamine/DMF solvent system.

To further illustrate the power of this domino Heck-aza-Michael methodology, a comparison for the synthesis of the carboxylic acid isoindoline follows (Scheme 4.14). In a recent publication the preparation of the Boc-isoindoline acid **302** was completed in 6 steps from 2-bromobenzylamine hydrochloride **291** as part of a larger synthesis of dipeptides as ligands for the melanocortin subtype-4 receptor (Figure 4.5).[293]



Scheme 4.14 Comparison of methodology to access the isoindoline carboxylic acid derivative

Employing the newly developed domino Heck-aza-Michael methodology it was possible to access a similar tosyl-isoindoline acid **299** from 2-bromobenzylamine hydrochloride **291** in 84% yield over 2 steps. This allows for a much more efficient synthesis of substituted *N*-heterocycles without the need for lengthy and costly purification of intermediates, saving time, money and the subsequent generation of waste.

4.2.5 Summary

Following the successful development of a domino Heck-aza-Michael reaction for the synthesis of the tetrahydro-*β*-carbolines,[329] the scope of this new methodology was expanded to include the tetrahydroisoquinoline and isoindoline *N*-heterocyclic scaffolds. Unfortunately, attempts to also apply this methodology to the synthesis of both the *O*- and *S*-analogues of the tetrahydro-*β*-carbolines were not high yielding and more optimisation is required. For the benzofuran derivatives, the conditions trialled were not sufficient in producing the Heck adduct prior to intermolecular aza-Michael addition. While the domino reaction with the benzothiophene derivative appeared promising, an efficient synthesis of the domino precursor was not achieved.

The key considerations of the domino Heck-aza-Michael methodology were identified as (i) the relatively quick formation of the Heck adduct (controlled through appropriate selection of Pd catalyst) and (ii) the nucleophilicity of the tethered amine (mediated through careful selection of the protecting group, base and solvent).

In determining the appropriate conditions for the Heck reaction, a palladium catalyst was required that facilitated a fast, high-yielding reaction between the aryl halide and the alkene, in the presence of a mild base and relatively non-polar solvent. It is important the acrylate is consumed rapidly by the Heck process so that intermolecular aza-Michael reaction does not take place. For the Heck reaction at the indole-2-position, $Pd(PPh_3)_4$ afforded the highest yields. In the case of the benzyl- and phenethylamine aryl halides, the use of $Pd(OAc)_2/PPh_3$ proved optimal.

Most importantly, an appropriate base is required; one that is able to sufficiently promote aza-Michael reaction, but not to the extent that it occurs before a high concentration of the Heck adduct is realised. Indeed, the outcome of reactions that were repeated, varying only the base used, ranged from rapid intermolecular Michael reaction prior to the Heck reaction through to the desired domino Heck-aza-Michael process. For the synthesis of both the TH*β*Cs and tetrahydroisoquinolines, K_2CO_3 was required for a rapid cyclisation, however, in the case of the isoindolines, the new *N*-heterocycle formed in the presence of a milder amine base (either NEt_3 or Cy_2NMe).

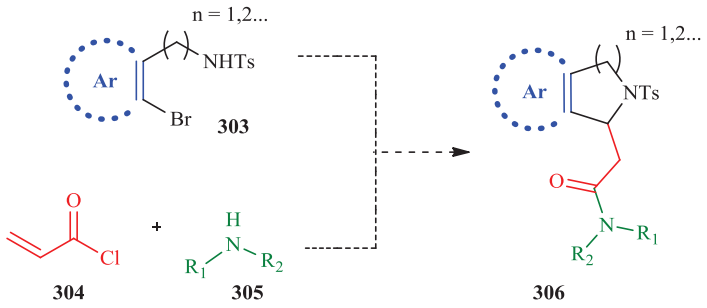
From the outset it was envisaged that reaction progress would be limited by (i) size of the *N*-heterocycle being formed and (ii) steric properties associated with the Heck reaction and subsequent Michael addition. If the steric bulk of a proximal sulfonamide (benzylamine *vs.* phenethylamine) was a critical factor, initial Heck reaction would be faster for formation of TH*β*Cs **249** and tetrahydroisoquinolines **252** over isoindoline **253**. Furthermore, for the 5 membered isoindoline series, a strained transition state in the Michael addition step may also hinder the progress of the domino reaction. Nevertheless, as little difference in the overall yields were observed for each of the domino processes studied herein, the role of ring size and steric properties appears to be minor.

In summary, a general approach to *N*-heterocycles using high yielding domino Heck-aza-Michael reactions to access C1-substituted tetrahydro-*β*-carbolines, tetrahydroisoquinolines and isoindolines have been successfully developed. These reactions employed mild conditions, readily available palladium catalysts and acrylates. The mild conditions described suggest this domino process may be applied to more complex substrates and possibly in key transformations in total syntheses. As indicated, the use of other highly active palladium catalysts may benefit the scope of this process and its functional group tolerance.

The expansion of the scope of these domino Heck-aza-Michael reactions to include tetrahydroisoquinolines and isoindolines resulted in a recent publication (see Appendix One).[396]

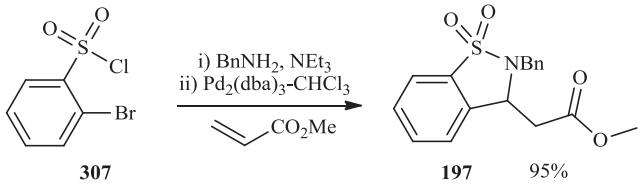
4.3 Multicomponent Domino Heck-aza-Michael Reactions

Of the domino Heck-aza-Michael reactions reported to date, including those investigated during this work, the alkene employed has been restricted to commercially available electron deficient terminal alkenes.[279-281, 283, 329] Therefore, it was envisaged that the scope of this domino Heck-aza-Michael methodology could be greatly improved if much more highly functionalised terminal alkenes were amenable to this process. Additionally, if the functionalised alkene was able to be synthesised in the same reaction from suitable starting materials prior to the domino reaction (for example acryloyl chloride (**304**) and an amine **305** – Scheme 4.15), a one-pot, three-component approach for the synthesis of more highly functionalised heterocycles **306** would then be possible.



Scheme 4.15 A three-component domino reaction approach to various *N*-heterocyclic amides

One pot, multicomponent processes, like domino reactions, are an efficient means of completing multiple synthetic steps without the need for purification of intermediates. Three-component domino Heck-aza-Michael reactions to date have involved variations in the domino precursor, that is, the first step of the multicomponent reaction was the preparation of the aryl-halide (Scheme 4.16).[279, 283, 397] In the reaction sequence developed by the group of Hanson, both alkyl and aryl amines that were employed in the initial coupling step with the sulfonyl chloride **307** proved successful.



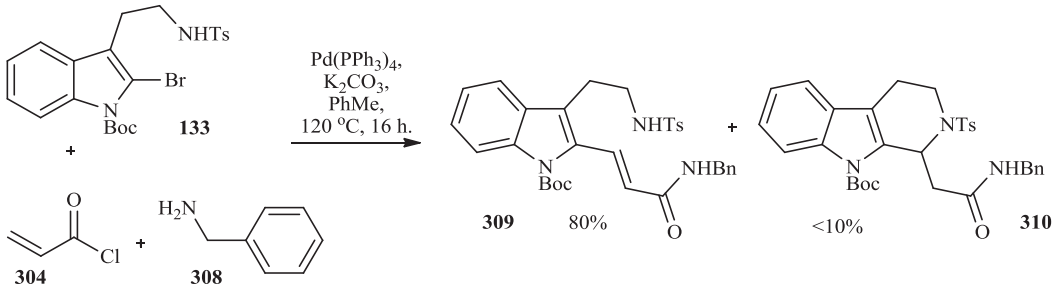
Scheme 4.16 A multicomponent domino Heck-aza-Michael reaction sequence where the aryl-halide is readily varied.

However, the electron deficient terminal alkene employed in these three-component domino reactions was limited to commercially available ester, carboxylic acid and ketone derivatives. The *in situ* generation of the functionalised alkene employed in domino Heck-aza-Michael processes has not been successfully developed.[279]

It was envisaged that by coupling acryloyl chloride (**304**) with a primary or secondary amine, a vast array of acrylamides would be produced, suitable for the domino Heck-aza-Michael reaction. If indeed acrylamide formation occurred under the same mildly basic conditions required for both the Heck and aza-Michael steps in this domino process, a sequential one-pot three-component domino Heck-aza-Michael reaction for the synthesis of amide substituted *N*-heterocycles was plausible.

Tetrahydro-β-carbolines

The first system investigated for the multicomponent domino Heck-aza-Michael process was the tetrahydro-*β*-carbolines. The requisite domino precursor was prepared in three steps from tryptamine as previously described (see Chapter Three). Initial investigations employed acryloyl chloride and benzylamine to afford the *N*-benzylacrylamide needed for the Heck reaction. The first reaction was carried out by adding acryloyl chloride (**304**) to a solution containing benzylamine (**308**) and K_2CO_3 in toluene. After stirring for one hour to allow sufficient time for acrylamide formation, the tosyl-2-bromotryptamine **133** and $Pd(PPh_3)_4$ were added and the reaction mixture was heated to 120 ^oC for 16 hours (Scheme 4.17).

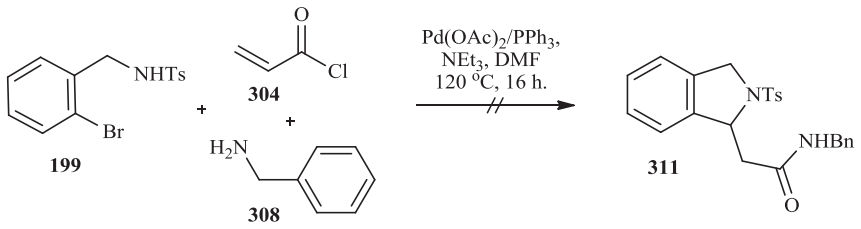


Scheme 4.17 Attempted multicomponent synthesis of tetrahydro-*β*-carbolines

Following a simple work up, analysis of the crude reaction mixture revealed that the major product from this reaction was in fact the Heck adduct **309** (isolated in 80% yield). A trace amount of the desired domino adduct **310** was observed in the ^1H NMR spectrum, but could not be separated from the other compounds present in the reaction mixture. As the Heck reaction was taking place in a good yield, it was known that acrylamide formation was successful. However, acrylamides are not as electron-deficient as acrylates, and following Heck reaction, aza-Michael addition did not occur. It was proposed that the electronic properties of the indole system were too unpredictable and as such, a simpler scaffold was investigated.

Isoindolines

The next system to be investigated in regards to the multicomponent approach to functionalised *N*-heterocycles was the isoindolines. In a similar fashion to that previously described for the tetrahydro-*β*-carbolines, the initial investigations were carried out using acryloyl chloride (**304**), benzylamine (**308**) and the 2-bromobenzylamine domino precursor **199**, under the conditions previously successful for the synthesis of isoindolines (Scheme 4.18).



Scheme 4.18 Attempted multicomponent synthesis of isoindolines

In this case, again only the Heck adduct was identified following analysis of the crude reaction mixture. The presence of the amide in the conjugated Michael acceptor, instead of the more electron-withdrawing ester alkenes, meant that aza-Michael addition did not proceed to form the desired isoindoline **311**. For previous cases employing the ester acrylates, the domino Heck-aza-Michael process occurred in excellent yields. However, as the acrylamides are typically not as inductively electron withdrawn as the esters, aza-Michael addition does not take place. These initial results once again confirmed how subtle electronic differences this time in the alkene used in the domino process can play a role in determining the success of *N*-heterocycle formation**.**

Tetrahydroisoquinolines

With the multicomponent approach to both the tetrahydro-*β*-carbolines and isoindolines proving unsuccessful, attention turned to the tetrahydroisoquinolines. The use of acrylamide for the previous domino Heck-aza-Michael reaction with this system was unsuccessful. Therefore, it was proposed that a multicomponent domino process would provide access to C1-acetamide tetrahydroisoquinolines similar to those used as potential pharmaceutical agents (Figure 4.8).[293, 398-402]

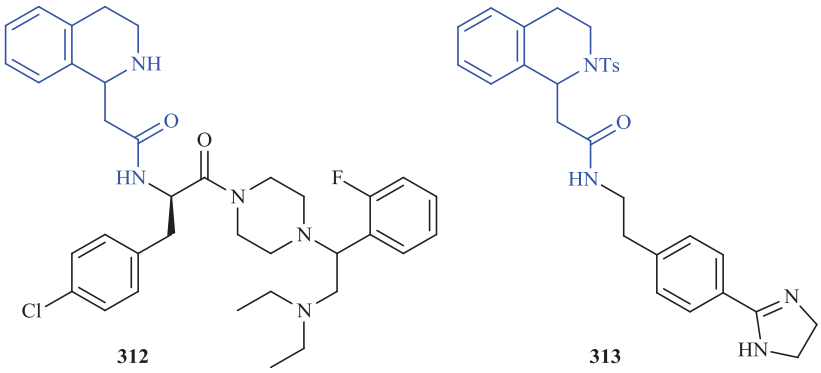
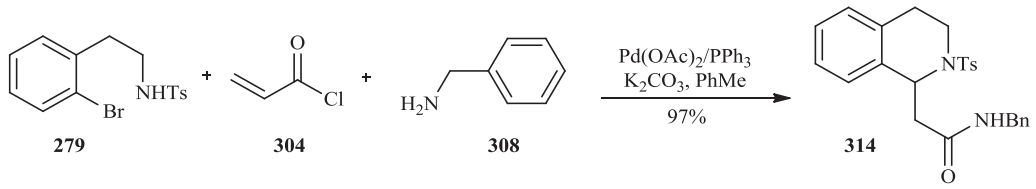


Figure 4.8 C1-acetamide tetrahydroisoquinoline medicinal chemistry agents

Benzylamine was again chosen as the amine substrate. This trial reaction involved the addition of acryloyl chloride (**304**) to a solution containing benzylamine (**308**), and potassium carbonate in toluene. After stirring at room temperature for one hour, the 2-bromophenethylsulfonamide **279** and $Pd(OAc)_2/PPh_3$ were added, and the resultant mixture heated to 120 ^oC for 16 hours (Scheme 4.19). A simple work up followed by flash chromatography afforded the desired tetrahydroisoquinoline **314** in an excellent yield of 97%.



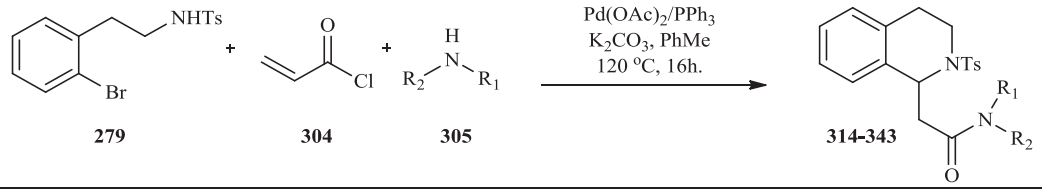
279 **304** **308** **314**

Scheme 4.19 Three-component synthesis of functionalised tetrahydroisoquinoline

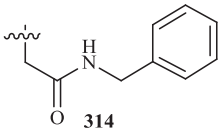
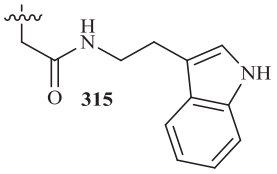
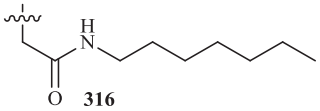
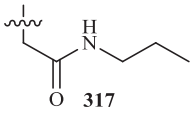
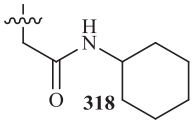
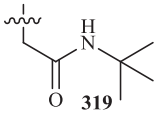
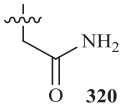
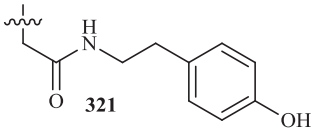
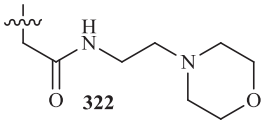
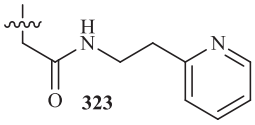
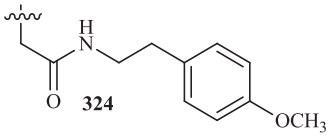
Following this initial success, a range of amines were subsequently used in this three-component domino Heck-aza-Michael reaction including alkyl primary amines (Table 4.6, entries 1-11), aryl amines (Table 4.6, entries 12-15), acyclic secondary amines (Table 4.6, entries 16-19), cyclic secondary amines (Table 4.6, entries 20-25), and amino acids (Table 4.6, entries 26-30).

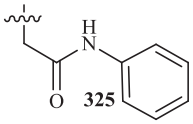
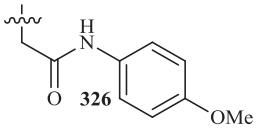
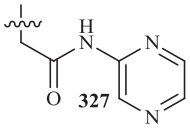
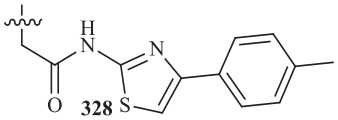
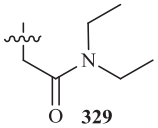
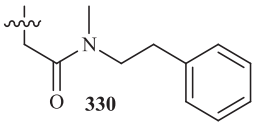
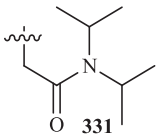
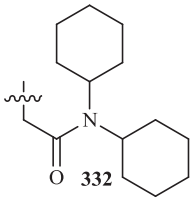
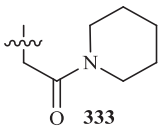
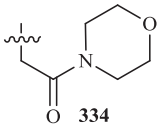
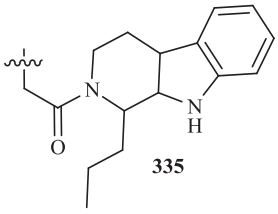
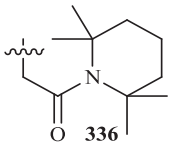
The first attempt with tryptamine (**2**) only resulted in trace amounts of the desired tetrahydroisoquinoline **315**. This lack of reactivity appeared to be due to the insolubility of either the initial amine or corresponding acrylamide in toluene. To overcome this, a few drops of DMF were added to the reaction mixture following the addition of the amine. This approach quickly proved successful, with the second attempt using tryptamine affording tetrahydroisoquinoline **315** in 92% yield (entry 2, Table 4.6). During the elaboration of the series of C1-amide substituted tetrahydroisoquinolines, a number of other amines also required the addition of DMF to improve their reaction mixture solubility.

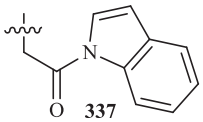
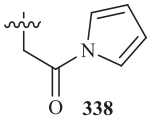
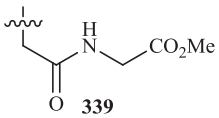
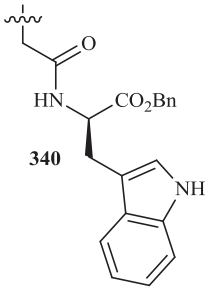
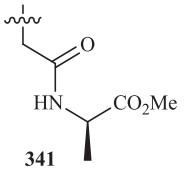
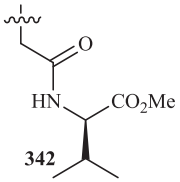
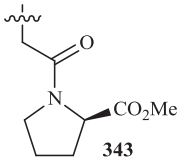
Table 4.6. Formation of functionalised tetrahydroisoquinolines using a three-component domino Heck-aza-Michael reaction



279 **304** **305** **314-343**

Entry	Amine	R	Yield (%)
1	benzylamine	 **314**	97
2	tryptamine [a]	 **315**	92
3	*n*-heptylamine	 **316**	89
4	propylamine	 **317**	42
5	cyclohexylamine	 **318**	77
6	*tert*-butylamine	 **319**	93
7	2-nitrobenzylamine hydrochloride [a]	 **320**	32 [b]
8	tyramine	 **321**	0 [c]
9	4-(2-aminoethyl) morpholine	 **322**	0 [d]
10	2-(2-aminoethyl) pyridine	 **323**	NR
11	4-methoxy phenethylamine	 **324**	0 [c]

Entry	Amine	R	Isolated Yield (%)
12	aniline	 **325**	83
13	*p*-anisidine	 **326**	79
14	2-aminopyrazine [a]	 **327**	28
15	2-(amino)-4-(*p*-tolyl)-thiazole	 **328**	NR
16	diethylamine	 **329**	57
17	*N*-methyl phenethylamine	 **330**	0 [e]
18	diisopropylamine	 **331**	NR
19	*N,N*-dicyclohexylamine	 **332**	NR
20	piperidine	 **333**	88
21	morpholine	 **334**	78
22	THβC	 **335**	NR
23	2,2,6,6-tetramethylpiperidine	 **336**	NR

Entry	Amine	R	Isolated Yield (%)
24	indole	 **337**	NR
25	pyrrole	 **338**	NR
26	glycine methyl ester hydrochloride [a]	 **339**	72
27	L-tryptophan benzyl ester hydrochloride [a]	 **340**	96 [f]
28	L-alanine methyl ester hydrochloride [a]	 **341**	54 [f]
29	L-valine methyl ester hydrochloride	 **342**	73 [g]
30	L-proline methyl ester hydrochloride	 **343**	0 [f]

a A few drops of DMF were added to aid in amine solubility in the reaction mixture

b *In situ* deprotection of the 2-nitrobenzyl group occurred during reaction and the product isolated was the tetrahydroisoquinoline acetamide in 32% yield.

c The Heck adduct was isolated

d Crude NMR indicated the product had formed in excellent yield but desired product was not isolated following column chromatography.

e The product formed from this reaction contains a di-substituted amide in which the two substituents are not equivalent which resulted in an inseparable mixture of regioisomers.

f The diastereomeric ratio was determined to be 1:1.

g The diastereomeric ratio in this case was 3:7 (determined by chiral HPLC).

Reaction was performed by the addition of acryloyl chloride (1.2 eq) to a sealed tube containing the amine (1.2 eq), base (3.0 eq.) and solvent (4 mL). After stirring for 1 hr. the aryl-halide (1.0 eq.), and palladium catalyst (10 mol%) were added and the reaction mixture heated to 120 ^{o}C for 16 h.

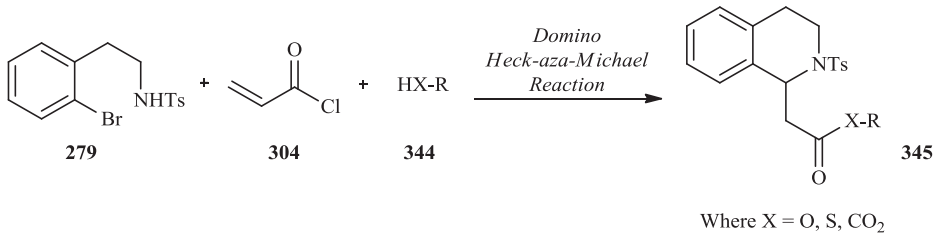
The one-pot, three-component domino Heck-aza-Michael process proved to be quite general, with high yields (up to 97%) of the C1-acetamide tetrahydroisoquinolines observed when alkyl amines, aryl amines, secondary amines and amino acids were used. The only

limiting factor in this process appeared to be solubility of the amine and corresponding acrylamide, rectified by the use of DMF as a co-solvent

For the domino process employing 2-nitrobenzylamine hydrochloride (Table 4.6, entry 7), the *in situ* deprotection of the 2-nitrobenzyl group to afford tetrahydroisoquinoline **320** was observed. The 2-nitrobenzyl group has been reported to be photolytically cleaved in polar solvents (typically 254-365nm).[403-405] As this reaction was carried out in toluene in a dark fume hood, deprotection of the 2-nitrobenzyl group under our reaction conditions was unexpected. In this instance, the basic conditions and high temperatures employed in this reaction sequence proved adequate in cleaving the 2-nitrobenzyl group.

Multicomponent reactions using a chiral amino acid precursor (Table 4.6, entries 27-30) were carried out to identify whether a stereoselective variant of this one-pot process was achievable. The introduction of a stereogenic centre at the C1-position of the newly formed tetrahydroisoquinoline was determined by both ^{1}H and ^{13}C NMR spectroscopy. Unfortunately, when L-tryptophan and L-alanine were used, a 1:1 mixture of diastereomers were produced. As such, in these cases the presence of a stereocentre in the acrylamide moiety had no significant induction effects on stereochemistry at the C1-position. However, in the case of the L-valine derivative **342** (Table 4.6, entry 29), the product was present as a 3:7 mixture of diastereomers. In this case, the L-valine moiety contained in the acrylamide induced some diastereo-discrimination (40% *de*) at the C1-position of the newly formed tetrahydroisoquinoline (the asymmetric domino Heck-aza-Michael reaction was further pursued in Section 4.4.2).

It was also envisaged that this domino process could be applied to the synthesis of esters, thioesters and anhydrides (Scheme 4.20). However, initial investigations into the formation of the necessary alkene revealed that these processes were not as facile as acrylamide formation. Due to time constraints this avenue of investigation was not pursued.



Scheme 4.20 This multicomponent process in the synthesis of ester, thioester and anhydride tethered tetrahydroisoquinolines

In summary, a domino Heck-aza-Michael process was developed where in one-pot, the electron deficient alkene generated from reaction between acryloyl chloride and an amine, underwent domino Heck-aza-Michael reaction to afford a series of C1-acetamide tetrahydroisoquinolines. This is the first example of a domino Heck-aza-Michael reaction that allows the electron deficient terminal alkene to be readily varied in a one-pot process. This multicomponent domino reaction proved to be quite general, using a range of primary and secondary amines to afford functionalised tetrahydroisoquinolines, in moderate to excellent yields (28-97%). This one pot process, when employed in a medicinal chemistry or combinatorial setting would facilitate the rapid generation of compound libraries.

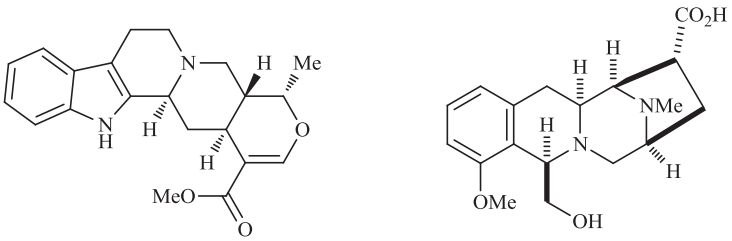
4.4 Asymmetric Domino Heck-aza-Michael Reactions

Chirality is a very important concept in chemistry, and a majority of the biological molecules found in nature occur as a single enantiomer. This property of molecules has also proven important in a medicinal chemistry setting, where many receptors discriminate between molecules to a degree where only one enantiomer induces activity. Approximately 70% of all pharmaceuticals currently available are enantiopure. The chirality of pharmaceuticals offers a number of advantages for example the administration of enantiomerically pure drugs is often through a decreased dosage to the racemic mixture, lowering the load on metabolism and an enhanced activity. Additionally, the use of chiral drugs results in increased specificity, which minimises the risk of side effects and possible cytotoxicity caused by the 'wrong' enantiomer. (for example the thalidomide tragedy may have been avoided if only the *R*-(+)-thalidomide was used, reportedly responsible for sedative effects whereas *S*-(-)-thalidomide and its derivatives were reported to be teratogenic).[406]

As such, the stereoselective synthesis of molecules has become a major focus of modern organic chemistry. A number of techniques have emerged to access compounds as their single enantiomer for example asymmetric epoxidation, hydrogenation and alkylation.[407-413‡‡] However, the resolution of a mixture of enantiomers can often be the cheapest, most practical way of obtaining enantiomerically pure material, although as only one enantiomer is generally required, a large amount of waste is generated from this process. Alternatively, the use of relatively cheap chiral starting materials from the chiral pool or chiral catalysts (organocatalysts or metal-based catalysts) can also result in the synthesis of one major stereoisomer.[415-416]

‡‡ The Nobel Prize in Chemistry in 2001 was awarded to W. S. Knowles, R. Noyori and K. B. Sharpless for the development of chirally catalysed hydrogenation and oxidation reactions.[414]

In the current context, a majority of the biologically active natural products containing the *N*-heterocyclic scaffolds have a stereocentre at the C1-position (Figure 4.9). As such, it would be useful if the methodology used to synthesise these *N*-heterocyclic systems could be modified such that only one enantiomer was produced.



Ajmalicine **8** *Quinocarcinol* **277**

Figure 4.9 Natural products containing a stereocentre at the C1-position of the *N*-heterocycle

Thus far, the focus of this project has been on new methodology for the construction of *N*-heterocyclic systems. With this accomplished, the next challenge lay in enforcing stereochemical bias during *N*-heterocycle formation. A number of synthetic strategies were envisaged for controlling the stereochemistry at the C1-position during the domino Heck-aza-Michael process, including the use of chiral catalysis and chiral amines and alkenes (Figure 4.10). Each of these approaches in the pursuit of an asymmetric domino Heck-aza-Michael reaction are discussed in detail in the following sections.

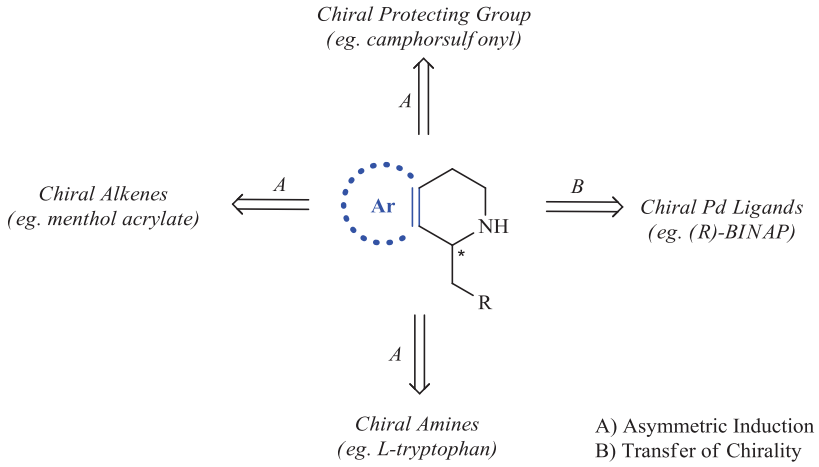


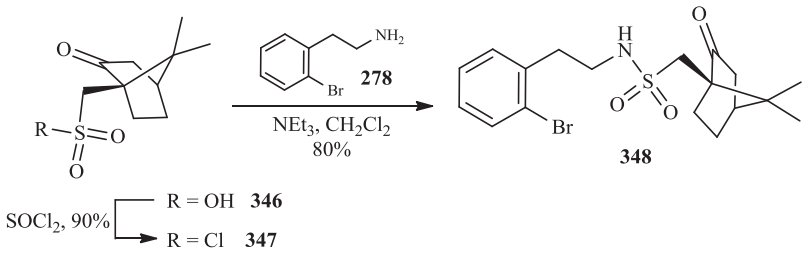
Figure 4.10 Four possible approaches were considered in the development of a stereoselective domino Heck-aza-Michael reaction.

4.4.1 Chiral Protecting Groups

The first approach for introducing an asymmetric centre at C1-position of the newly formed *N*-heterocycle was through the use of a chiral protecting group. The theory behind this

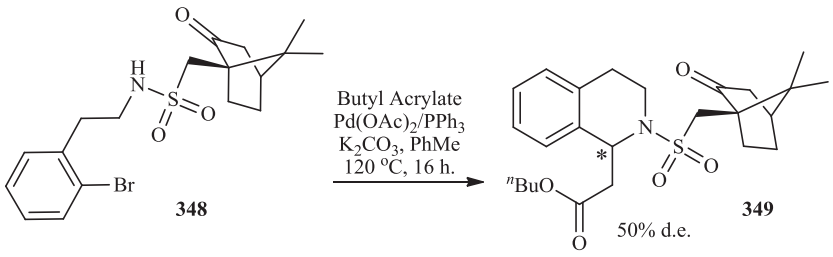
approach is that following Heck reaction, the bulky chiral protecting group on the nitrogen undergoing 1,4-addition would permit aza-Michael addition to occur preferentially from only one side of the double bond.

As sulfonyl protecting groups had performed best for the previous domino processes investigated, the (1*R*)-(-)-camphorsulfonyl group was chosen for this study. The sulfonic acid **346** was converted to the sulfonyl chloride **347** using thionyl chloride and then reacted with the amine **278** to afford the domino precursor **348** (Scheme 4.21).[417]



Scheme 4.21 The preparation of the (1*R*)-(-)-camphorsulfonyl domino substrate

With the requisite chiral precursor **348** in hand, the domino reaction was attempted using the same conditions previously identified for the formation of tetrahydroisoquinolines (Scheme 4.22).



Scheme 4.22 The asymmetric domino Heck-aza-Michael reaction using a chiral protecting group.

Following a simple work up, analysis of the NMR spectrum revealed that heterocycle formation had in fact taken place, with the characteristic C1-proton resonance detected at δ 5.40 ppm. The presence of two distinct C1-proton resonances in this region (Figure 4.11 - δ 5.40-5.45) indicated that the reaction had resulted in the formation of two diastereomers (in a ratio of 1:3 – 50% *de*).

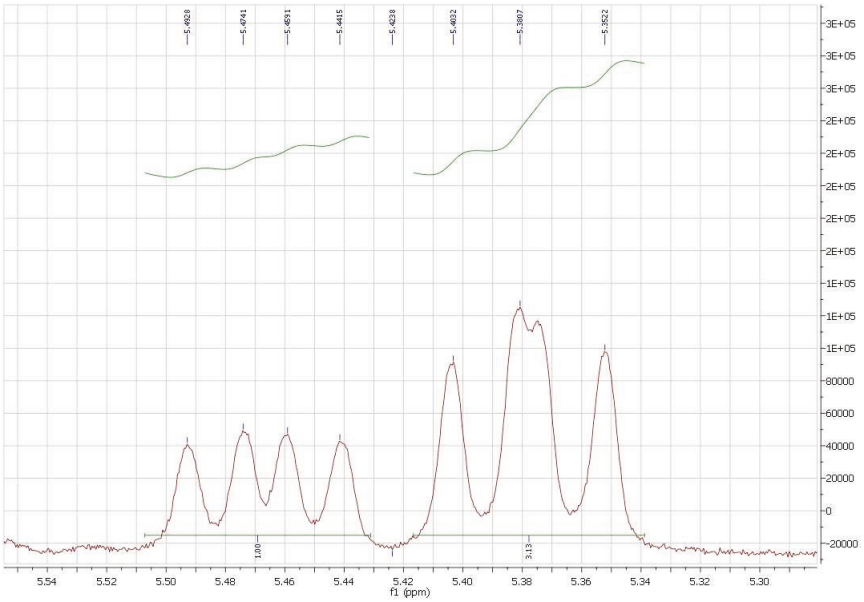
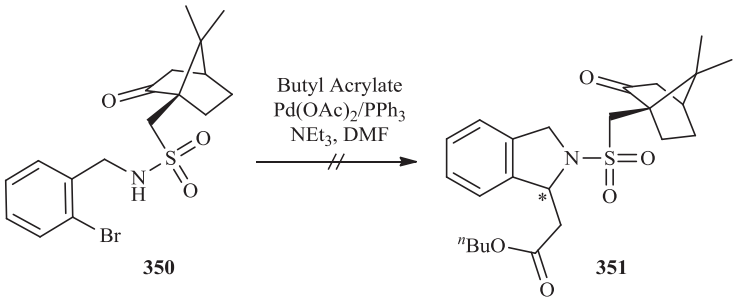


Figure 4.11 The presence of diastereomers (in a ratio of 1:3) was detected due to the two distinct C1-proton resonances

Attempts to separate the diastereomers and confirm which stereoisomer was the major one formed during the reaction proved unsuccessful, and a clean NMR spectrum of the major diastereomer was not obtained. However, mass spectrometry confirmed the desired product **349** was present in the reaction mixture.

A similar attempt was made using the chiral protecting group to access isoindolines in a stereoselective fashion. In this example, the 2-bromobenzylamine was treated with sulfonyl chloride **347** in a solution containing triethylamine and CH_2Cl_2 to prepare the domino precursor **350** in 83% yield. Following this, the domino reaction was attempted using the conditions previously identified for isoindoline formation (Scheme 4.23).



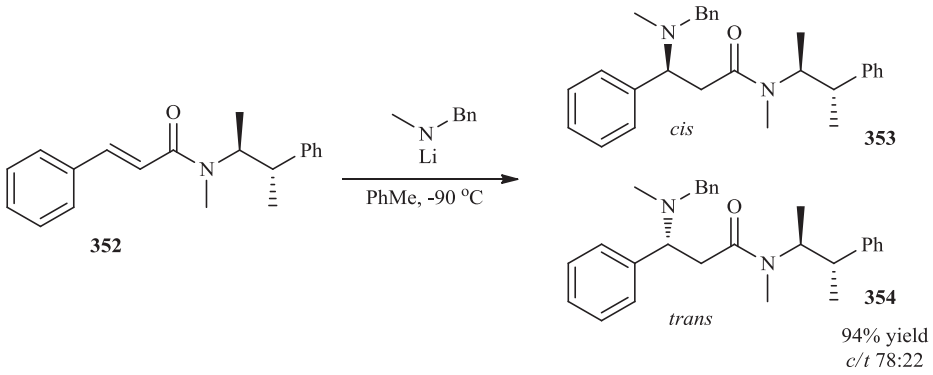
Scheme 4.23 Attempted stereoselective synthesis of isoindolines using a chiral protecting group

Unfortunately, analysis of the crude reaction mixture by NMR spectroscopy indicated no domino Heck-aza-Michael reaction had occurred. These results once again confirm how

subtle electronic differences, this time in the sulfonamide moiety (when compared to the tosyl derivative) involved in the domino process can play a role in determining the success of *N*-heterocycle formation.

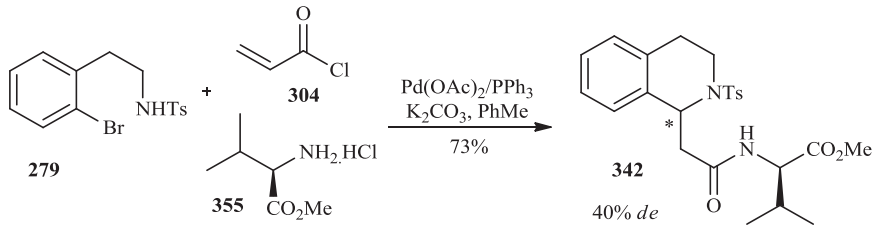
4.4.2 Chiral Alkenes

Conjugated Michael acceptors containing chiral auxiliaries have been successfully employed in asymmetric synthesis, and facilitate the introduction of a stereocentre during 1,4-addition by an achiral amine (For example Scheme 4.24).[298, 415, 418-422]



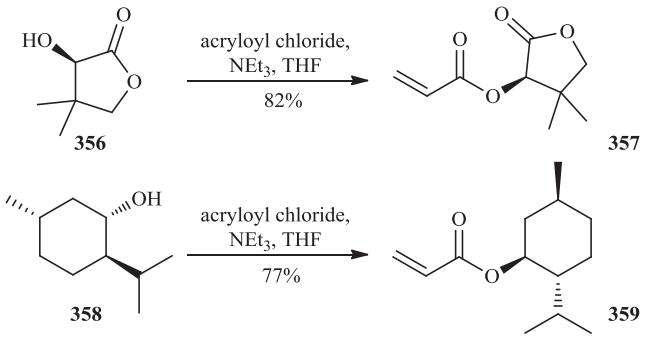
Scheme 4.24 Asymmetric aza-Michael addition in the presence of a chiral acrylamide[421]

During the multicomponent synthesis of functionalised tetrahydroisoquinolines (see section 4.3) it was observed that the valine acrylamide lead to a 3:7 mixture of diastereomers (40% *de*) following the domino Heck-aza-Michael process (Scheme 4.25).



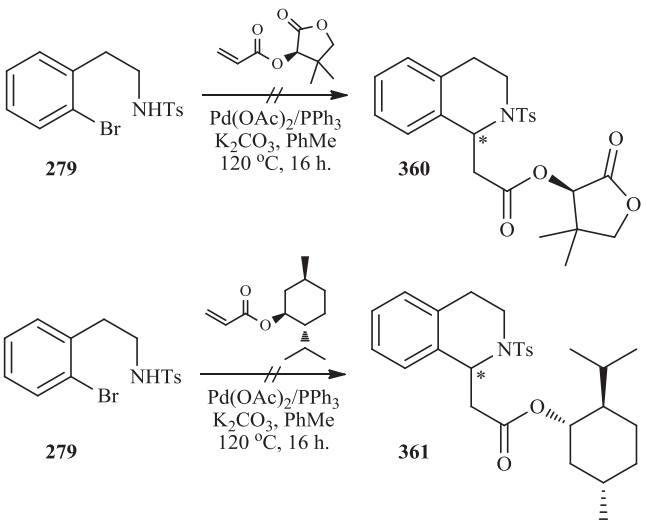
Scheme 4.25 The multicomponent asymmetric synthesis of tetrahydroisoquinolines

It was envisaged that chiral alkenes could induce an even greater degree of stereoselectivity during the domino Heck-aza-Michael process. To this end, (*R*)-(-)-pantolactone acrylate **357** and (1*S*,2*R*,5*S*)-(+)-menthol acrylate **359** were prepared through reaction of acryloyl chloride (**304**) with the corresponding alcohol (Scheme 4.26).[423-424]



Scheme 4.26 The preparation of chiral acrylates

With the chiral acrylates in hand, the 2-bromophenethylamine substrate **297** was subject to the previously identified domino conditions for the synthesis of tetrahydroisoquinolines. It was proposed that the chiral auxiliary now present would induce aza-Michael addition preferentially from one side of the double bond (Scheme 4.27).



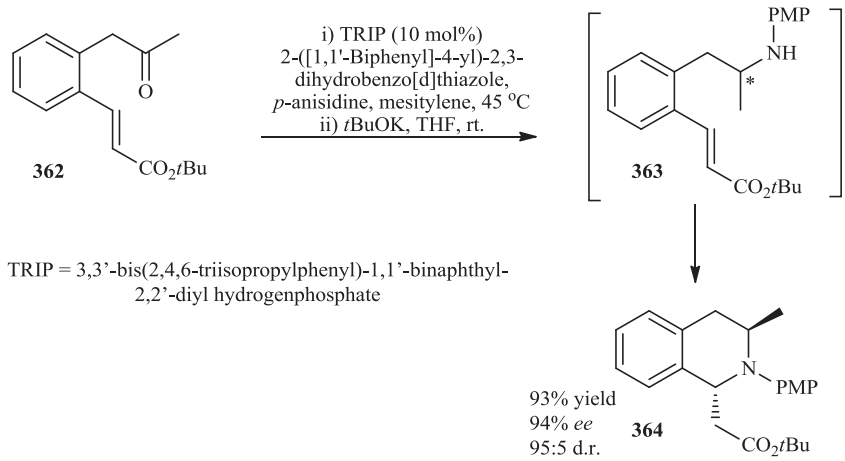
Scheme 4.27 Attempted stereoselective synthesis of tetrahydroisoquinolines using chiral alkenes

The attempted stereoselective domino Heck-aza-Michael reaction using both the menthol and pantolactone acrylates did not result in the formation of the desired heterocycles. Attempts to induce a stereocentre at the C1-position of both the isoindoline and tetrahydro-*β*-carboline ring systems, using these chiral alkenes also proved unsuccessful.

As both the chiral protecting group and chiral alkene strategies had failed to provide a general and efficient stereoselective synthesis of the desired *N*-heterocyclic scaffolds, attention turned to the use of chiral amine starting materials.

4.4.3 Chiral Amines

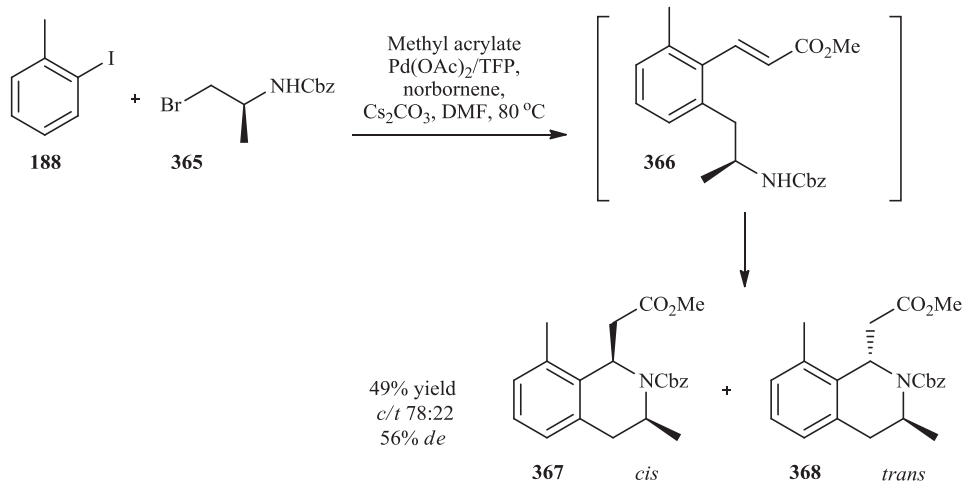
In recent years, chiral amines have been used to great effect in asymmetric synthesis, especially in the case of the stereoselective aza-Michael addition.[395, 425-432] The most common amines used for these asymmetric aza-Michael additions contain a chiral carbon alpha to the amine. One example of this was recently published by Enders *et al.* (Scheme 4.28).



Scheme 4.28 The Enders stereoselective synthesis of tetrahydroisoquinolines[426]

Formation of the imine from reaction of the methyl ketone with *p*-anisidine occurred first, followed by the enantioselective reductive amination in the presence of List's TRIP catalyst (3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2-diylhydrogenphosphate)[433] and a biphenyl-substituted benzothiazole to afford the chiral amine **363**. The tetrahydroisoquinoline **364** is then formed by asymmetric aza-Michael addition, furnishing the *trans*-isomer as the major product in excellent yield (in a diastereomeric ratio of 95:5). A similar process was also applied to the stereoselective synthesis of tetrahydro-*β*-carboline to great effect (85% yield, 94% *ee*, 95:5 d.r.).[426]

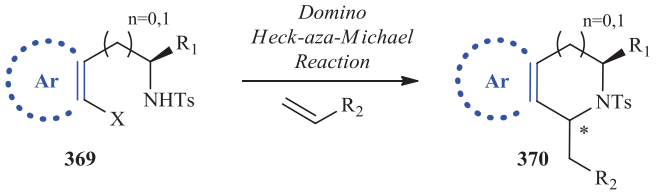
In terms of asymmetric domino Heck-aza-Michael reactions, the stereoselective synthesis of tetrahydroisoquinolines using a three-component process was reported in 2007 by Ferracioli *et al.* (Scheme 4.29).



Scheme 4.29 The Ferracioli three-component process involving an asymmetric domino Heck-aza-Michael reaction

Following *ortho*-vinylation to install the amine tether, Heck reaction and subsequent asymmetric aza-Michael addition afforded the tetrahydroisoquinoline in 49% yield (diastereomeric ratio *cis/trans* 78:22). Of particular interest in this case is formation of the *cis*-isomer **367** as the major isomer during the reaction process, whereas for the aforementioned reductive amination/aza-Michael addition reaction sequence (Scheme 4.28), the *trans*-isomer **364** was the major product. Although this three-component reaction proves that an asymmetric domino Heck-aza-Michael reaction is possible using chiral amine substrates, the process suffers from low overall yields and only moderate diastereoselectivity (56% *de*).

The introduction of a stereocentre at the 1-position of the *N*-heterocycles employing naturally occurring amino acids was investigated, with the hope of increasing both the reaction yield and diastereoselectivity compared to the Ferracioli asymmetric synthesis (Scheme 4.30). At this point it was unknown which diastereomer would be the major one formed during the reaction process, as both the Enders and Ferracioli synthesis (employing a similar asymmetric aza-Michael addition) reported the opposite major stereoisomer.

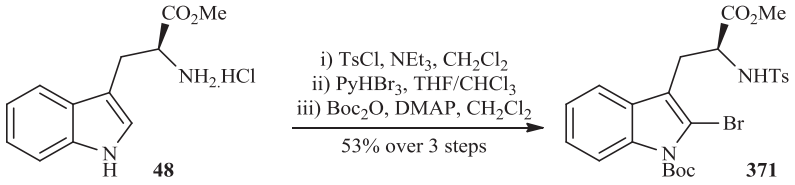


Scheme 4.30 The proposed stereoselective domino Heck-aza-Michael reaction employing chiral amine substrates

Tetrahydro-β-carbolines

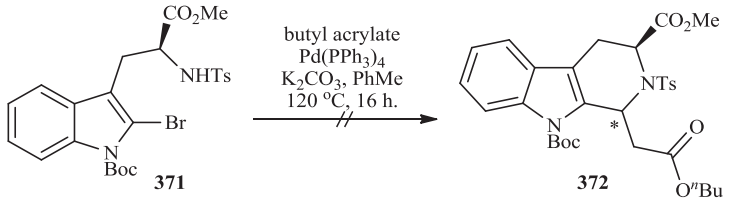
The introduction of a stereocentre at the C1-position of the tetrahydro-*β*-carboline, using tryptophan with a protected carboxylic acid moiety, has been employed in the Pictet-Spengler reaction.[35, 246, 434-436] Through the use of L-tryptophan instead of tryptamine for the domino Heck-aza-Michael reaction, it was expected the stereocentre present would induce specific stereochemistry at the C1-position of the TH*β*C formed.

The N_{10}-amine of L-tryptophan methyl ester hydrochloride (**48**) was protected with the tosyl group (88% yield), with subsequent bromination of the indole-2-position to afford the 2-bromoindole in yield of 69%. The indole nitrogen was then protected with the Boc group in an excellent yield (87%) to afford the domino precursor **371** (Scheme 4.31).



Scheme 4.31 Preparation of the domino substrate for the stereoselective synthesis of tetrahydro-*β*-carbolines from tryptophan (major isomer shown)

The only product isolated from the reaction to protect the indole-nitrogen was the mono-protected compound as desired. No side reaction at the sulfonamide was observed as in previous cases (Scheme 2.6), indicating that the sulfonamide of the tryptophan was not as nucleophilic as that of the protected tryptamine **132**. This was quickly confirmed when 2-bromotryptophan **371** was subject to the previously identified domino Heck-aza-Michael conditions.

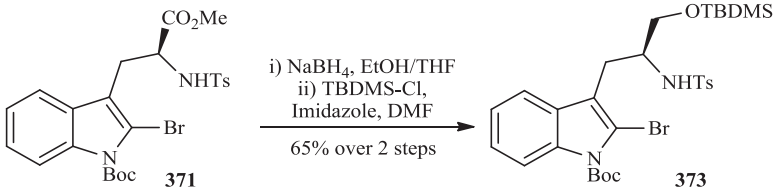


Scheme 4.32 Attempted asymmetric domino Heck-aza-Michael reaction

Following a simple work up, analysis of the crude product reaction mixture indicated that only Heck reaction had occurred (identifiable by the alkene proton resonances present as well as the sulfonamide proton resonance still clearly visible in the ^{1}H NMR spectrum), and no intramolecular aza-Michael adduct was observed. The methyl ester in close proximity to

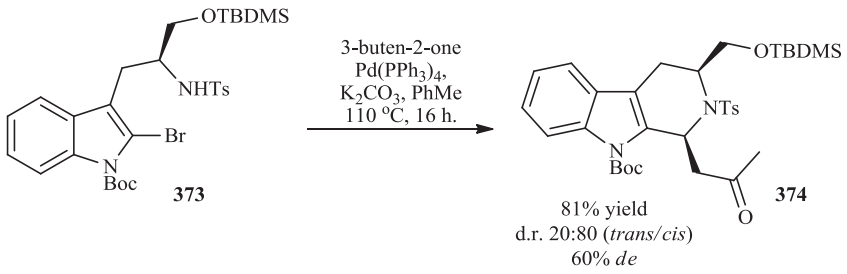
the sulfonamide was inductively drawing electron density away from the sulfonamide, making it much less nucleophilic than in the case of tryptamine, preventing aza-Michael addition to form the new heterocycle.

In an effort to tune the nucleophilicity of N_{10}-amine of tryptophan,[§§] a slight modification to the domino substrate was proposed. By reducing the ester to the corresponding alcohol, followed by conversion to the silyl-ether, the nucleophilicity of the amine should become similar to that of the tryptamine-sulfonamide **133**, whilst preserving the requisite chirality (Scheme 4.33). In fact, the additional bulk of the *tert*-butyldimethylsilyl ether should further enhance the stereoselectivity of this domino process.



Scheme 4.33 Modification of the domino precursor

The methyl ester **371** was reduced to the corresponding alcohol, using sodium borohydride in a solution of THF/ethanol using literature protocol, without affecting the tosyl, bromo, or Boc groups.[437] The success of this reaction was confirmed by the loss of the methyl ester proton resonance in the ^{1}H NMR spectrum, as well as the addition of the CH_2 and OH proton resonances. The alcohol was then converted to the silyl ether **373** through reaction with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole (in 65% yield over the 2 steps from the methyl ester).[264, 438-439] With the modified domino substrate **373** in hand, the asymmetric domino process was again attempted, this time using 3-buten-2-one with the previously identified domino conditions (Scheme 4.34).



Scheme 4.34 The asymmetric domino Heck-aza-Michael reaction for the synthesis of C1-substituted tetrahydro-*β*-carbolines

[§§] Previous studies (see Section 3.2.3) had discounted the use of stronger bases and more polar solvents for the domino process, as intermolecular aza-Michael addition occurred before Heck reaction.

Following a simple work up, the crude product was purified by column chromatography to afford the desired tetrahydro-*β*-carboline ketone derivative **374** in 81% yield as an inseparable mixture of diastereomers (Scheme 4.34). The diastereomeric ratio of the product was confirmed following analysis by chiral HPLC (60% *de*). The major product formed during this domino process was the *cis*-isomer, determined using Nuclear Overhauser effect (NOE) NMR experiments, with the through space interaction of both the C1- and C3-protons with the aromatic proton of the tosyl group identified, an interaction which can only be conceived when the molecule is in the *cis*-conformation (Figure 4.12).

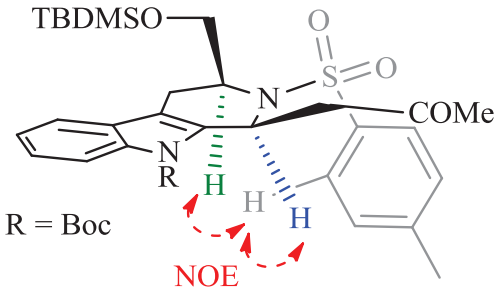


Figure 4.12 The NOE NMR experiments confirmed the *cis*-isomer was the major diastereomer formed during the tetrahydro-*β*-carboline asymmetric domino process

The reaction was repeated at a range of temperatures, however, degradation of the starting material occurred above 120 ^{o}C, and reducing the reaction temperature lead to formation of only the Heck adduct. Further attempts to expand the scope of this asymmetric domino process using additional alkenes (including butyl acrylate, methyl acrylate and acrylonitrile) for the synthesis of 1,3-disubstituted tetrahydro-*β*-carbolines proved unsuccessful, with only the Heck adduct identified following each reaction. These results once again confirm how subtle electronic differences this time in the alkene and sulfonamide substrates can play a role in determining the success of *N*-heterocycle formation**.**

With an asymmetric domino Heck-aza-Michael process developed for the synthesis of the 1,3-disubsituted tetrahydro-*β*-carboline, attention turned to the two other *N*-heterocyclic systems successfully accessed using domino Heck-aza-Michael processes during this research project, namely the tetrahydroisoquinolines and isoindolines.

Tetrahydroisoquinolines

As the requisite 2-halophenylalanine derivatives were relatively expensive and not readily available, the preparation of such compounds was investigated. The *ortho*-iodination of the L-phenylalanine has been reported by Barluenga to occur in good yield and excellent selectivity (>95% conversion, 10:1, *ortho*:*para*-iodinated product).[440] However, as this

methodology cannot be applied to the synthesis of the *ortho*-halogenated phenylglycine derivative (to be used to investigate the asymmetric synthesis of isoindolines), a more general method to *ortho*-halogenate the amino acids required for this investigation was sought.

Palladacycles have attracted a large amount of interest recently as they have shown great potential as both catalysts and medicinal chemistry agents.[195, 441] The development of palladacycle catalysts (usually as a source of highly active Pd(0), for example the Herrmann-Beller palladacycle) has facilitated the catalysis of a number of synthetic transformations.[162, 195, 442-443] Palladacycles have also found use as medicinal chemistry agents, showing activity as both cytotoxic agents and cathepsin B inhibitors, an enzyme thought to be involved with a number of cancer related events.[444-447] ***

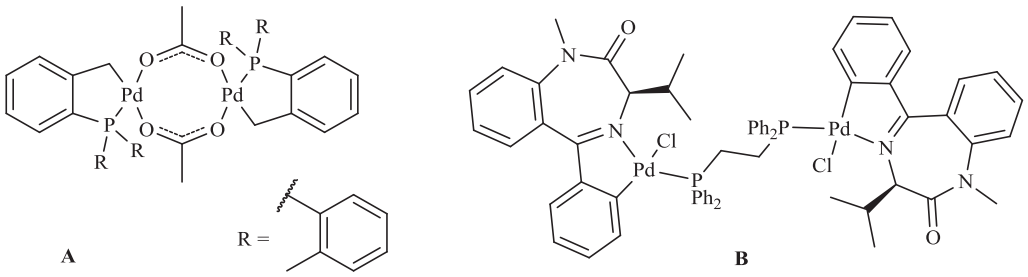
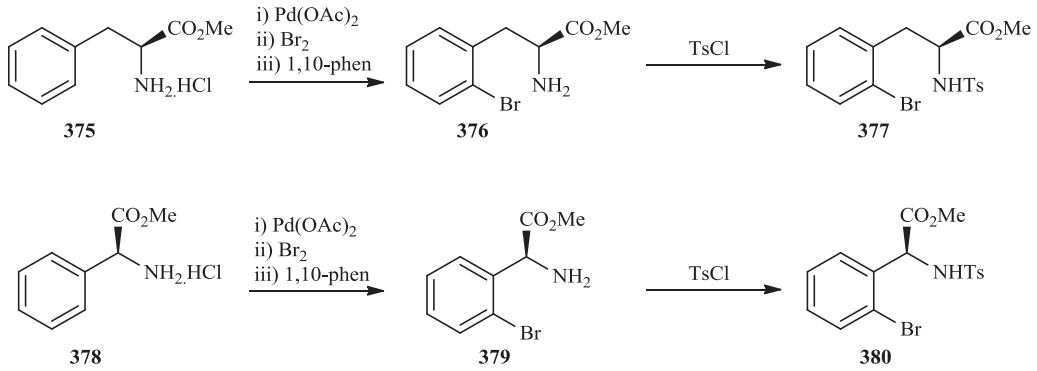


Figure 4.13 The Herrmann-Beller palladacycle (A) and a palladacycle found to exhibit cytotoxic effects (B)

Traditionally, palladacycles were only isolated when a tertiary amine was employed.[448-449] However, in recent years, the *ortho*-palladation of both primary and secondary amines has been reported.[134, 450-458] This has allowed the development of several protocols for functionalising aryl-amines *via* palladacycle intermediates, including *ortho*-halogenation.[134-135, 246, 452, 454, 459]

The *ortho*-halogenation of phenethylamines, *via* a palladacycle intermediate was recently published by Vicente.[452] In a similar fashion, the *ortho*-halogenation of phenylglycine derivatives has also been reported to occur, utilising palladacycle intermediates.[460] As such, the domino substrates for the synthesis of tetrahydroisoquinolines and isoindolines could both be prepared following *ortho*-palladation of the necessary amino acid derivatives (Scheme 4.35).

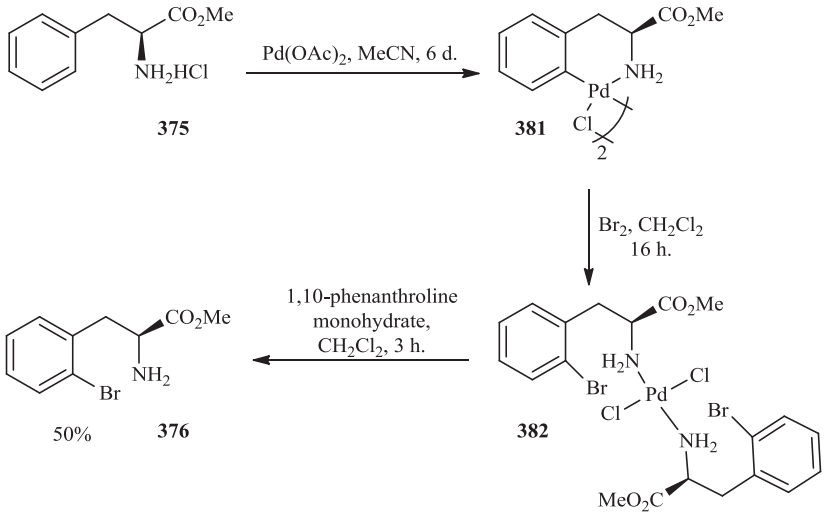
*** For a comprehensive review of palladacycles refer to *The potential of palladacycles: More than just precatalysts.* (Chemical Reviews, **2005**, 105, (6), 2527-2571)[441] and *Palladacycles: Synthesis, Characterisation and Applications* (Dupont, J.; Pfeffer, M., Wiley-VCH Verlag GmbH & Co.: Weinheim, 2008).[447]



Scheme 4.35 The proposed synthesis of the domino precursors, with *ortho*-halogenation *via* a palladacycle intermediate

The palladacycle methodology allows for both iodination and bromination of the *ortho*-position of appropriate amino acids (**375** and **378**), however as the domino Heck-aza-Michael process performed well previously for the 2-bromoarylamines, at this point of the investigation, bromination was favoured.

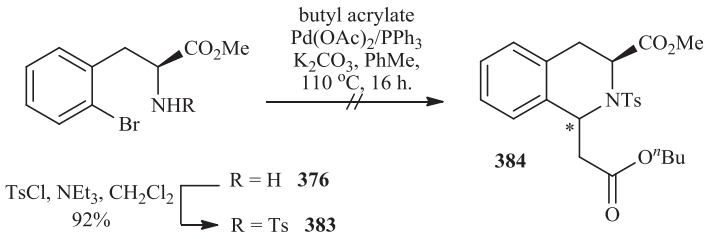
In this study, the *ortho*-bromination of L-phenylalanine **375** was carried out in three steps using the protocol described by Vicente.[452] The initial formation of the palladacycle was accomplished by reacting L-phenylalanine methyl ester hydrochloride (**378**) with one equivalent of palladium acetate in acetonitrile for 6 days (Scheme 4.36). *Ortho*-bromination of the L-phenylalanine was then readily accomplished in two steps by (i) reaction of the palladacycle **381** with bromine, and then (ii) reaction with 1,10-phenanthroline (which chelates to the palladium, resulting in the formation of the bright yellow $PdBr_2$(Phen) complex).[452]



Scheme 4.36 *Ortho*-bromination of L-phenylalanine methyl ester

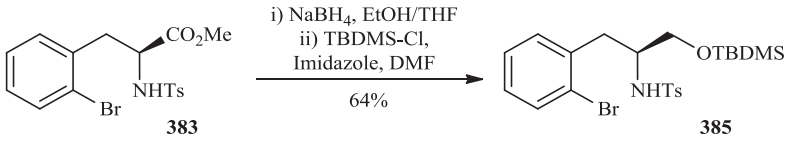
After a simple work, up the L-2-bromophenylalanine methyl ester **376** was isolated in 50% yield over three steps (Scheme 4.36). The aryl-halide was fully characterised by NMR spectroscopy and mass spectrometry, with the presence of only four aromatic proton resonances in the ^{1}H NMR spectrum confirming bromination and the presence of the free amine proton resonance confirming palladium decoordination.

With the L-2-bromophenylalanine **376** in hand the free amine was protected with the tosyl group (found optimal for previous domino reactions) in 92% yield, and the domino substrate **383** subjected to the previously identified domino conditions for tetrahydroisoquinoline synthesis (Scheme 4.37).



Scheme 4.37 Attempted stereoselective synthesis of 1,3-disubstituted tetrahydroisoquinolines

Once again, the formation of the chiral tetrahydroisoquinoline scaffold **384** did not proceed in the presence of the methyl ester. Using the same approach applied to the tetrahydro-*β*-carboline stereoselective synthesis, the domino substrate was modified with the methyl ester **383** reduced to the corresponding alcohol using $NaBH_4$, and was subsequently converted to the silyl ether **385** upon reaction with TBDMS-Cl (Scheme 4.38)

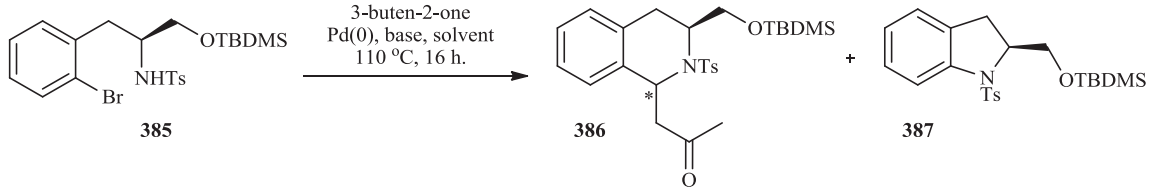


Scheme 4.38 Modification of the domino precursor for the asymmetric synthesis of tetrahydroisoquinolines

The stereoselective synthesis of tetrahydroisoquinolines was then investigated using a range of catalytic conditions and the major product in each attempt was determined by ^{1}H NMR spectroscopy (Table 4.7). It was remarkable that during these optimisation studies, the major by-product identified was due to the intramolecular C-N cross-coupling to form the 5-membered indoline scaffold **387**.[†††]

[†††] Although always considered a possibility, the product formed due to C-N coupling had not been observed during previous investigations into the domino Heck-aza-Michael process.

Table 4.7 Optimisation of the asymmetric domino process for tetrahydroisoquinoline synthesis

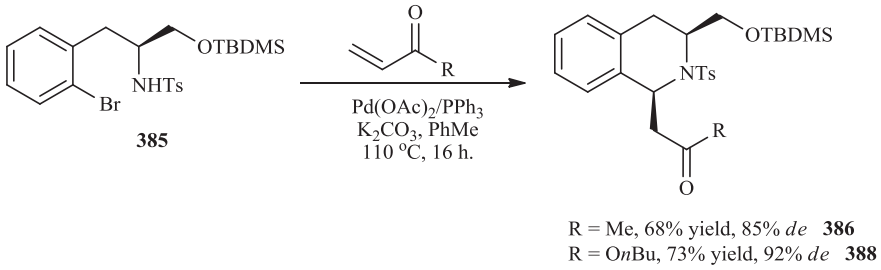


Entry	Pd Catalyst [a]	Base	Solvent	Major Products (% Conversion)
1	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	THIQ **386** (30%)
2	$Pd_2(dba)_3$/DavePhos	K_2CO_3	PhMe	THIQ **386** (50%), Indoline **387** (50%)
3	$Pd_2(dba)_3/P(t\text{Bu})_3$	K_2CO_3	PhMe	Indoline **387** (100%)
4	$Pd_2(dba)_3/PPh_3$	K_2CO_3	PhMe	THIQ **386** (10%), Indoline **387** (90%)
5	$Pd(OAc)_2/P(t\text{Bu})_3$	K_2CO_3	PhMe	Indoline **387** (100%) [b]
6	$Pd(OAc)_2/PPh_3$	Cy_2NMe	PhMe	NR
7	$Pd(OAc)_2/PPh_3$	Na_2CO_3	PhMe	NR
8	$Pd(OAc)_2/PPh_3$	K_2CO_3 [c]	PhMe	THIQ **386** (70%)[d], Indoline **387** (30%)

a Palladium catalyst loading 10 mol%. Pd:Ligand ratio was 1:1.
b The C-N cross coupling adduct was isolated in a yield of 97%
c 5.0 equivalents of K_2CO_3 and 2.0 equivalents of 3-buten-2-one were used
d The domino adduct was isolated in a yield of 68%
Reaction was performed in a sealed tube containing the aryl-halide (1.0 eq.), 3-buten-2-one (1.2 eq), palladium catalyst (10 mol%), and base (3.0 eq.) in solvent (4 mL). The reaction mixture was then heated to 120 °C for 16 h.

The first reaction was trialled using the conditions previously successful for the domino process for the synthesis of tetrahydroisoquinolines (Table 4.7, entry 1). The major product identified from this reaction was the Heck-aza-Michael adduct **386**, however following several attempts, conversion above 30% was not realised. To increase the rate of the Heck reaction, several more active catalytic conditions were trialled (Table 4.7, entries 2-5) in the presence of K_2CO_3 and toluene. The conversion to the desired domino product was increased (up to 50%, entry 2), however the formation of the indoline **387** through an intramolecular C-N cross coupling reaction (Buchwald-Hartwig reaction) was favoured under these more active catalytic conditions. In fact, complete conversion to this indoline **387** was realised when the Fu salt was employed (isolated in 97% yield, entries 3 and 5). Further attempts using the $Pd(OAc)_2/PPh_3$ catalyst with a range of bases failed to product the domino adduct (Table 4.7, entries 6-7). Eventually it was determined that by increasing the equivalents of alkene (from 1.2 to 2.0 equivalents) and base (from 3.0 to 5.0 equivalents), the domino reaction produced tetrahydroisoquinoline **386** in 70% conversion (with 30% of the C-N adduct **387** also identified, Table 4.7 entry 8). Following column chromatography, the tetrahydroisoquinoline ketone **386** was isolated in a yield of 68%. The diastereomeric ratio, determined by NMR was approximately 19:1, with chiral HPLC confirming the asymmetric domino reaction had afforded the major diastereomer in 85% *de*.

To further investigate the asymmetric domino reaction, butyl acrylate was employed as the alkene substrate, affording the butyl ester tetrahydroisoquinoline **388** in 73% yield (92% *de*, Scheme 4.39).



Scheme 4.39 The asymmetric domino Heck-aza-Michael reaction for the synthesis of chiral 1,3-disubstituted tetrahydroisoquinolines

The major isomer formed during this domino process was again confirmed to be the *cis*-diastereomer, with both the C1- and C3-proton resonances exhibiting a through space NOE interaction with the aromatic protons of the tosyl protecting group closest to the sulfonyl motif, an interaction that can only be conceived if both of these protons are in the same configuration.

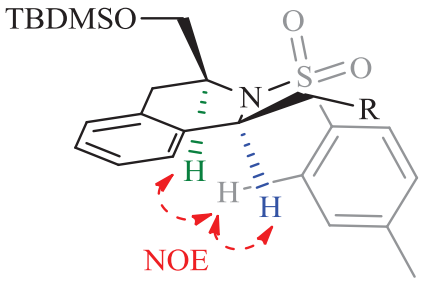
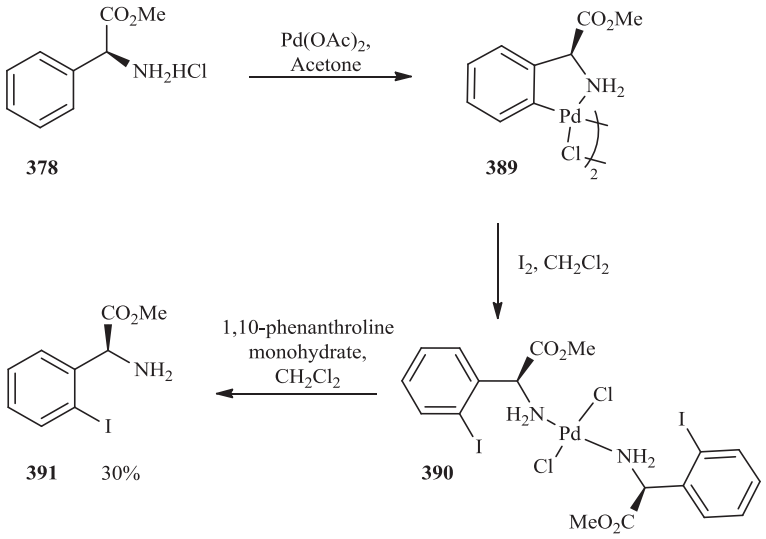


Figure 4.14 The NOE NMR experiments confirmed the *cis*-isomer was the major diastereomer formed during the tetrahydroisoquinoline asymmetric domino process

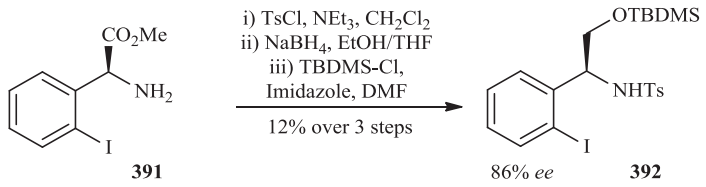
Isoindolines

In a similar fashion to that employed for the preparation of the domino substrate for the asymmetric synthesis of tetrahydroisoquinolines, *ortho*-halogenation of (*S*)-(+)-phenylglycine methyl ester **378** was carried out following *ortho*-palladation (Scheme 4.40).



Scheme 4.40 *Ortho*-iodination of the phenylglycine derivative

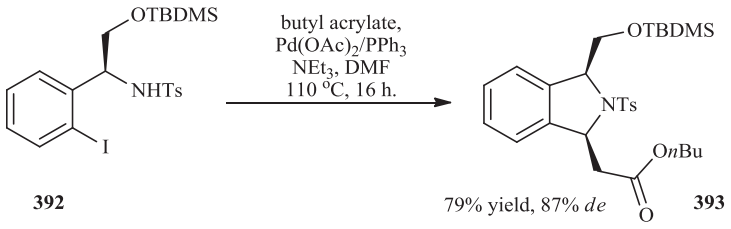
Initial investigations involved *ortho*-bromination of the phenylglycine methyl ester **378**, however for reasons unknown, following attempted tosylation of the free amine a clean product could not be obtained. Alternatively, the *ortho*-iodination was then investigated (Scheme 3.36). Formation of the palladacycle **389** was achieved by refluxing the phenylglycine methyl ester **378** with palladium acetate in acetone overnight. Following recrystallisation of the palladacycle **389**, it was treated with iodine in dichloromethane to furnish the *ortho*-iodinated product **390**. Once again, the addition of 1,10-phenanthroline monohydrate to the solution containing the aryl-halide facilitated the release of the palladium to afford the 2-iodoamine **391** in 30% over three steps. As previous attempts at the domino reaction with the methyl ester substrates were unsuccessful, following tosylation of the amine, the ester was again reduced with $NaBH_4$ and readily converted to the silyl ether **392** in an unoptimised yield of 12% over three steps (Scheme 4.41)



Scheme 4.41 Preparation of the domino precursor for the asymmetric synthesis of isoindolines.

As previously reported, *ortho*-halogenation *via* the palladacycle intermediate results in slight racemisation of the phenylglycine.[460] Indeed the enantiopurity of the 2-iodosulfonamide **392** prepared during this project was confirmed by chiral HPLC as 86% *ee*. With the domino substrate in hand, the asymmetric domino Heck-aza-Michael reaction for the synthesis of

chiral 1,3-disubstituted isoindolines was attempted with butyl acrylate using the conditions previously identified for isoindoline formation (Scheme 4.42).



Scheme 4.42 The asymmetric domino reaction for the synthesis of 1,3 disubstituted isoindolines

The butyl ester isoindoline **393** was formed in 79% yield, in a diastereomeric ratio of approximately 19:1 (determined by ^{1}H NMR spectroscopy). The stereoselectivity of this domino process was confirmed by chiral HPLC (revealing an 87% *de*). Further attempts employing 3-buten-2-one resulted in formation of the desired isoindoline, however this product could not be separated from the remaining starting material. This success also proved that the domino Heck-aza-Michael reaction was also plausible using aryl-iodides.

In accordance with previous experiments, the major diastereomer from the isoindoline reaction sequence (Scheme 4.42) was again identified as the *cis*-isomer with NOE NMR experiments confirming the through space interactions of the C1- and C3- proton resonances with each other, as well as with the aromatic protons of the tosyl group.

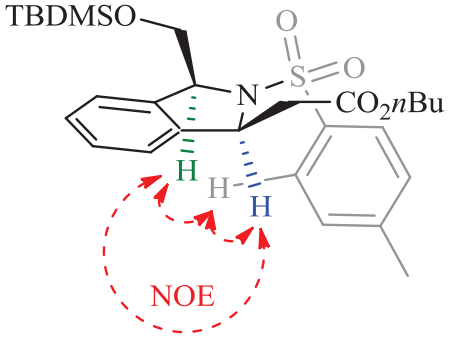


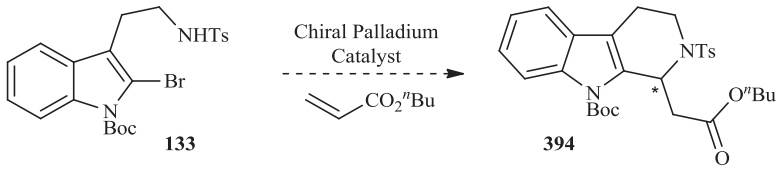
Figure 4.15 The NOE NMR experiments confirmed the *cis*-isomer was the major diastereomer formed during the isoindoline asymmetric domino process

An asymmetric domino Heck-aza-Michael process was successfully developed for the synthesis of chiral 1,3-disubstituted tetrahydro-*β*-carbolines, tetrahydroisoquinolines and isoindolines in good yields and with moderate to excellent diastereoselectivity. These disubstituted *N*-heterocycles contain orthogonal functionality readily available for further functionalisation (an ester or ketone at C1 and a protected alcohol at C3).

To further illustrate how this methodology provides access to *N*-heterocycles that are useful as building blocks in the synthesis of more complex molecules, the silyl alcohol protecting group could be readily cleaved,[264] and the alcohol oxidised to form the carboxylic acid. Following reaction of this carboxylic acid to form the activated Barton ester, this ester could be cleaved through a reductive decarboxylation process to produce the C1-monosubstituted *N*-heterocycle, or utilised in the formation of new carbon-carbon, carbon-halide and carbon-heteroatom bonds.[461]

4.4.4 Chiral Catalysis

Asymmetric catalysis is an especially appealing method for realising asymmetric syntheses. Small amounts of a catalyst can often be used to control the stereochemical outcome of a reaction.[462] The use of a catalyst often makes the isolation of the product easier, as there is less unwanted material to remove at the end of a reaction.[416] A number of enantioselective palladium-catalysed transformations, in particular the Heck reaction, have been recently reported.[201]



Scheme 4.43 The potential stereoselective synthesis of THBCs using chiral palladium catalysis

One approach considered for the development of an asymmetric domino Heck-aza-Michael reaction was the use of chiral palladium catalysts containing chiral ligands (such as (*R*)-BINAP) to potentially induce stereochemistry (Scheme 4.43). The mechanism of this *N*-heterocycle formation would require the chiral Pd-catalyst to be in close proximity to one face of the double bond following Heck reaction, allowing aza-Michael addition to only occur from the opposite face of the double bond, resulting in the formation of one stereoisomer. As the palladium catalyst was not considered to play a major role in the stereodefining step during formation of the *N*-heterocycle, the use of chiral palladium catalysis at this point was not investigated.

4.5 Conclusion

The syntheses of tetrahydroisoquinolines and isoindolines using a domino Heck-aza-Michael reaction were achieved in good yield, providing access to these *N*-heterocycles containing a variety of functional groups. The expansion of the domino methodology to

include these two additional heterocyclic systems resulted in a publication in *Organic & Biomolecular Chemistry* (see Appendix One).[396]

The synthesis of benzofuran and benzothiophene-based *N*-heterocycles was also attempted using the domino Heck-aza-Michael methodology. The benzofuran domino precursor was able to be accessed in good yield from 2-hydroxyacetophenone, however the rate of the Heck reaction at the benzofuran-2-position was not sufficient enough that Heck reaction took place before intermolecular aza-Michael addition. The benzothiophene analogue of tryptamine was synthesised in good yield over several steps from thiophenol, but bromination of the benzothiophene-2-position was not readily achieved. A domino process attempted using the benzothiophene domino precursor did reveal that some of the desired *N*-heterocycle had formed, however further investigation into both these systems is required.

The domino Heck-aza-Michael reactions reported to date, including those investigated during this research project, had only proved successful using the limited range of commercially available electron-deficient terminal alkenes. To further expand the scope of this methodology, a three-component domino process for the synthesis of C1-acetamide tetrahydroisoquinolines was developed. The first reaction in the one-pot reaction sequence involved the coupling of acryloyl chloride to a primary or secondary amine. This acrylamide formation was followed by domino Heck-aza-Michael reaction to furnish a series of 16 amide functionalised *N*-heterocycles. The expansion of the domino methodology to a three-component protocol, allowing synthesis of the requisite alkene in the same pot as the domino process, resulted in a publication in *European Journal of Organic Chemistry* (see Appendix One).[463]

To further explore the domino Heck-aza-Michael process an asymmetric version was investigated using a variety of approaches including chiral protecting groups, chiral alkenes and chiral amine substrates. This eventually lead to the development of an asymmetric domino reaction, using chiral amino acid starting materials, for the synthesis of 1,3-disubstituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines in good yield and with moderate to good diastereoselectivity. In comparison to existing techniques employing a similar approach to asymmetric *N*-heterocycle synthesis (see Scheme 4.29), both higher reaction yields, and greater diastereoselectivity were achieved using the methodology developed during this project (a publication presenting these results is currently in preparation).

Chapter Five
Indole-Based PPARγ Agonists

5.1 Chapter Overview

Following the development of novel palladium-catalysed methodology to access functionalised *N*-heterocycles, a new project involving the application of indole-based *N*-heterocycles in the synthesis of PPARγ agonists was investigated.

Focus turned to the indole-scaffold in an attempt to increase the insulin-sensitising activity of potential PPARγ agonists previously identified.[2] Conformationally restricted analogues were designed by varying the size and functionality contained within the indole-based *N*-heterocyclic scaffold. A number of indole-based scaffolds, synthesised from tryptamine, were functionalised as required as PPARγ agonists.

5.2 PPARγ Agonists for Treating Type-2 Diabetes

There are currently a range of pharmaceutical agents available for the treatment of type 2 diabetes (T2D), acting at different biological targets within the body. Before the discussion of new treatments can take place, an understanding of type 2 diabetes is required and the role the PPARγ plays in mediating blood glucose levels.

5.2.1 Type-2 Diabetes

Diabetes Mellitus (DM) is a group of diseases characterised by the abnormally persistent elevation of blood-glucose levels within the body (hyperglycaemia).[221, 464] Chronic hyperglycaemia can result in long term complications including kidney failure, coronary heart disease and stroke. More than half of those patients diagnosed with type 2 diabetes eventually die of cardiovascular related causes.[221]

In 2005, over 1.1 million people worldwide died from diabetes.[220] However, this number is more likely closer to 3 million, as many deaths where diabetes was a predominant factor were attributed to heart disease or kidney failure.[220] Currently, over 180 million people worldwide have been diagnosed with diabetes. Alarmingly, the number of sufferers is expected to more than double by the year 2030, as this chronic disease reaches epidemic status.[220]

Whereas type 1 (insulin dependent) diabetes is caused by a *lack* of insulin production, type 2 (non-insulin dependent) diabetes is a result of *impaired* insulin action (or insulin resistance).[465] Insulin resistance is a characteristic metabolic defect in a number of patients affected by diabetes.[221] Symptoms of patients with type 2 diabetes often include excessive urination, thirst, constant hunger, weight loss and changes to vision and tiredness.

Insulin is predominantly produced by the β cells of the islets of Langerhans, with over one million islets contained in the pancreas.[465] The hormone insulin stimulates glucose transport from blood into muscles and tissues, and is responsible for controlling the metabolism of proteins, fats and carbohydrates.[465-466] The insulin produced is utilised by the body to maintain acceptable levels of glucose within the body (typically 700-1500 mg/L). The onset of type 2 diabetes generally occurs when glucose levels in the body move above this range for an extended period of time.[221, 465] Furthermore, many of the symptoms of diabetes can be moderated by reducing the level of glucose in the blood.[465, 467-468]

The term *insulin resistance* is defined by the failure of the β cells of the pancreas to keep up with the body's requirements. This resistance to insulin results in the ineffective removal of glucose from the blood.[221, 369, 465-466] ‡‡‡

Treating Type 2 Diabetes

For thousands of years, there were no treatments for diabetes.[470] Children who developed diabetes often died within days, and older people were forced to live with the demoralising symptoms. A variety of remedies were employed ranging from the use of assorted herbs to more extreme methods, including "opening the veins".[470]

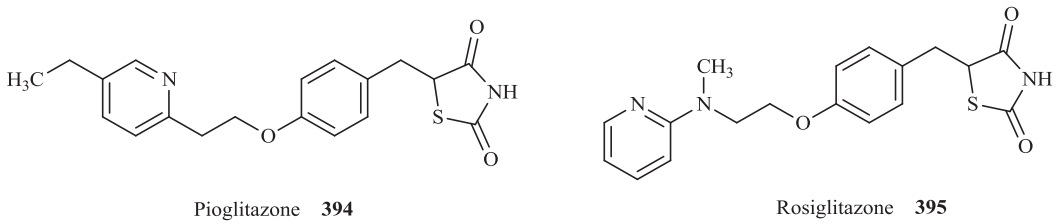
Although the management of diet and exercise is the front line treatment for type 2 diabetes, it is usually accompanied by one or more of the available pharmaceutical treatments, especially where lifestyle changes are difficult. Current pharmaceutical agents focus on either increasing the inadequate level of insulin production or increasing the sensitivity of target tissues to insulin.[467] Unfortunately, associated with each of the current treatments are a number of side effects (Table 5.1).

Table 5.1 Current therapeutic agents for the treatment of type 2 diabetes [471]

Drug Class	Molecular Target	Site(s) of Action	Adverse Effects
Insulin	Insulin Receptor	Liver, muscle, fat	Hypoglycaemia, weight gain
Sulfonylureas	Sulfonylurea Receptor/ K^+ ATP channel	Pancreatic β-cell	Hypoglycaemia, weight gain
Metformin	Unknown	Liver (muscle)	Gastrointestinal disturbances, lactic acidosis
Acarbose	α-glucosidase	Intestine	Gastrointestinal disturbances
Thiazolidinediones	PPARγ	Fat, muscle, liver	Weight gain, oedema, anaemia

‡‡‡ For a more comprehensive discussion of insulin resistance refer to the book by Reaven and Laws (*Insulin Resistance: The Metabolic Syndrome X*; Humana Press Inc.: Totowa, New Jersey, 1999.)[469]

The thiazolidinediones (TZDs) and their target, the Peroxisome Proliferator-Activated Receptors (PPARs), are the particular focus of this project. Thiazolidinediones are insulin-sensitising antidiabetic drugs.[221] TZDs are used in the treatment of overweight patients whose diabetic condition cannot be adequately controlled by diet and exercise, and where metformin is inappropriate.[472] There are currently only two TZDs available on the market; Pioglitazone **394** and Rosiglitazone **395** (Figure 5.1). The first available TZD (Troglitazone) was withdrawn after severe liver toxicity was observed.[473]



Pioglitazone **394** Rosiglitazone **395**

Figure 5.1 The structure of the two commercially available thiazolidinediones.

Thiazolidinediones are agonists of the Peroxisome Proliferator-Activated Receptor gamma (PPARγ) which is predominantly found in skeletal and muscle cells.[221] Unfortunately, associated with the TZDs are a number of side effects including upper respiratory tract infection and weight gain, and they have also been linked with a number of cardiovascular problems.[221] In fact, there has been so much controversy surrounding the safety profile of Rosiglitazone **395** (marketed as Avandia) that the European Medicines Agency (EMA) has decided to remove the troubled diabetes drug from the market, while the US Food and Drug Administration (FDA) will 'significantly restrict' it's use.[474]

Although a large range of antidiabetic drugs are currently available there is still no ideal treatment or cure for diabetes.[221] As such, there is still a great need for the development of new or improved treatments with better safety profiles. Herein the focus is on the synthesis of new antidiabetic agents that act at the same biological target as the TZDs- the Peroxisome Proliferator-Activated Receptors.

Peroxisome Proliferator-Activated Receptors (PPARs)

The Peroxisome Proliferator-Activated Receptors (PPARs) are a subfamily of the nuclear receptor superfamily that control many metabolic and cellular processes [475-476] The PPARs are ligand-activated transcription factors that regulate target gene expression.[477] They play an essential role in controlling glucose levels, acting as lipid sensors, and regulating the storage and catabolism of dietary fats.[478-479]

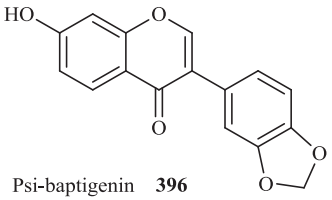
After the binding of an agonist (usually a small, lipophilic molecule)[480] to a receptor, the conformation of the PPAR is altered to create a binding cleft and the recruitment of transcriptional coactivators is initiated.[481] A process known as transactivation ensues that results in a greater expression level of mRNAs encoded by PPAR target genes, increasing the rate of transcription of these genes.[481] The final result is an increased differentiation of adipocytes (fat cells).[482] For a comprehensive review of PPAR action, refer to Willson *et. al* [479] and Berger *et. al.*[481]

There are three PPAR nuclear receptor isotypes; PPARα, PPARγ and PPARδ.[481] PPARα is expressed predominantly in tissues that extract their energy requirements from lipids (the liver, heart and kidney) and holds an essential role in the regulation of fatty acid oxidation.[478, 483] PPARδ is expressed in many tissues at a low level, but little is known regarding its mechanism of action and biological role.[381, 478]

PPARγ is critical in the regulation of adipocyte expression and differentiation, and has been linked with several genes found to influence the action of insulin.[479, 481] Activation of the PPARγ causes a reduction in insulin resistance by enhancing the sensitivity of insulin target tissues. This increases the removal of glucose from the blood, and therefore provides a valuable target for antidiabetic treatments.[479] There is also strong evidence to suggest that PPARγ agonists may be employed therapeutically in the treatment of cancer and atherosclerosis (a chronic inflammatory response in the walls of arteries).[479]

Natural Ligands of PPARγ

Recent studies have revealed that several naturally occurring fatty acids, eicosinoids, prostaglandins and their metabolites weakly activate PPARγ at micromolar concentrations.[389, 475] Additionally, several reports have recently emerged detailing a range of seed, herb and plant extracts that stimulate the PPARγ.[484-489] Attempts to confirm the identity of these naturally occurring PPARγ agonists have identified several potential lead compounds for further development of pharmaceutical treatments for type 2 diabetes.[490-492] One specific example of this is psi-baptigenin **396** (Figure 5.2), which was shown to activate the PPARγ, inducing an insulin-sensitising effect, in addition to the well known anti-inflammatory properties of such flavonoids and related compounds.[491, 493]



Psi-baptigenin **396**

Figure 5.2 Psi-baptigenin was identified as a novel PPARγ agonist

Synthetic Ligands of PPARγ

Thiazolidinediones (TZDs) or "glitazones" were the first reported synthetic compounds demonstrating high-affinity as PPARγ agonists.[479] TZDs have been shown to reduce insulin resistance by increasing the quantity of sugars absorbed by muscle tissues, while reducing the amount of sugar released by the liver.[464] The thiazolidinediones bind to the PPARγ receptor, initiating transcription of insulin responsive genes.[494] Certain effects of insulin are enhanced or partially mimicked, allowing the target tissues to once again become sensitive to the action of insulin.[494-495] A large number of genes activated or suppressed by TZDs are involved in the metabolism of carbohydrates and lipids and are thus responsible for the desired antihyperglycaemic effect.[473]

The large number of side effects associated with the TZDs (Section 5.2.1) has directed the research of several groups towards the search for new compounds, which, similarly to the thiazolidinediones, target the PPARγ, but minimises the associated side effects.[475, 477, 480, 482, 496-513] It is the aim of this project to also develop new compounds that act as PPARγ agonists.

Selective PPARγ Modulators

Recently, a number of compounds have been shown to bind to more than one isotype of the PPAR family. This class of compounds is known as dual-agonists or pan-agonists. It is proposed that dual agonists may provide an improved safety profile for PPAR agonists.[514] Evidence also exists that a number of the side effects associated with the current TZDs for treating type 2 diabetes can be minimised by only partially activating the PPARγ (compounds that allow this are called selective PPARγ modulators or SPPARMs). These SPPARMs operate by a different mode of action, binding different residues in the receptor than the full PPARγ agonists. This leads to a less dramatic conformational change in the receptor and therefore the recruitment of a different combination of coactivators, resulting in a different outcome and an improved safety profile.[515-517]

5.2.2 Design of Indole-Based PPARγ Agonists

From the literature, a general molecular template has been identified for those compounds reported to show a degree of selectivity for the PPARγ (Figure 5.3).[499, 508, 510] The template for the design of a successful PPARγ agonist consists of an acidic head, attached to an aromatic scaffold, which is then linked to a hydrophobic hetero-aromatic tail (Acid-Ar-Linker-Ar). [499, 508, 510] Whilst the template allows for diversity in the Ar-Linker-Ar moieties employed, compounds without an acidic head were found to be biologically inactive in binding and functional assays.[508] In the commercially available TZDs for treating type 2 diabetes, the thiazolidinedione moiety functions as the acidic head group.

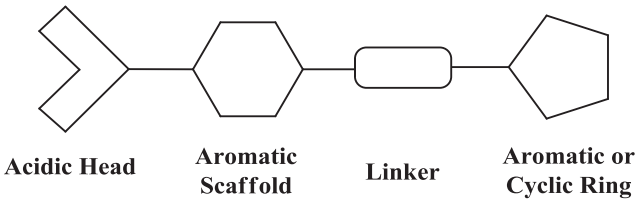


Figure 5.3 The molecular template of a PPARγ agonist

As outlined in chapter one, the indole scaffold has been utilised in pharmaceuticals for the treatment of numerous medical conditions.[1, 5, 505] The indole scaffold allows for further derivatisation at numerous positions, making it ideal for drug development and optimisation.[9, 505] Furthermore, several of the more effective compounds in activating the PPARγ are also built around an indole scaffold (Figure 5.4).[496, 499-500, 502, 505, 507-508, 510, 518-520] Evidence exists that the indole scaffold interacts with a number of amino acid residues of the PPARγ binding cleft,[508-510] and as such the indole moiety was also chosen as the aromatic scaffold for the work herein.

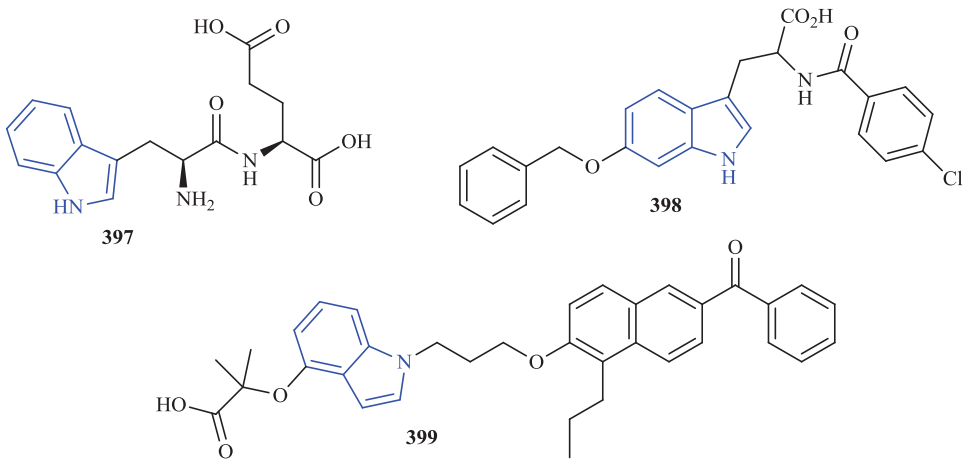
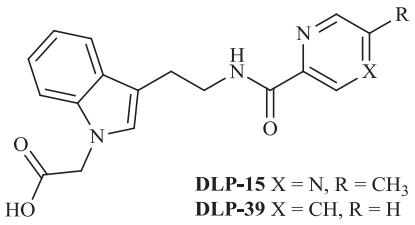


Figure 5.4 Several indole-based PPARγ agonists have been reported[499, 509, 521]

In previous studies, two indole-based compounds synthesised from tryptamine (**109** and **110**, Figure 5.5) exhibited a moderate insulin-sensitising effect, when compared to rosiglitazone **395**.[2-3] These compounds were identified as lead compounds in the development of new potential PPARγ agonists for the treatment of type 2 diabetes

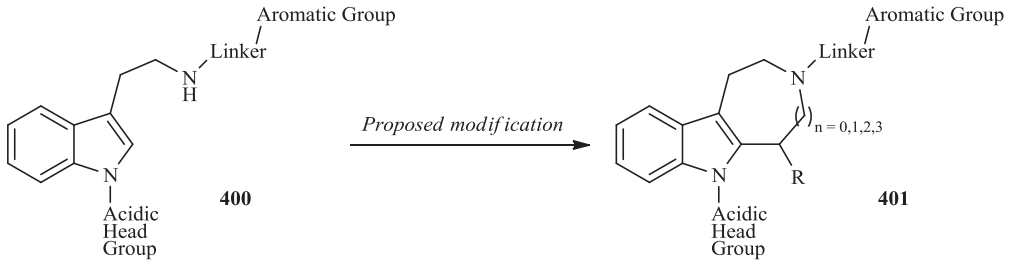


DLP-15 X = N, R = CH_3 **109**
DLP-39 X = CH, R = H **110**

Figure 5.5 Two lead compounds that exhibited a moderate insulin-sensitising ability

It was considered that modification of these lead compounds could increase their insulin-sensitising ability. Furthermore, the introduction of key characteristics identified from naturally occurring PPARγ agonists, for example the multiple fused heterocyclic groups observed in the flavonoids, could both improve biological activity and the safety profile of the potential PPARγ agonists.

A simple modification to the indole-based aromatic scaffold was proposed through the introduction of a second *N*-heterocycle (Scheme 5.1), whilst keeping the acidic head group and aromatic tail group relatively similar to those previously used.

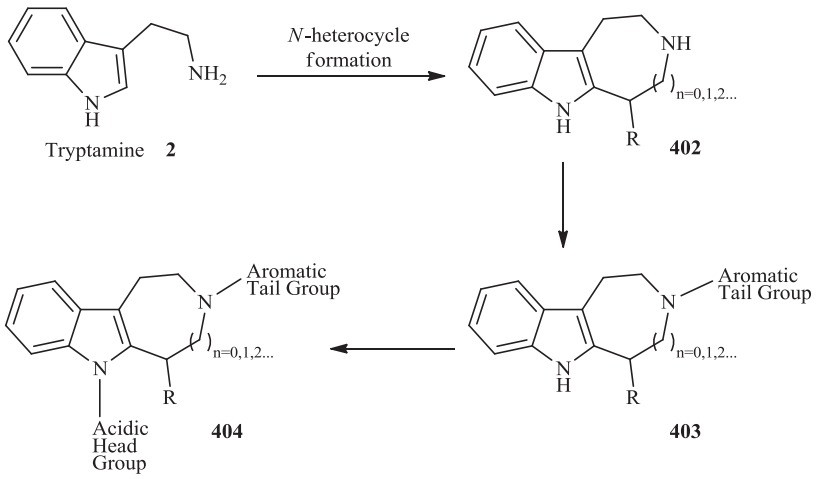


Scheme 5.1 The proposed modification to improve the biological activity of the PPARγ agonists

By introducing a second *N*-heterocycle onto the requisite aromatic scaffold **401**, a higher level of preorganisation would be achieved. For tryptamine derivatives **400** (Figure 5.5), there is a large amount of flexibility in the linker group between the indole scaffold and the aromatic group. However, if a tetrahydro-*β*-carboline is employed, the conformational restriction, and therefore the direction of the tethered aromatic tail group, can be altered. Through the introduction of a *N*-heterocycle of differing size (e.g. 5, 6, 7, or 8-membered heterocycles), the degree of conformational restriction could ultimately be tuned to target

different amino acid residues within the large PPARγ binding cleft. In the case of the tetrahydro-*β*-carboline scaffold, the 6-membered *N*-heterocyclic ring lies almost planar to the indole ring. However, for the indoloazocine scaffold, the 8-membered *N*-heterocyclic ring is much more likely to adopt a distorted, non-planar conformation, allowing the aromatic tail group to be tethered at a much different angle than for the TH*β*C scaffold. The possibility of introducing additional groups during the cyclisation process to improve solubility or participate in the binding process also exists.

There are currently a range of methodologies available for accessing indole-based *N*-heterocyclic scaffolds from tryptamine (**2**) (see Chapter One). Following synthesis of the selected polycyclic indole-based scaffold **402**, the introduction of both the aromatic tail and the carboxylic acid head group would complete the functionalisation of the PPARγ agonists **404** (Scheme 5.2) and a number of established methods exist for this purpose.



Scheme 5.2 The proposed synthetic pathway to PPARγ agonists from tryptamine

Once complete, the potential PPARγ agonists **404** were to be submitted for biochemical evaluation using a glucose uptake assay and adipocyte differentiation assay. If this initial analysis proved successful, further evaluation of these compounds employing more specific assays including the PPARγ transcription factor assay and mRNA analysis were planned.[493, 522]

5.3 Synthesis of Indole-Based PPARγ Agonists

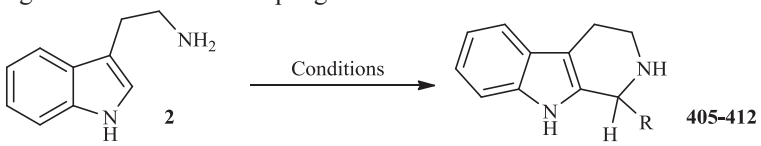
Several methods for the formation of indole-based *N*-heterocycles from tryptamine were selected. Initial investigations were carried out using the Pictet-Spengler reaction to access the tetrahydro-*β*-carboline scaffold. The Bischler-Napieralski and the gold-catalysed cyclisation of indolyl-alkynes to access ring systems of differing size and functionality were also trialled.

5.3.1 The Pictet-Spengler Reaction

The Pictet-Spengler reaction takes place between tryptamine (**2**) and an appropriate carbonyl compound (typically an aldehyde) under acid-catalysed conditions (usually TFA). In recent years, a number of modified protocols have been developed, including microwave heating,[48-49] the use of H_2O as a solvent,[523] non-acid catalysts[43-44, 46, 524] and modified aldehyde reagents (for example nitriles and alkynes).[22-23, 25, 47]

Herein, tryptamine was employed in the Pictet-Spengler reaction with an appropriate aldehyde partner using a range of conditions (Table 5.2). While asymmetric variants of the Pictet-Spengler reaction have been widely reported,[51] the *β*-carboline scaffolds synthesised during this project were obtained as racemic mixtures.

Table 5.2 Investigations into the Pictet-Spengler reaction



Entry	Aldehyde	Conditions	R	Yield (%)
1	butyraldehyde	10% TFA/H_2O	-$(CH)_2CH_3$ (**405**)	79
2	butyraldehyde	10% TFA/CH_2Cl_2	-$(CH)_2CH_3$ (**405**)	99
3	benzaldehyde	10% TFA/H_2O	-Ph (**406**)	88
4	cinnamaldehyde	10% TFA/H_2O	-CH=CHPh (**407**)	0[a]
5	4-pyridinecarboxaldehyde	10% TFA/H_2O	-4-Pyridine (**408**)	NR
6	4-pyridinecarboxaldehyde	1% I_2 in Ethanol	-4-Pyridine (**408**)	NR
7	formaldehyde	10% TFA/H_2O	-H (**409**)	NR
8	propionaldehyde	10% TFA/H_2O	-CH_2CH_3 (**410**)	0[a]
9	propionaldehyde	10% TFA/CH_2Cl_2	-CH_2CH_3 (**410**)	0[a]
10	methyl 4-formylbenzoate	10% TFA/CH_2Cl_2	-4-methylbenzoate (**411**)	69
11	methyl 3-formylbenzoate	10% TFA/ CH_2Cl_2	-3-methylbenzoate (**412**)	87

a The desired product could not be separated from the excess aldehyde using column chromatography

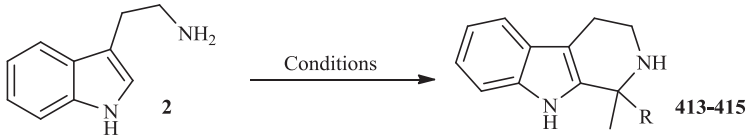
The Pictet-Spengler reaction using 10% TFA in H_2O was successful for the synthesis of the C1-substituted tetrahydro-*β*-carbolines using butyraldehyde and benzaldehyde (Table 5.2, entries 1, 3). The use of 10% TFA in CH_2Cl_2 also furnished the butyraldehyde derivative **405** in a greater yield (99%), due to the increased solubility of both the starting materials and

products (Table 5.2, entry 2). Using these same conditions (10% TFA/CH_2Cl_2), access to several other functionalised indole scaffolds was realised (Table 5.2, entries 10-11). Unfortunately the desired product was not isolated following reaction with propionaldehyde, cinnamaldehyde, 4-pyridinecarboxaldehyde and formaldehyde (Table 5.2, entries 4-9). The modified Pictet-Spengler reaction using iodine as a catalyst in ethanol did not provide access to the pyridine derivative **408** (Table 5.2 entry 6).[524]

The success of each reaction was readily determined by NMR spectroscopy and mass spectrometry. In the ^{1}H NMR spectrum, the characteristic proton from the C1-position is observed between δ 4.0-5.5 ppm as a singlet or triplet depending on the substrate. In addition to this, the loss of the indole-C2-proton resonance, and the downfield shift and additional splitting patterns of the tryptamine ethylene CH_2 proton resonances, confirm cyclisation.

To further investigate the range of scaffolds available using this methodology, the Pictet-Spengler reaction with ketones was trialled (Table 5.3). Traditionally, when using ketones, the Pictet-Spengler reaction does not occur as readily as it does for aldehydes, and often higher temperatures and longer reaction times are required.[49] The advent of microwave irradiation as an effective way of reducing reaction times now means that the Pictet-Spengler reaction with ketones can be readily accomplished in a matter of minutes.[525]

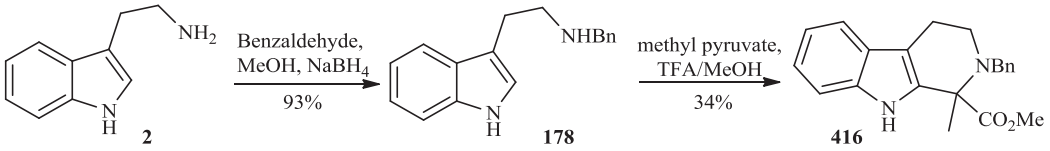
Table 5.3 The Pictet-Spengler reaction between tryptamine and a ketone



Entry	Ketone	Conditions	R	Yield (%)
1	methyl pyruvate	10% TFA/methanol, 70 °C for 4 days	CO_2Me (**413**)	99
2	acetone	$CHCl_3$ 62 °C for 3 days	CH_3 (**415**)	58
3	acetone	$CHCl_3$ 60 °C MW for 20 mins.	CH_3 (**415**)	96

The reaction with methyl pyruvate (Table 5.3, entry 1) afforded the C1-disubstituted tetrahydro-*β*-carboline **413** in exceptional yield (99%), however a long reaction time was required (typically 4 days).[526] The first reaction attempted with acetone (Table 5.3, entry 2) to access the dimethyl-derivative **415** was performed under conventional heating methods (for 3 days) and produced the requisite tetrahydro-*β*-carboline in yield of 58%.[527] The yield of this reaction was significantly enhanced (96% - Table 5.3, entry 3) when microwave heating was employed, allowing the reaction to take place in only 20 minutes, confirming the advantages of microwave irradiation.

The Pictet-Spengler reactions trialled so far had taken place with a primary amine at the N_{10}-position of tryptamine. To investigate whether the Pictet-Spengler was also possible using a functionalised tryptamine, reductive amination with benzaldehyde afforded the N_{10}-benzyl tryptamine **178**,[528] which was then subject to reaction with methyl pyruvate (Scheme 5.3).



Scheme 5.3 The Pictet-Spengler reaction using a functionalised tryptamine derivative

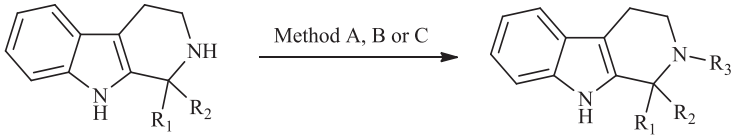
Although successful, the yield for this reaction was significantly lower than that observed for the unfunctionalised tryptamine (Table 5.3, entry 1). This may be explained by that fact that with the N_{10}-amine functionalised, the Pictet-Spengler reaction is hindered by the steric properties associated with the formation of the congested tetrasubstituted tetrahydro-*β*-carboline.

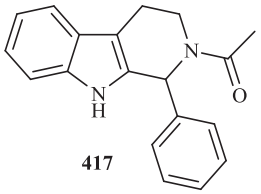
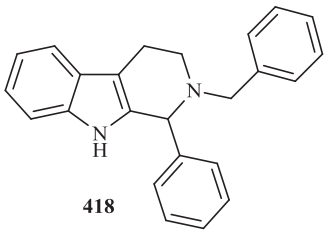
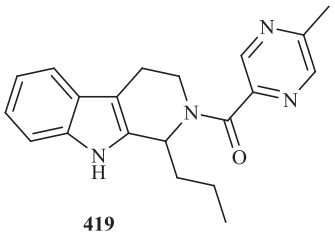
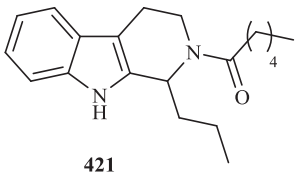
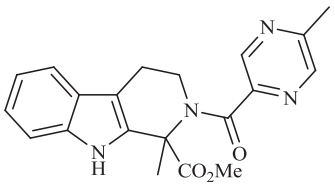
Functionalisation of the Tetrahydro-β-carboline Scaffolds

A number of the scaffolds synthesised using Pictet-Spengler reactions were to be functionalised at both available nitrogens to afford potential PPARγ agonists. As the secondary amine is more reactive than the indole nitrogen this amine was functionalised first. The reactivity of this secondary amine was investigated using a range of approaches including amide-bond formation, acylation, alkylation and aza-Michael addition (Table 5.4).[529]

When the secondary amine of the TH*β*C scaffold was coupled with a carboxylic acid to form an amide bond, the reaction was carried out in the presence of the dehydrating reagents EDCI and HOBt in dichloromethane.[530-534] When reacting with an acid chloride, the reaction was performed under basic conditions in the presence of a catalytic amount of DMAP.[535-536] When functionalisation of the carboline with an alkyl halide was required, the reaction was performed under neutral conditions in dichloromethane.

Table 5.4. Investigations into the functionalisation of theC1-substituted tetrahydro-*β*-carbolines

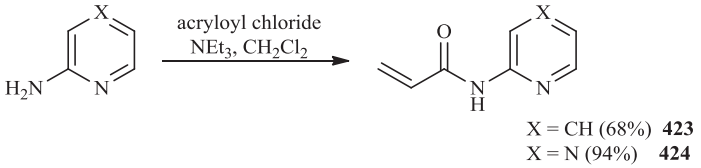


Entry	R_1	R_2	Reagent (Method)	Product	Yield (%)
1	Ph	H	acetyl chloride (A)	 **417**	100
2	Ph	H	benzyl bromide (B)	 **418**	69
3	$(CH_2)_2CH_3$	H	5-methyl-2-pyrazine carboxylic acid (C)	 **419**	34
4	$(CH_2)_2CH_3$	H	hexanoyl chloride (A)	 **421**	60
5	CH_3	CO_2Me	5-methyl-2-pyrazine carboxylic acid (C)	 **422**	44

Method A: Tetrahydro-*β*-carboline (1.0 eq), acid chloride (1.2 eq), Net_3 (1.2 eq), DMAP (0.5 eq) in CH_2Cl_2 or DMF, 16 h.
Method B: Tetrahydro-*β*-carboline (1.0 eq), benzyl bromide (1.2 eq), CH_2Cl_2, 16 h.
Method C: Tetrahydro-*β*-carboline (1.0 eq), carboxylic acid (1.5 eq), EDCI (1.2 eq), HOBt (0.3 eq) in CH_2Cl_2, 16 h.

Following investigation into the reactivity of selected tetrahydro-*β*-carboline scaffolds, it was determined that the secondary amine was readily functionalised in moderate to excellent yields using acid chlorides (Table 5.4, entries 1 and 4), carboxylic acids (Table 5.4, entries 3 and 5) and alkyl halides (Table 5.4, entry 2). Typically, the reactions with the acid chlorides and alkyl halides performed better than those using carboxylic acids.

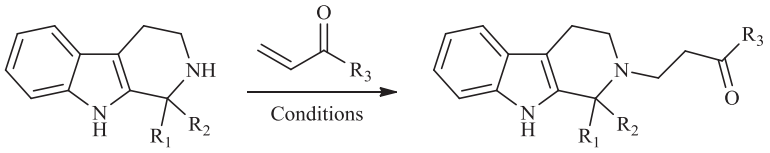
This reaction sequence allowed access to a series of highly functionalised tetrahydro-*β*-carbolines (**417** – **422**) in two steps from tryptamine (**2**). To access a second series of analogues, an alternate approach to functionalising the secondary amine of the tetrahydro-*β*-carbolines was envisaged, employing aza-Michael addition. To investigate this approach, a number of suitable conjugated Michael acceptors were prepared through reaction of acryloyl chloride with the requisite nitrogenous aromatic amines (Scheme 5.5).



Scheme 5.4 Preparation of the acrylamide Michael acceptors

With both the pyrazine (Scheme 5.4, X = N) and 2-pyridine (Scheme 5.4, X = CH) acrylamides in hand, the investigation into aza-Michael addition for the functionalisation of the carboline scaffold was carried out (Table 5.5).

Table 5.5 Optimisation of aza-Michael addition of the tetrahydro-*β*-carboline



Entry	R_1	R_2	R_3	Conditions	Yield (%)
1	Me	Me	pyrazine (**425**)	MeOH, 25 ^oC, 60 h.	NR
2	Me	Me	pyrazine (**425**)	$NaHCO_3$, MeOH, 25 ^oC, 16 h.	NR
3	Me	Me	pyrazine (**425**)	K_2CO_3, $CHCl_3$	NR
4	Me	Me	OMe (**426**)	$NaHCO_3$, $CHCl_3$	NR
5	Me	Me	OMe (**426**)	Methanol	NR
6	Me	Me	2-pyridine (**427**)	K_2CO_3, DMF	NR
7	Me	Me	2-pyridine (**427**)	MeOH, THF	18
8	$(CH_2)_2CH_3$	H	2-pyridine (**428**)	MeOH, THF	44

NR = No reaction

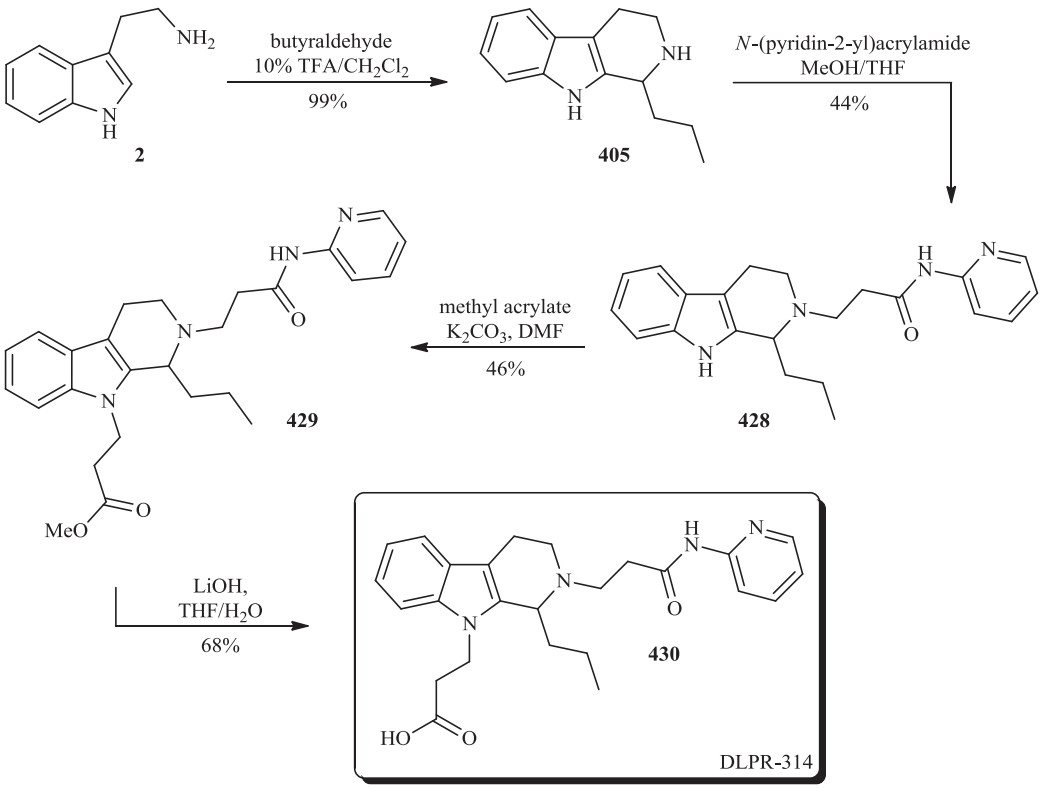
The initial reactions in this series were carried out using the C1-dimethylcarboline derivative **415** obtained from reaction of tryptamine with acetone. Reaction of this carboline with the pyrazine acrylamide **424** under a range of conditions known to promote aza-Michael addition (Table 5.5, entries 1-3) proved unsuccessful.[537-540] It was considered that the visible lack of solubility of the acrylamide **424** was impeding the progress of the reaction. As such, four more reactions using either methyl acrylate or 2-pyrazine acrylamide **423**, were carried out (Table 5.5, entries 4-7). When using methyl acrylate the additional attempts failed to afford the functionalised carboline. However, when the 2-pyridine acrylamide was reacted

with the carboline **415** in MeOH/THF at 60 ^{o}C for 16 hours (Table 5.5, entry 7), the desired 2-pyridinylcarboline **427** was isolated in a modest yield (18%). The identity of the isolated product was readily confirmed by NMR spectroscopy, with the addition of the two extra alkyl CH_2 proton resonances and the downfield shift of the amide proton resonance following Michael addition (δ 9.13 ppm to δ 10.69 ppm). Thus, aza-Michael addition was a plausible approach for tethering the requisite aromatic tail group.

The propyl-carboline derivative **405** was also subjected to reaction with 2-pyridine acrylamide **423** (Table 5.5, entry 8), using the same conditions previously successful for the aza-Michael addition step. Following purification of the crude material by column chromatography the desired product **428** from this reaction was isolated in yield of 44%. Once again, the dramatic downfield movement of the amide NH (δ 9.13 ppm to δ 10.91 ppm) confirmed aza-Michael addition had taken place. Although, not occurring in exceptional yields, aza-Michael addition was seen as an appropriate method for installing the aromatic tail group on the tetrahydro-*β*-carboline, and as such, was used for the remainder of the project.

Synthesis of the PPARγ agonist

With the "Aryl-Linker-Aryl" portion of the tetrahydro-*β*-carboline PPARγ agonists accessed in two steps from tryptamine, the synthesis of the PPARγ agonist could be completed through introduction of the carboxylic acid group. To install the acidic head group onto the aromatic scaffold, a masked carboxylic acid (as an ester) would be introduced onto the indole-nitrogen followed by deprotection to reveal the free carboxylic acid. A number of approaches were considered, for example alkylation using ethyl bromoacetate. However, aza-Michael addition from the indole nitrogen using butyl or methyl acrylate, followed by saponification to reveal the carboxylic acid head, was considered the most efficient and as such, was investigated first.



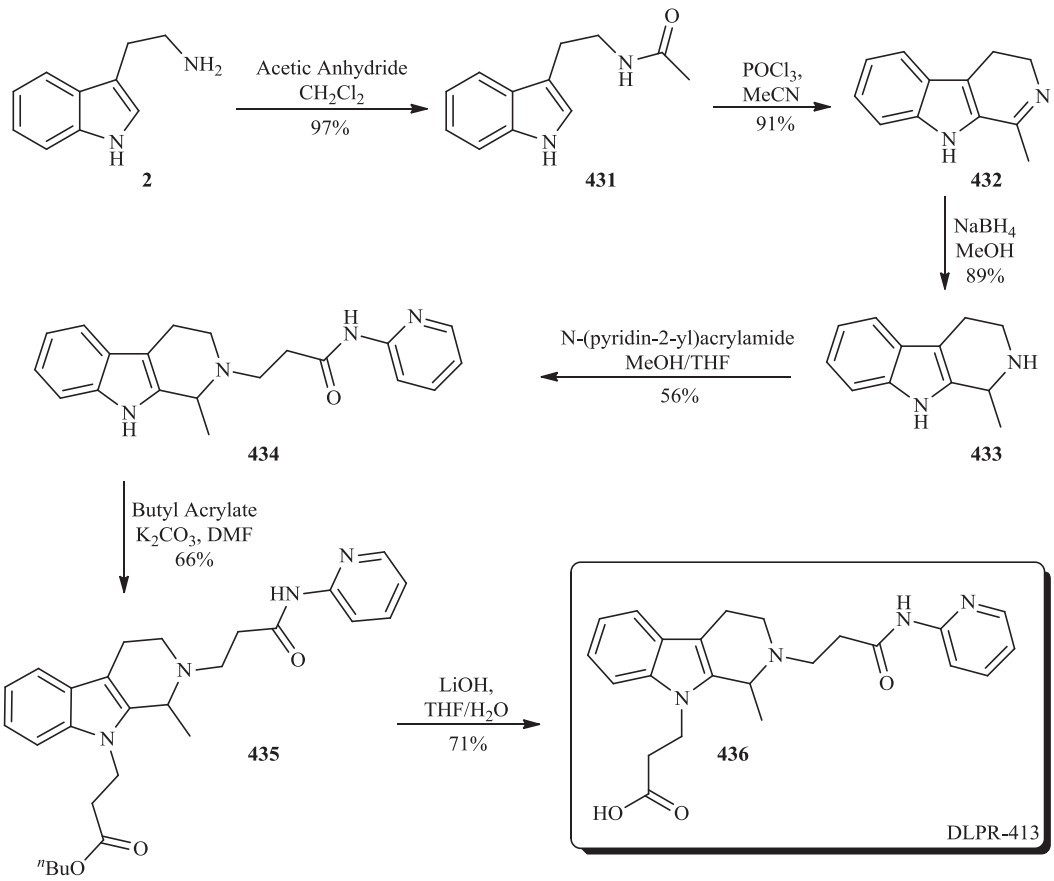
Scheme 5.5 Synthesis of the propyl THβC PPARγ agonist from tryptamine

A number of literature methods have been reported for functionalisation of the indole-nitrogen through aza-Michael addition.[541-550] In our hands, the ester **429** was furnished in highest yield (46%, Scheme 5.5) when heating the propyl THβC **428** with methyl acrylate in K_2CO_3 and DMF at 100 ^oC for 16 hours. Saponification of the methyl ester using aqueous lithium hydroxide in THF[264, 551-553] afforded the PPARγ agonist **430** in 68% yield (DLPR-314). The synthesis was accomplished in only four steps from tryptamine (Scheme 5.5).

5.3.2 The Bischler-Napieralski Reaction

An alternative synthesis to the related methyl THβC was envisaged employing a Bischler-Napieralski reaction. To install the methyl group at the C1-position of the THβC scaffold using a Bischler-Napieralski reaction, tryptamine (**2**) was first reacted with acetic anhydride to afford the N_{10}-acetyl tryptamine **431** in 97% yield (Scheme 5.6). Cyclisation to form the new 6-membered *N*-heterocycle was then performed using phosphorous oxychloride in refluxing acetonitrile. Following a simple work, up the β-carboline **432** was isolated in 91% yield, with loss of the indole-C2-proton resonance and the slight downfield shift of the ethylene CH_2 proton resonances confirming that cyclisation had taken place.

Following reduction of the imine **432** to free up the secondary amine, the aromatic tail group was installed by aza-Michael reaction, affording the functionalised methyl-THβC **434** in 50% over two steps. The success of the aza-Michael addition step was once again confirmed by the downfield shift of the amide proton resonance following Michael addition (Scheme 5.6).



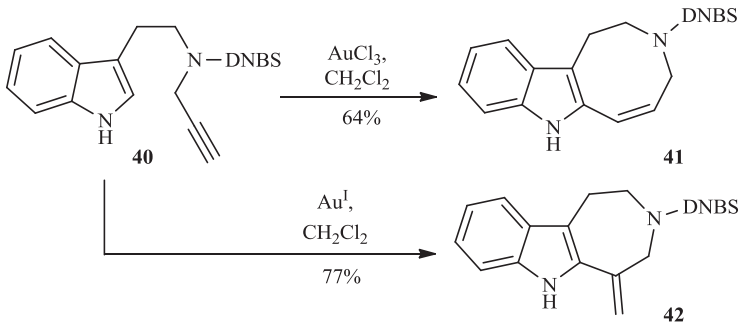
Scheme 5.6 Synthesis of the methyl THβC PPARγ agonist from tryptamine

To install the necessary carboxylic acid functionality at the indole-nitrogen, Michael addition of an acrylate was again employed. Initial attempts were carried out using methyl acrylate; however, the desired product was inseparable from the starting material. Subsequent reactions were performed using the less polar butyl acrylate, and the desired THβC ester **435** was isolated in 66% yield (Scheme 5.6). The final step in the reaction sequence was saponification of the butyl ester to afford the carboxylic acid **436** using aqueous lithium hydroxide in THF (71 %).[264, 554]

5.3.3 Gold-Catalysed Cyclisations

With the synthesis of two tetrahydro-β-carboline based PPARγ agonists complete, attention turned to the increasing the size of the *N*-heterocycle to include 7- and 8-membered rings.

Gold-catalysed cyclisation of indoles with alkynes was chosen as an efficient route to access 7- and 8-membered indole-based *N*-heterocycles (see Section 1.2.5).[99-100]

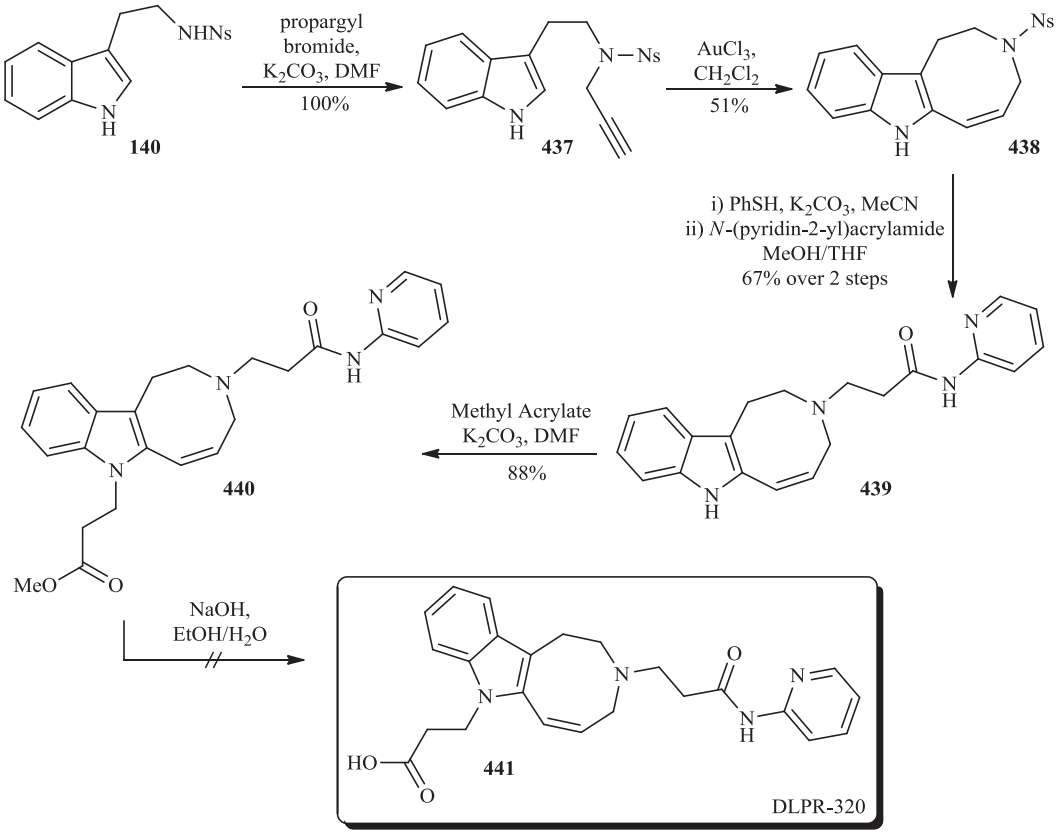


Scheme 5.7 The gold-catalysed synthesis of indole-based *N*-heterocycles
Au^I = (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate DNBS = Dinitrobenzenesulfonyl

The size of the ring formed depends on the catalyst used with the cationic gold(I) catalyst forming the 7-membered ring **42** and the more electrophilic gold(III) catalyst predominantly resulting in the formation of the 8-membered ring **41** (Scheme 5.7).

Au(III) cyclisation to form the 8-membered N-heterocycle

The first system pursued was the 8-membered ring (Scheme 5.8). The cyclisation precursor was prepared from nosyl-tryptamine **140**. The requisite alkyne tether was installed in quantitative yield by reaction of the N_{10}-sulfonamide with propargyl bromide, in the presence of K_2CO_3 in DMF (Scheme 4.10). The successful reaction was confirmed by NMR spectroscopy and mass spectrometry, with the ^{1}H NMR spectrum revealing the absence of the sulfonamide proton resonance, as well as the addition of the resonances attributed to the alkyne tether (CH_2 δ 4.28 ppm, CH δ 2.24 ppm).



Scheme 5.8 The attempted synthesis of the indoloazocine PPARγ agonist

To facilitate cyclisation to form the new 8-membered heterocycle, the indole-alkyne **437** was reacted with $AuCl_3$ in dichloromethane for 16 hours.[99-100] After this time, analysis of the crude reaction mixture confirmed that the 8-membered ring had formed (due to the alkene proton resonances now present) and the indoloazocine scaffold **438** was isolated in a modest yield of 51% (Scheme 5.8).

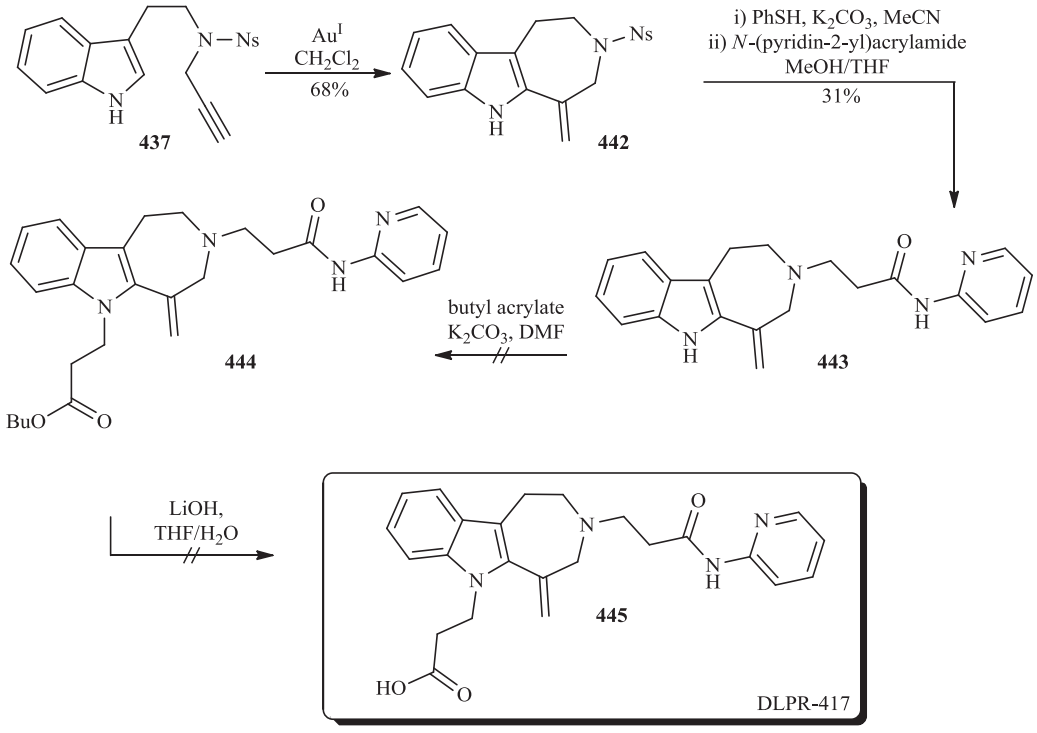
Deprotection of the nosyl group was carried out using thiophenol under basic conditions to afford the secondary amine.[555-557] Reaction of the deprotected indoloazocine with 2-pyridine acrylamide **423** afforded the desired aza-Michael adduct **439** in 67% yield over two steps. To install the carboxylic acid head group, the indoloazocine was again subject to reaction with methyl acrylate and K_2CO_3 in DMF (Scheme 5.8). The successful aza-Michael addition of the indole-nitrogen (in 88% yield) was confirmed through the absence of the indole-NH proton in the ^{1}H NMR spectrum in addition to the new proton resonances attributed to the alkyl-ester now present.

Saponification of the methyl ester **440** was attempted using aqueous sodium hydroxide, in ethanol.[264] A trace amount of the desired product **441** was identified; however a pure sample could not be produced. Further attempts to scale up this reaction sequence to allow access to

synthetically useful amounts of the desired indoloazocine PPARγ agonist **441** (DLPR-320) were unsuccessful, with the aza-Michael addition of the acrylamide not performing as well as previously. As access to the expensive gold-catalysts at this point was limited, the successful synthesis of the carboxylic acid was not realised.

Au(I) cyclisation to form the 7-membered N-heterocycle

The synthesis of an azepinoindole PPARγ agonist was envisaged employing a gold-catalysed reaction between the indole and an appropriately tethered alkyne to form the new 7-membered *N*-heterocycle. The nosyl-tryptamine alkyne **437** was subjected to reaction with the Au(I) catalyst (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate in CH_2Cl_2 to afford the 7-membered heterocycle **442** in good yield of 68% (Scheme 5.9).[94, 99-100, 558-559] The identity of this product was confirmed by mass spectrometry and NMR spectroscopy, with the absence of the indole-C2-proton resonance and the addition of the terminal alkene proton resonances integrating for 2 protons. As observed in previous studies, once the new *N*-heterocycle has formed, a slight downfield shift and altered splitting pattern of the ethylene CH_2 proton resonances was noted.



Scheme 5.9 The attempted synthesis of the azepinoindole PPARγ agonist

Following isolation of the azepinoindole **442**, the 2-nitrobenzenesulfonyl protecting group was cleaved using thiophenol under basic conditions.[555-557] Aza-Michael addition with 2-

pyridine acrylamide was again used to tether the requisite aromatic tail from the secondary amine of the indole scaffold (in 31% yield over 2 steps). To install the masked carboxylic acid, the indole-nitrogen was subject to aza-Michael addition with methyl acrylate. Although the NMR analysis of the crude reaction mixture indicated the reaction was successful, the desired product **444** was inseparable from the unreacted starting material (Scheme 5.9). The reaction sequence was scaled up, so that the functionalisation of the indole-nitrogen could be attempted with the less polar butyl acrylate to allow efficient separation. However, as in the case of the indoloazocine PPARγ agonist (Scheme 5.8), aza-Michael addition did not provide a synthetically useful yield of the amide **443**, and as access to the expensive gold-catalysts at this point was limited, the successful synthesis of the carboxylic acid **445** was not accomplished.

5.4 Conclusion

A number of current methodologies to access tricyclic indole-based scaffolds from tryptamine were investigated during the synthesis of PPARγ agonists. Each of these methodologies had advantages in terms of the size and functionality that could be introduced during the formation of the new C-N heterocycle.

The Pictet-Spengler reaction provided access to 6-membered heterocycles where a variety of substituents were able to be installed at the C1-position of the tetrahydro-*β*-carboline (including alkyl, aryl and ester functional groups). The secondary amine of the tetrahydro-*β*-carboline was then shown to be readily functionalised using acylation, alkylation and aza-Michael addition. The synthesis of propyl-TH*β*C PPARγ agonist **430** (DLPR-314) was completed in four steps from tryptamine.

A second method for accessing the tetrahydro-*β*-carboline scaffold, a Bischler-Napieralski reaction to synthesise the C1-methyl derivative was also used successfully. Further functionalisation of this indole-based scaffold afforded the methyl-TH*β*C PPARγ agonist **436** (DLPR-413) in good yield over 6 steps from tryptamine.

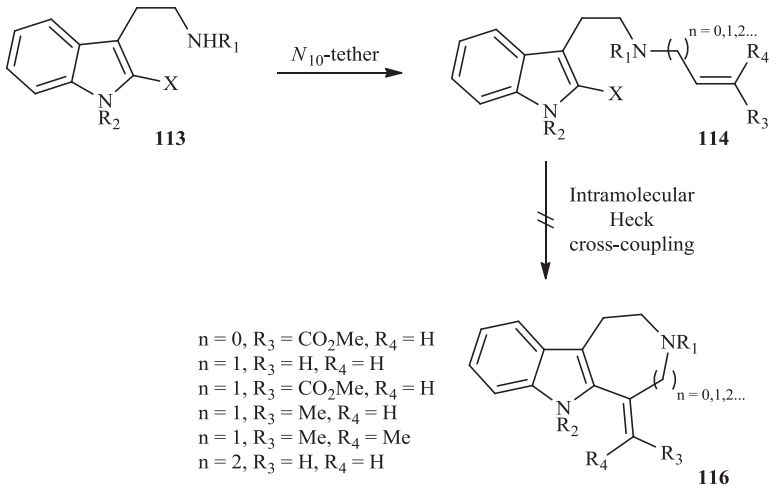
Construction of 7- and 8-membered indole-based *N*-heterocyclic scaffolds as PPARγ agonists was also pursued. A reaction pathway involving a gold-catalysed cyclisation step was identified for the synthesis of these functionalised indoles. However, low yielding aza-Michael addition steps, difficulties encountered during purification and limited access to the expensive gold-catalysts required means that to date, the reaction sequence has not been successfully completed to furnish both the azepinoindole **445** (DLPR-417) and the indoloazocine **441** (DLPR-320) PPARγ agonists.

The THβC PPARγ agonists (DLPR-314 and DLPR-413) were submitted for biochemical evaluation using glucose uptake and adipocyte differentiation assays to determine their potential as insulin-sensitising agents for the treatment of type 2 diabetes. Results from this analysis are still pending.

Chapter Six
Conclusion

6.1 New Methodology for the Synthesis of Indole-Based *N*-Heterocycles

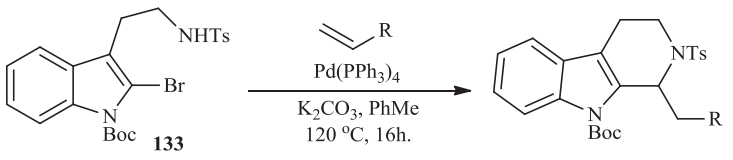
To complement existing methodology, two strategies were identified for the synthesis of indole-based *N*-heterocycles from tryptamine employing a Heck reaction at the indole-2-position. The first approach involved the tethering of a suitable olefinic cross-coupling partner from the N_{10}-amine of tryptamine **113** followed by intramolecular Heck reaction at the indole-2-position to form the *N*-heterocycle **116** (Scheme 6.1).



Scheme 6.1 The attempted synthesis of indole-based *N*-heterocycles using an intramolecular Heck reaction

Following the investigation into both single-step and domino processes for a number of these substrates, a range of olefin tethers were installed in good yields, however the intramolecular Heck reaction failed in each case to produce the new *N*-heterocycle in synthetically useful amounts.

The second approach investigated for the synthesis of indole-based *N*-heterocycles utilised an intermolecular Heck reaction at the indole-2-position followed by nucleophilic amine addition. This ultimately lead to the development of a domino Heck-aza-Michael process for the synthesis of a series C1-substituted tetrahydro-*β*-carbolines (Scheme 6.2).



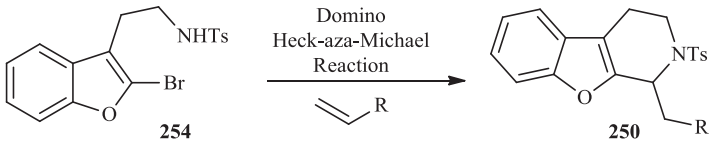
R = $CO_2(CH_2)_3CH_3$ **214** (83%) = $CONH_2$ **239** (80%)
= CO_2CH_3 **236** (79%) = CN **240** (67%)
= $CO_2(CH_2)_2OH$ **237** (64%) = $COCH_3$ **241** (78%)
= CHO **238** (64%)

Scheme 6.2 The domino Heck-aza-Michael reaction for the synthesis of TH*β*Cs

6.2 Domino Heck-aza-Michael Reactions

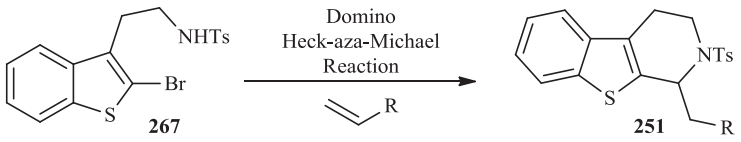
To further expand the scope of the domino Heck-aza-Michael reaction, the preparation of several additional *N*-heterocycles using this methodology was investigated (Schemes 6.3-6.6). This domino process allowed access to a range of heterocyclic ring systems where the C1-subsituent could be readily varied through appropriate alkene selection.

For the synthesis of benzofuran based *N*-heterocycles, the domino substrate **254** was prepared in good yield over 7 steps from 2-hydroxyacetophenone. Unfortunately, following the screening of several reaction conditions, only trace amounts of the domino adduct **250** were produced (Scheme 6.3)



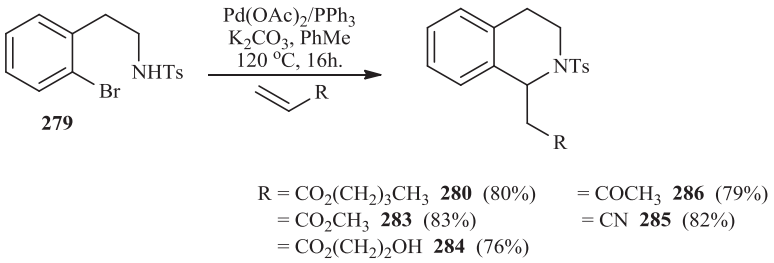
Scheme 6.3 The attempted synthesis of benzofuran based *N*-heterocycles using the domino Heck-aza-Michael methodology

In a similar fashion to investigations into the benzofuran system, the benzothiophene domino substrate **267** was prepared in 6 steps from thiophenol. Unfortunately, the bromination of the benzothiophene could not be optimised above 27%, and as such investigation into the domino Heck-aza-Michael process was not synthetically viable (Scheme 6.4).



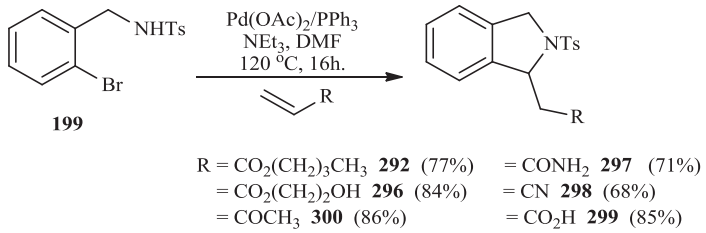
Scheme 6.4 The proposed synthesis of benzothiophene based *N*-heterocycles

The domino Heck-aza-Michael reaction sequence was next used for the synthesis of C1-substituted tetrahydroisoquinolines (Scheme 6.5). Optimisation studies using butyl acrylate identified high yielding conditions for the domino process that was then applied to a range of electron deficient terminal alkenes to afford a series of functionalised tetrahydroisoquinolines.



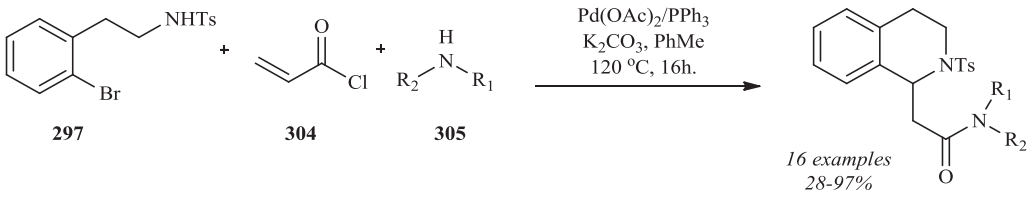
Scheme 6.5 The synthesis of a series of C1-subsituted tetrahydroisoquinolines

The final heterocyclic system constructed using the domino Heck-aza-Michael process was the isoindoline. A series of six isoindolines were successfully prepared using this methodology in high yields containing a variety of substituents at the C1-position (Scheme 6.6).



Scheme 6.6 The domino Heck-aza-Michael reaction developed for the synthesis of isoindolines

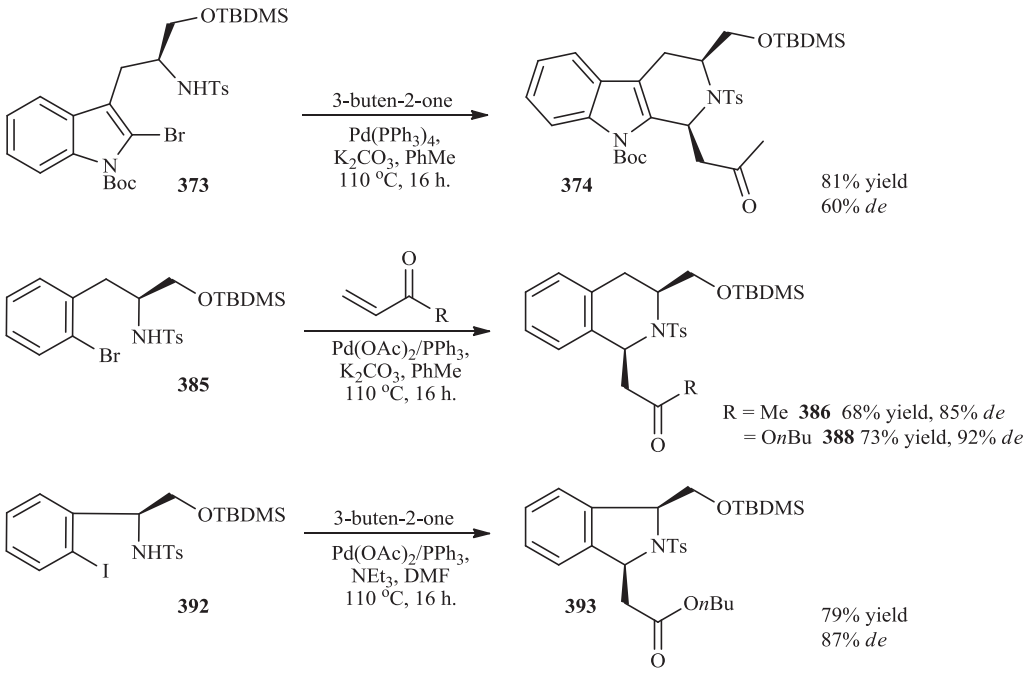
Only commercially available electron-deficient alkenes had been employed for the domino Heck-aza-Michael reactions. To allow greater variation in the substituent introduced at the C1-position of the newly formed tetrahydroisoquinolines, a three-component process was developed where both acrylamide formation and the domino reaction took place in one-pot. A series of sixteen C1-substituted tetrahydroisoquinolines were prepared using primary amines, secondary amines and amino acids (Scheme 6.7).



Scheme 6.7 The three-component, one-pot approach to functionalised tetrahydroisoquinolines

To further extend the scope of this domino Heck-aza-Michael methodology, an asymmetric variant of this reaction was developed. Initial investigations were performed using chiral

protecting groups (up to 50% *de*) and chiral alkenes (up to 40% *de*). However the best results for this domino process were obtained when chiral amine substrates were employed (up to 92% *de*, Scheme 6.8). The synthesis of chiral 1,3-disubstituted tetrahydro-*β*-carbolines, tetrahydroisoquinolines and isoindolines from naturally occurring amino acids was completed in good to excellent yields and moderate to good diastereoselectivity (with the major isomer determined as the *cis*-diastereomer by NOE NMR experiments).



Scheme 6.8 The asymmetric domino Heck-aza-Michael reaction

6.3 Synthesis of Indole-Based PPARγ Agonists

Following investigations into the new methods for the preparation of indole-based N-heterocycles from tryptamine, the design and synthesis of conformationally restricted PPARγ agonists for the treatment of type 2 diabetes was carried out. These PPARγ agonists were constructed around the indole-based *N*-heterocyclic scaffold, where, during heterocycle formation, the size and functionality of the new ring system formed could be readily varied.

Two tetrahydro-*β*-carboline PPARγ agonists were constructed employing the Pictet-Spengler reaction (DLPR-314 – four steps from tryptamine) or the related Bischler-Napieralski methodology (DLPR-413 – six steps from tryptamine), and these have been submitted for biochemical evaluation.

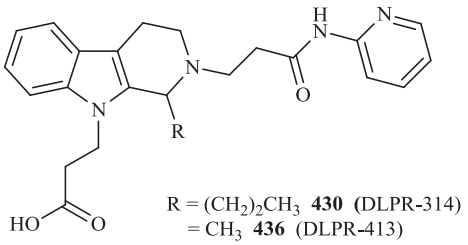


Figure 6.1 The synthesis of two THβC PPARγ agonists from tryptamine was completed

To further investigate these PPARγ agonists, the synthesis of both 7- and 8-membered heterocyclic systems was achieved using a gold-catalysed cyclisation process. The further elaboration of these indole scaffolds to afford the fully functionalised PPARγ agonists was only partially completed.

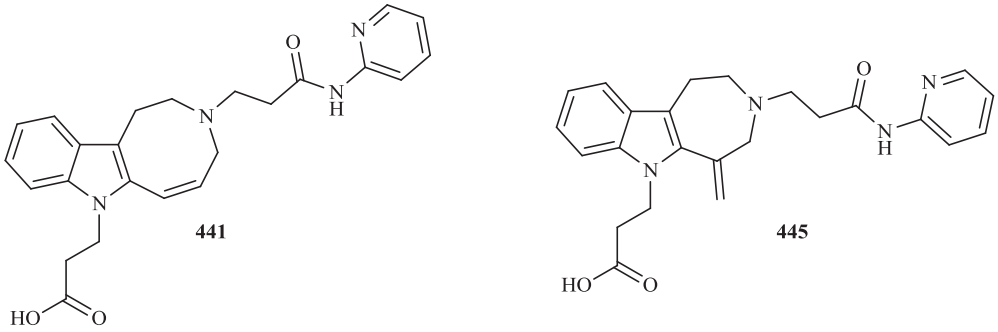


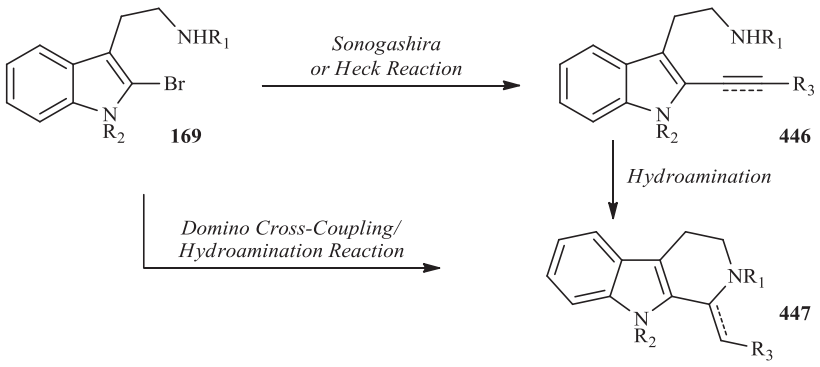
Figure 6.2 The synthesis of PPARγ agonists containing a 7- or 8-membered *N*-heterocycle was partially completed

6.4 Future Work

A number of additional ideas stemming from this research project are presented in the following section.

6.4.1 New Methodology for the Synthesis of Indole-Based *N*-Heterocycles

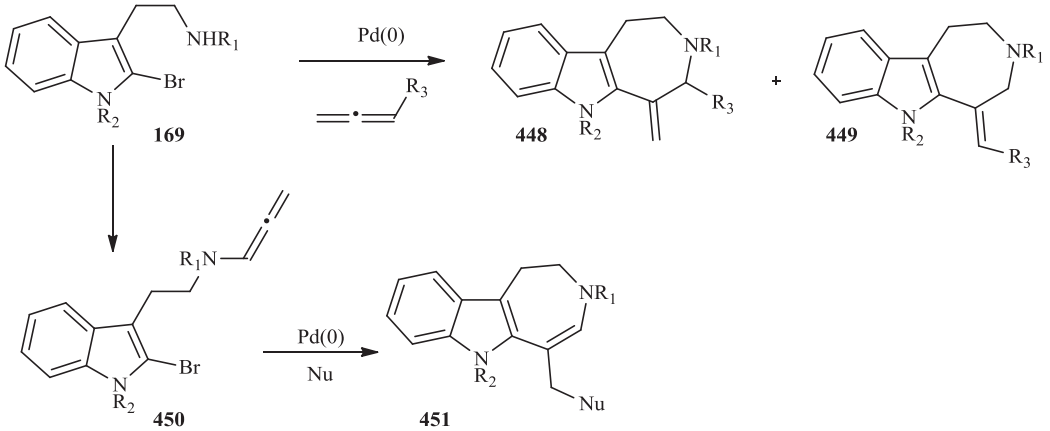
Further to the new methods investigated during this work for the synthesis of indole-based *N*-heterocycles, two additional approaches were identified. The first would involve a palladium-mediated cross-coupling/hydroamination pathway for the synthesis of *β*-carbolines (Scheme 6.9).



Scheme 6.9 The proposed cross-coupling/hydroamination reaction to access *β*-carbolines

Following either the Heck reaction or Sonogashira reaction at the indole-2-position to install an alkene or alkyne respectively,[235, 560] hydroamination of the N_{10}-amine would form the new *N*-heterocycle. A range of appropriately functionalised alkenes and alkynes would lead to a series of C1-substituted *β*-carbolines **447**. A similar reaction sequence for the synthesis of benzofused sultams was reported by Hanson *et al.*[261] Hydroamination of both alkenes and alkynes is reported using palladium catalysis, in addition to a range of other conditions.[439, 561-570] Ideally, the reaction conditions could be tuned to facilitate a domino cross-coupling/hydroamination pathway.

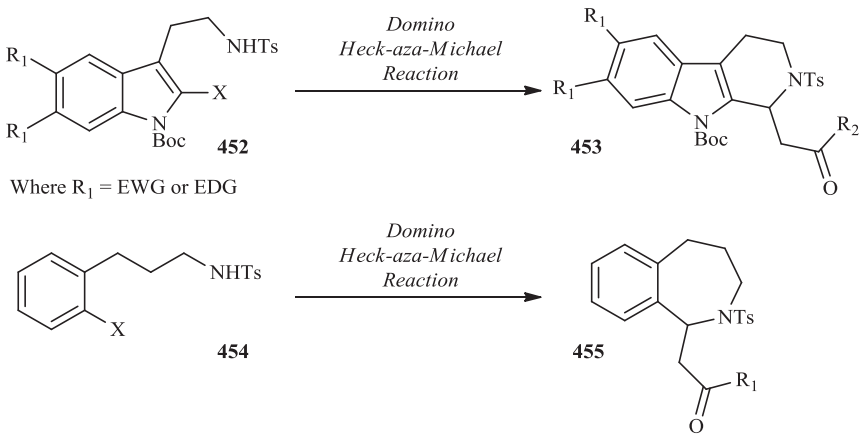
New methodology for the synthesis of azepinoindoles could be accomplished employing allenes. One reaction sequence would involve a palladium-mediated C-C cross coupling reaction at the indole-2-position followed by the addition of the N_{10}-amine, providing access to a series of functionalised azepinoindoles **448** or **449** (Scheme 6.10).[571] Similarly, by first tethering an allene to the N_{10}-amine of tryptamine,[572-574] followed by the palladium-catalysed cross coupling at the indole-2-position, functionalised 7-membered heterocycles **451** would be produced (Scheme 6.10). A similar strategy, using these allenamide intermediates was employed in the synthesis of functionalised indoles.[575]



Scheme 6.10 Allenes could also be used in the synthesis of azepinoindoles

6.4.2 Further applications of the Domino Heck-aza-Michael reaction

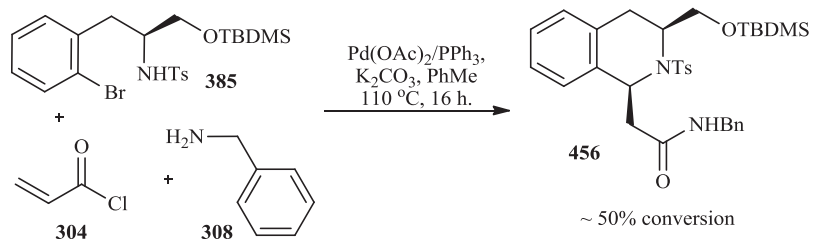
To further explore the potential of the domino Heck-aza-Michael methodology, there are several additional factors that could be investigated (Scheme 6.11). These include the use of aryl-iodides to increase the rate of the Heck reaction, the use of more highly functionalised aryl-halides **452** (with both electron-withdrawing and electron-donating groups) and further investigations into the synthesis of ring systems of greater size (for example benzazepines **455**).



Scheme 6.11 Further application of the domino Heck-aza-Michael methodology

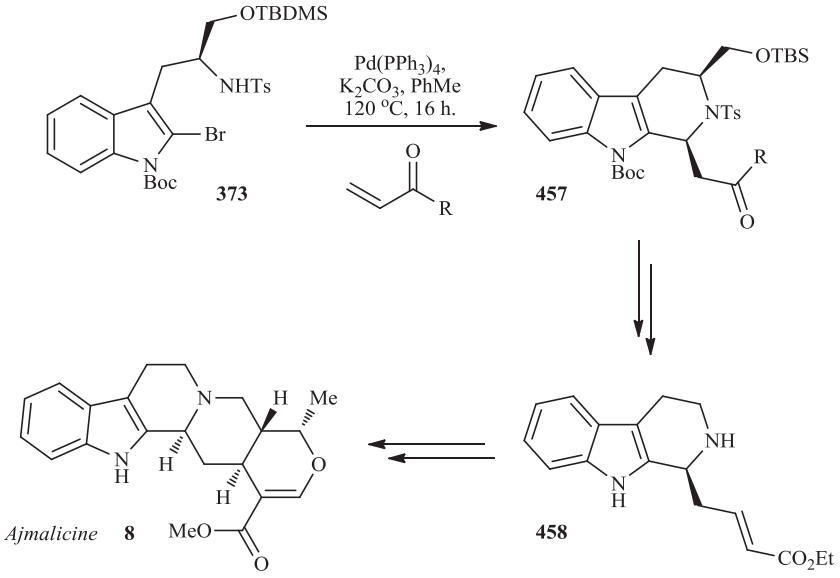
It was also considered that the use of an alternative amine protecting group (for example trifluoromethansulfonyl instead of the tosyl group) would allow aza-Michael addition to proceed for those instances where only the Heck adduct was produced. The particular systems where this may apply include the multicomponent approach to the tetrahydro-*β*-carboline and isoindoline heterocycles, as well as for the asymmetric variant with the methyl ester intact.

Further optimisation of substrate preparation and the domino reaction itself is also required for the asymmetric variant, to expand the scope of this process to allow the use of additional alkene coupling partners. The further development of a stereoselective three-component domino process also warrants investigation. Initial reactions employing the chiral phenethylamine substrate **385** resulted in 50% conversion to the domino adduct **456**, however this was inseparable from the other major product produced, the Heck adduct (Scheme 6.12).



Scheme 6.12 The asymmetric three-component domino process

The application of the domino Heck-aza-Michael methodology in total synthesis could also be investigated. Utilising the asymmetric variant, it was envisaged that access to intermediates in a proposed total synthesis of both Elaeocarpidine and Ajmalicine **8** would be available (Scheme 6.13).[22-23, 576]



Scheme 6.13 The domino Heck-aza-Michael reaction potentially employed in the total synthesis of natural products

6.4.3 Indole-Based PPARγ Agonists

The synthesis of both the indoloazocine and azepinoindole PPARγ agonists would need to be completed, and biochemical evaluation would confirm the role the size and functionality contained with the *N*-heterocyclic scaffold has on conformational restriction and therefore binding within the PPARγ. To further investigate the role of indole-based *N*-heterocycles, there are several other synthetic strategies available to access these scaffolds, each allowing for variation in the ring size and functionality introduced during *N*-heterocycle formation.

Chapter Seven
Experimental

7.1 General Experimental

All compounds synthesised were analysed by high resolution TOFMS, ^{1}H NMR spectroscopy, and ^{13}C NMR spectroscopy. In addition, melting points (mp) were collected where possible.

Instrumentation

NMR spectra were collected on either a JEOL JNM-GX 270 MHz FT-NMR spectrometer (Tokyo, Japan), a JEOL JNM-ECP 400 MHz FT-NMR spectrometer (Tokyo, Japan), or a Varian Unity + 300 MHz FT-NMR spectrometer (Palo Alto, USA) where indicated. Samples were dissolved in $CDCl_3$, d_3-MeOH, d_6-acetone or d_6-DMSO (~1 mL) and referenced against TMS = 0.00 ppm. Proton spectra are reported as: chemical shift (ppm) δ (multiplicity, coupling constant (Hz), integral, assignment). Carbon spectra are reported as the corresponding δ.

High resolution TOFMS spectra were collected on an Agilent 6210 LC/MSDTOF spectrometer (California, USA). Analyte solutions (concentration ~ 1 mM) were prepared in HPLC grade MeCN and recorded in the positive or negative ion mode with a mobile phase (MeCN) flow rate of 5 µl min-1. HRMS spectra are reported as: molecular formula, calculated parent ion (*m/z*), observed parent ion (*m/z*).

Chiral HPLC traces were collected on an Agilent 1200 series HPLC spectrometer (California, USA) using a UV detector. The column used was a Chiralpak AD-H column, and samples were run at a flow rate of 1.0 mL/min, injection volume 20 µL, at 25 ^{o}C. Analyte solutions (concentration ~ 1 mM) were prepared in HPLC grade 10% isopropanol/*n*-hexane.

Reactions employing microwave irradiation were completed in a 10 mL capped vial using a CEM Discover microwave.

All melting points were obtained using Stuart Scientific SMP3 melting point apparatus and are uncorrected.

Chromatography

Thin layer chromatography was achieved using Merck 60 F_{254} silica plates backed with aluminium. Visualisation employed a UVP Mineralight 254 nm UV lamp or an oxidising dip containing $KMnO_4$ (1.0 g), K_2CO_3 (1.0 g) and H_2O (100 mL). Heating of the ‘dipped‘ TLC plate with a heat-gun ensured all oxidisable compounds became visible.

Column chromatography was performed using Merck Kieselgel 60 (70 – 230 mesh). Columns were generally prepared from a slurry in a mixture of ethyl acetate/petroleum spirit. Products were eluted (gradient) with mixtures of EtOAc/Pet Sp and MeOH. All solvents were of AR grade.

Dry Solvents

THF, $CHCl_3$ and DMF were dried using the *Pure Solv* (Innovative Technologies) solvent drying system. Solvents are degassed, and passed through two drying chambers of alumina and stored and collected under a positive pressure of nitrogen gas.

Reagents

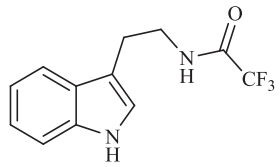
All general reagents were analytical grade and used as supplied unless otherwise stated. Purification and/or drying of general reagents was performed according to *Perrin*.[577] Specialist reagents such as peptide coupling reagents and isothiocyanates were supplied by Aldrich Chemical Co.[578] or A.K Scientific Inc.[579] and used as supplied. Palladium tetrakis(triphenylphosphine) was prepared according to a literature procedure.[580]

7.2 Specific Experimental

The following sections detail the specific experimental conditions for each of the compounds successfully synthesised during this research project. The compounds are listed in chronological order according to the chapter in which they first appear.

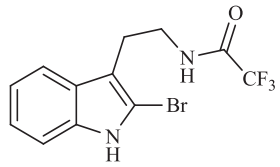
7.2.1 Chapter Two

_N_-(2-(1_H_-indol-3-yl)ethyl)-trifluoroacetamide (459)



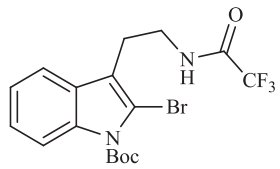
To a stirring solution of tryptamine (4.0 g, 25.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C, was added trifluoroacetic anhydride (5.24 g, 25.0 mmol). After 30 mins. a solution of $NaHCO_3$ (saturated aqueous, 20 mL) was added and stirring continued for an additional 15 mins. After this time, the aqueous phase was extracted (CH_2Cl_2, 3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a light brown amorphous solid (5.444 g, 21.2 mmol, 85%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.05 (brs, 1H, indole-NH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.40 (d, J = 7.9 Hz, 1H, ArH), 7.11-7.23 (m, 2H, ArH), 7.05 (d, J = 2.5 Hz, 1H, indole-C2- ArH), 6.29 (brs, 1H, $NHCOCF_3$), 3.70 (q, J = 6.5 Hz, 2H, CH_2CH_2NH), 3.05 (t, J = 7.0 Hz, 2H, CH_2CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 159.7 (q, J = 35 Hz), 137.4, 128.5, 127.2, 121.3, 120.9, 117.9, 116.1 (q, J = 279 Hz), 112.1, 111.6, 41.4, 24.1; HRMS-ESI (*m/z*) $[C_{12}H_{11}F_3N_2O + H]^+$ calcd 257.0896, found 257.0907.

_N_-(2-(2-bromo-1_H_-indol-3-yl)ethyl)-trifluoroacetamide (460)



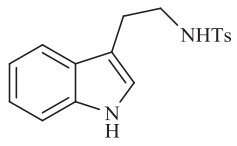
To a solution of trifluoroacetamide-indole **459** (542 mg, 2.12 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *N*-bromosuccinimide (377 mg, 2.33 mmol) and the reaction stirred at room temperature for 30 mins. After this time the reaction mixture was concentrated and purified by column chromatography (1:9 EtOAc:Pet Sp.) to afford the title compound as a yellow oil that solidified on standing (587 mg, 1.75 mmol, 83%). M.p. 101–103 °C. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 8.13 (brs, 1H, indole-NH), 7.51 (d, J = 8.0 Hz, 1H, ArH), 7.30 (d, J = 7.9 Hz, 1H, ArH), 7.12-7.20 (m, 2H, ArH), 6.32 (brs, 1H, $NHCOCF_3$), 3.66 (q, J = 6.4 Hz, 2H, CH_2CH_2NH), 3.02 (t, J = 6.6 Hz, 2H. CH_2CH_2NH). ^{13}C NMR (125.8 MHz, d_6-acetone, δ): 157.7 (q, J = 36 Hz), 137.5, 128.5, 122.8, 120.5, 118.6, 117.1 (q, J = 288 Hz), 112.1, 111.6, 109.6, 40.4, 24.9. HRMS-ESI (*m/z*) $[C_{12}H_{10}BrF_3N_2O + H]^+$ calcd 335.0001, found 334.9989.

***tert*-butyl 2-bromo-3-(2-(trifluoroacetamido)ethyl)-1_H_-indole-1-carboxylate (60)**



To a stirred solution of trifluoroacetate-2-bromoindole **460** (1218 mg, 3.63 mmol) and DMAP (45 mg, 0.36 mmol) in THF (30 mL) was added di-*tert*-butyl dicarbonate (873 mg, 4.0 mmol) in one portion. The resulting solution was heated to 40 °C for 30 mins. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), and water (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:9 EtOAc:Pet Sp.) afforded the title compound as as a white solid (1000 mg, 2.30 mmol, 63%) M.p. 115-116 °C. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 8.09 (d, J = 8.4 Hz, 1H, ArH), 7.46 (d, J = 7.6 Hz, 1H, ArH), 7.24-7.32 (m, 2H, ArH), 6.43 (brs, 1H, $NHCOCF_3$), 3.62 (q, J = 6.4 Hz, 2H, CH_2CH_2NH), 3.05 (t, J = 6.7 Hz, 2H, CH_2CH_2NH), 1.71 (s, 9H, Boc-*t*Bu); ^{13}C NMR (125.8 MHz, $CDCl_3$ δ): 157.5 (q, J = 37.1 Hz), 149.1, 136.7, 128.6, 125.0, 123.4, 119.2, 117.8, 115.8 (q, J = 287.9 Hz), 115.6, 110.0, 85.4, 39.3, 28.3, 24.8; HRMS-ESI (*m/z*) $[C_{17}H_{18}BrF_3N_2O_3 + H]^+$ calc. 435.0526; found 435.0535.

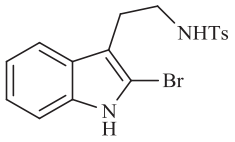
3-(2-(_p_-toluenesulfonamido)ethyl)indole (131)



To a cooled solution (0 °C) of tryptamine (1.0 g, 6.2 mmol) and triethylamine (695 mg, 6.9 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (1.43 g, 7.5 mmol) in one portion. The reaction mixture was stirred for 2 h. at ambient temperature before being treated with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated to afford the title compound as a pale orange solid (1.94 g, 6.2 mmol, 99%). FT-IR (ν, cm^{-1}, KBr) 3406, 3282, 1316, 1154, 744; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.11 (brs, 1H, indole-NH), 7.63 (d, J = 8.4 Hz, 2H, ArH), 7.40 (d, J = 8.0 Hz, 1H, ArH), 7.34 (d, J = 8.0 Hz, 1H, ArH), 7.21 (d, J = 8.0 Hz, 1H, ArH), 7.17 (d, J = 8.0 Hz, 1H, ArH), 7.05 (t, J = 8.0 Hz, 2H, ArH), 6.97 (d, J = 2.4 Hz, 1H, indole-C2- ArH), 4.45 (brt, J = 6.4 Hz, 1H, NHTs), 3.26 (q, J = 6.4 Hz, 2H, CH_2CH_2NH), 2.93 (t, J = 6.4 Hz, 2H, CH_2CH_2NH), 2.39 (s, 3H, Ts-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 142.1, 135.5, 135.2, 128.4, 125.8, 125.7, 121.4, 121.0, 118.2, 117.2, 110.3,

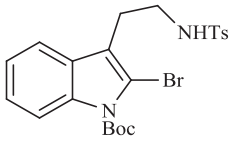
110.1, 41.8, 24.3, 20.3; HRMS-ESI (*m/z*) $[C_{17}H_{18}N_2O_2S + H]^+$ calcd 315.1162, found 315.1160.

2-bromo-3-(2-(*p*-toluenesulfonamido)ethyl)indole (132)



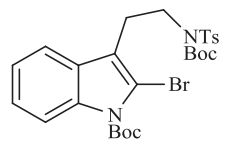
A solution of tosyl-indole **131** (600 mg, 1.9 mmol) in THF:$CHCl_3$ (1:1, 100 mL) was stirred at 0 °C for 15 mins. Pyridinium tribromide (671 mg, 2.1 mmol) was then added portion-wise over 1 h. Saturated aqueous sodium sulphite (10 mL) was added, and following a colour change to orange, saturated aqueous $NaHCO_3$ (10 mL) was also added. The aqueous phase was extracted with $CHCl_3$ (2 × 5 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was subjected to column chromatography (1:3 EtOAc:Pet Spirits) to afford the title compound as a clear colourless oil (673 mg, 90%). FT-IR (ν, cm^{-1}, KBr) 3385, 1701, 1620, 1472, 1323, 1156, 754; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.52 (brs, 1H, indole-NH), 7.64 (d, *J* = 8.2 Hz, 2H, ArH), 7.34 (d, *J* = 7.9 Hz, 1H, ArH), 7.24 (m, 1H, ArH), 7.17 (d, *J* = 8.5 Hz, 1H, ArH), 7.17 (m, 1H, ArH), 7.04 (m, 2H, ArH), 4.72 (brt, *J* = 6.1 Hz, 1H, NHTs), 3.25 (q, *J* = 6.7 Hz, 2H, CH_2CH_2NH), 2.88 (t, *J* = 7.0 Hz, 2H, CH_2CH_2NH), 2.36 (s, 3H, $TsCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 142.1, 135.4, 134.9, 128.4, 126.0, 125.7, 121.1, 118.9, 116.5, 109.8, 109.6, 107.7, 41.5, 24.1, 20.3; HRMS-ESI (*m/z*) $[C_{17}H_{17}BrN_2O_2S + H]^+$ calcd 393.0278, found 393.0289.

***tert*-butyl 2-bromo-3-(2-(*p*-toluenesulfonamido)ethyl)-1*H*-indole-1-carboxylate (133)**



To a solution containing tosyl-2-bromoindole **132** (940 mg, 2.39 mmol) and DMAP (15 mg, 0.120 mmol) in CH_2Cl_2 (50 mL) was added di-*tert*-butyl dicarbonate (574 mg, 2.63 mmol). After stirring for 2 h. at ambient temperature, water (10 mL) was added. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (1:4 EtOAc:Pet Spirits) afforded the title compound as a clear colourless oil (633 mg, 1.28 mmol, 56%). FT-IR (ν, cm^{-1}, KBr) 2980, 1732vs, 1450, 1353, 1155, 1100; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.61 (d, *J* = 8.3 Hz, 2H, ArH), 7.35 (d, *J* = 7.8 Hz, 1H, ArH), 7.12-7.25 (m, 4H, ArH), 4.91 (brt, 1H, NHTs), 3.23 (q, *J* = 6.8 Hz, 2H, CH_2CH_2NH), 2.89 (t, *J* = 7.0 Hz, 2H, CH_2CH_2NH), 2.35 (s, 3H, $TsCH_3$), 1.69 (s, 9H, Boc-*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 147.7, 142.0, 135.6, 135.2, 128.3, 127.2, 125.7, 123.3, 121.9, 118.0, 116.7, 114.1, 108.5, 83.9, 40.8, 27.0, 24.7, 20.3; HRMS-ESI (*m/z*) $[C_{22}H_{25}BrN_2O_4S + H]^+$ calcd 493.0791, found 493.0810.

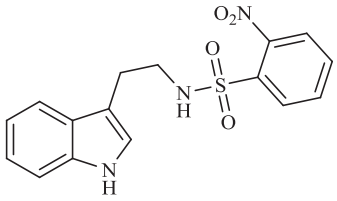
***tert*-butyl 2-bromo-3-(2-(*N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamido)ethyl)-1*H*-indole-1-carboxylate (134)**



To a solution containing tosyl-2-bromoindole **132** (650 mg, 1.65 mmol) and DMAP (10 mg, 0.08 mmol) in THF (20 mL) was added di-*tert*-butyl dicarbonate (397 mg, 1.81 mmol). After stirring for 2 h. at 40 °C, water (10 mL) was added. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (1:4 EtOAc:Pet Spirits) to afford the title compound as a clear colourless oil (426 mg, 0.72 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.07 (dd, *J* = 1.9 and 7.0 Hz, 1H, ArH), 7.74 (d, *J* = 8.3 Hz, 2H, ArH), 7.67 (dd, *J* = 2.2 and 6.7 Hz, 1H, ArH), 7.24-7.30 (m, 4H, ArH), 3.99 (t, *J* = 7.8 Hz, 2H, CH_2CH_2NH), 3.19 (t, *J* = 8.1 Hz, 2H,

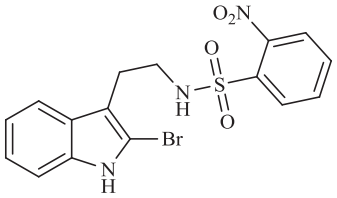
C<u>H</u>$_2$CH$_2$NH), 2.41 (s, 3H, TsC<u>H</u>$_3$), 1.69 (s, 9H, Indole-N<u>Boc</u>), 1.36 (s, 9H, TsN<u>Boc</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.0, 149.2, 144.2, 137.3, 136.6, 129.3, 128.9, 128.0, 124.6, 123.2, 119.7, 118.6, 115.3, 109.9, 85.5, 84.4, 45.7, 28.3, 28.0, 26.5, 21.7; HRMS-ESI (*m/z*) $[C_{27}H_{33}BrN_2O_6S + H]^+$ calcd 593.1315, found 593.1306.

_N_-(2-(1_H_-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (140)



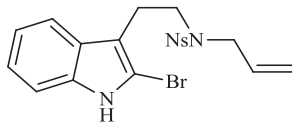
To a solution of tryptamine (500 mg, 3.12 mmol) and triethylamine (473 mg, 4.68 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 2-nitrobenzenesulfonyl chloride (761 mg, 3.43 mmol). The reaction mixture was stirred for 2 h. at ambient temperature before being treated with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated to afford the title compound as a pale orange solid (1.017 g, 2.94 mmol, 94%). M.p. 131.5-133.6 °C ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.01 (m, 1H, Ar<u>H</u>), 7.97 (brs, 1H, indole-N<u>H</u>), 7.57-7.67 (m, 3H, Ar<u>H</u>), 7.30 (t, *J* = 7.9 Hz, 2H, Ar<u>H</u>), 7.13 (ddd, *J* = 1.1 and 7.0 and 8.2 Hz, 1H, Ar<u>H</u>), 7.01 (d, *J* = 2.2 Hz, 1H, Ar<u>H</u>), 6.95 (ddd, *J* = 1.1 and 7.0 and 8.0 Hz, 1H, Ar<u>H</u>), 5.32 (t, *J* = 5.9 Hz, 1H, NsN<u>H</u>), 3.45 (q, *J* = 6.5 Hz, 2H, CH$_2$C<u>H</u>$_2$NH), 2.99 (t, *J* = 6.6 Hz, 2H, C<u>H</u>$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 136.5, 135.2, 133.4, 132.7, 130.9, 126.7, 125.4, 124.4, 122.9, 122.3, 119.6, 118.3, 111.4, 111.3, 43.8, 25.5; HRMS-ESI (*m/z*) $[C_{16}H_{15}N_3O_4S + Na]^+$ calcd 368.0675, found 368.0683. (*NB*: 2-nitrobenzenesulfonyl is abbreviated as nosyl or Ns).

_N_-(2-(2-bromo-1_H_-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (141)



To a solution of *N*-nosyltryptamine **140** (500 mg, 1.45 mmol) in THF/$CHCl_3$ (1:1, 100 mL) kept at 0 °C was added pyridinium tribromide (509 mg, 1.60 mmol) portionwise over 1 h. After stirring for an additional 15 mins. the reaction was quenched by the addition of saturated aqueous Na_2SO_4 (10 mL) and following a colour change saturated aqueous $NaHCO_3$ (10 mL). After stirring for 15 minutes the reaction mixture was exctracted (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography (20% EtOAc/Pet. Sp.) to afford the title compound as a yellow oil (560 mg, 1.32 mmol, 91%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.09 (brs, 1H, indole-N<u>H</u>), 7.96 (m, 1H, Ar<u>H</u>), 7.64 (m, 1H, Ar<u>H</u>), 7.56 (m, 2H, Ar<u>H</u>), 7.29 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 7.17 (dt, *J* = 1.0 and 8.1 Hz, 1H, Ar<u>H</u>), 7.10 (dt, *J* = 1.2 and 7.0 Hz, 1H, Ar<u>H</u>), 6.98 (ddd, *J* = 1.2 and 7.0 and 8.0 Hz, 1H, Ar<u>H</u>), 5.36 (t, *J* = 5.5 Hz, 1H, NsN<u>H</u>), 3.46 (q, *J* = 6.8 Hz, 2H, CH$_2$C<u>H</u>$_2$NH), 2.95 (t, *J* = 6.9 Hz, 2H, C<u>H</u>$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 147.5, 136.1, 133.6, 133.3, 132.7, 130.7, 127.2, 125.4, 122.6, 120.4, 117.7, 111.0, 110.7, 109.3, 43.4, 25.4; HRMS-ESI (*m/z*) $[C_{16}H_{14}N_3O_4BrS + H]^+$ calcd 423.9961, found 423.9947.

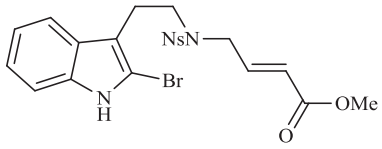
_N_-allyl-_N_-(2-(2-bromo-1_H_-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (142)



A solution of nosyl-2-bromotryptamine **141** (173 mg, 0.41 mmol), allyl bromide (54 mg, 0.45 mmol) and K_2CO_3 (85 mg, 0.61 mmol) in acetonitrile (5 mL) was heated to 50 °C for 16h. The solvent was removed and the reaction mixture purified by

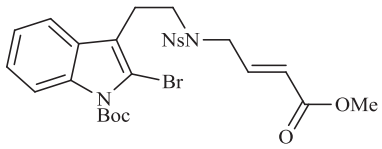
column chromatography (1:2 EtOAc:Pet Sp.) to afford the title compound as a pale orange oil (176 mg, 0.38 mmol, 93%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.14 (brs, 1H, indole-NH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH), 7.56 (m, 3H, ArH), 7.46 (d, *J* = 7.7 Hz, 1H, ArH), 7.22 (d, *J* = 7.9 Hz, 1H, ArH), 7.12 (m, 2H, ArH), 5.79 (m, 1H, CH_2CH=CH_2) 5.29 (dd, *J* = 17.1 and 24.1 Hz, 2H, CH_2CH=CH_2), 4.08 (d, *J* = 6.4 Hz, 2H, CH_2CH=CH_2), 3.49 (m, 2H, CH_2CH_2NH), 2.96 (m, 2H, CH_2CH_2NH); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 136.3, 133.8, 133.4, 133.1, 132.5, 131.7, 131.0, 127.2, 124.3, 122.2, 120.1, 119.8, 117.1, 113.2, 111.2, 109.8, 50.6, 46.3, 24.7; HRMS-ESI (*m/z*) $[C_{19}H_{18}N_3O_4SBr + H]^+$ calcd 464.0274, found 464.0279.

(*E*)-methyl 4-(*N*-(2-(2-bromo-1*H*-indol-3-yl)ethyl)-2-nitrophenylsulfonamido)but-2-enoate (143)



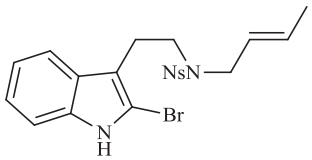
A solution containing nosyl-2-bromotryptamine **141** (238 mg, 0.56 mmol), methyl-4-bromocrotonate (110 mg, 0.62 mmol) and K_2CO_3 (116 mg, 0.84 mmol) in acetonitrile (5 mL) was stirred at 60 °C for 4 h. After this time the solvent was evaporated. The reaction mixture was diluted with EtOAC (5 mL) and washed with H_2O (10 mL) then brine. The organic phase was separated and dried over $MgSO_4$. Purification by column chromatography (1:3 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (258 mg, 0.49 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.24 (brs, 1H, indole-NH), 7.96 (dd, *J* = 0.6 and 7.5 Hz, 1H, ArH), 7.58 (m, 3H, ArH), 7.40 (d, *J* = 7.5 Hz, 1H, ArH), 7.21 (d, *J* = 14.0 Hz, 1H, ArH), 7.06-7.16 (m, 2H, ArH), 6.85 (dt, *J*= 6.0 and 15.7 Hz, 1H, CH_2CH=CH), 6.02 (d, *J* = 15.7 Hz, 1H, CH_2CH=CH), 4.23 (dd, *J* = 1.2 and 6.0 Hz, 2H, CH_2CH=CH), 3.73 (s, 3H, CO_2Me), 3.51 (t, *J*= 7.4 Hz, 2H, CH_2CH_2NH), 2.94 (dd, *J* = 5.9 and 8.0 Hz, 2H, CH_2CH_2NH); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 166.2, 147.6, 142.8, 136.1, 133.8, 133.2, 131.9, 130.9, 127.3, 124.4, 124.2, 122.5, 120.3, 117.9, 111.2, 110.8, 108.9, 52.0, 48.6, 47.0, 24.1; HRMS-ESI (*m/z*) $[C_{21}H_{20}N_3O_6SBr + H]^+$ calcd 522.0329, found 522.0322.

(*E*)-*tert*-butyl 2-bromo-3-(2-(*N*-(4-methoxy-4-oxobut-2-en-1-yl)-2-nitrophenylsulfonamido)ethyl)-1*H*-indole-1-carboxylate (146)



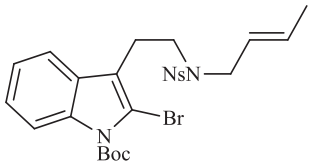
A solution containing 2-bromoindole crotonate **143** (186 mg, 0.36 mmol), di-*tert*-butyl dicarbonate (94 mg, 0.43 mmol) and DMAP (4 mg, 0.04 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 h. After this time H_2O (10 mL) was added to quench the reaction and the aqueous phase extracted with CH_2Cl_2 (3 × 5mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography afforded the title compound as a pale yellow oil (152 mg, 0.24 mmol, 69%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.99 (m, 1H, ArH), 7.96 (dd, *J* = 1.3 and 1.8 Hz, 1H, ArH), 7.91 (dd, *J* = 1.0 and 7.8 Hz, 1H, ArH) 7.48-7.59 (m, 2H, ArH), 7.41 (m, 1H, ArH), 7.22 (m, 2H, ArH), 6.86 (dt, *J* = 6.0 and 15.7 Hz, 1H, CH_2CH=CH), 6.00 (dt, *J* = 1.4 and 15.7 Hz, 1H, CH_2CH=CH), 4.26 (dd, *J* = 1.4 and 6.0 Hz, 2H, CH_2CH=CH), 3.71 (s, 3H, CO_2Me), 3.48 (m, 2H, CH_2CH_2NH), 2.95 (m, 2H, CH_2CH_2NH), 1.67 (s, 9H, Boc-*t*Bu); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 166.0, 148.9, 147.6, 142.5, 133.7, 133.3, 131.8, 131.0, 128.3, 124.8, 124.6, 124.4, 123.3, 119.1, 118.0, 115.5, 109.8, 103.0, 85.3, 51.9, 48.7, 46.2, 28.3, 24.6; HRMS-ESI (*m/z*) $[C_{26}H_{28}N_3O_8SBr + H]^+$ calcd 622.0853, found 622.0838.

(*E*)-*N*-(2-(2-bromo-1*H*-indol-3-yl)ethyl)-*N*-(but-2-en-1-yl)-2-nitrobenzenesulfonamide (144)



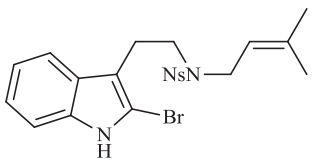
A solution containing nosyl-2-bromotryptamine **141** (295 mg, 0.70 mmol), crotyl bromide (103 mg, 0.76 mmol), and K_2CO_3 (145 mg, 1.05 mmol) in acetonitrile (5 mL) was stirred at 60 °C for 3 h. After this time the solvent was removed and the crude dissolved in EtOAC (10 mL) and washed with H_2O (10 mL) then brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (281 mg, 0.59 mmol, 84%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.14 (brs, 1H, indole-NH), 7.94 (m, 1H, ArH), 7.53-7.59 (m, 3H, ArH), 7.44 (dd, J = 1.2 and 6.9 Hz, 1H, ArH), 7.21 (m, 1H, ArH), 7.10 (dquin, J = 1.4 and 7.0 Hz, 2H, ArH), 5.72 (m, 1H, CH_2CH=$CHCH_3$), 5.40 (m, 1H, CH_2CH=$CHCH_3$), 3.99 (d, J = 6.9 Hz, 2H, CH_2CH=$CHCH_3$), 3.46 (m, 2H, CH_2CH_2NH), 2.95 (m, 2H, CH_2CH_2NH), 1.70 (dd, J = 1.3 and 6.4 Hz, 3H, CH_2CH=$CHCH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 136.2, 133.2, 131.6, 130.9, 128.7, 127.2, 125.6, 125.5, 124.2, 122.0, 120.0, 118.2, 115.4, 113.0, 111.1, 109.8, 50.0, 46.7, 24.7, 17.7; HRMS-ESI (*m/z*) $[C_{20}H_{20}N_3O_4SBr + H]^+$ calcd 478.0431, found 478.0429.

(*E*)-*tert*-butyl 2-bromo-3-(2-(*N*-(but-2-en-1-yl)-2-nitrophenylsulfonamido)ethyl)-1*H*-indole-1-carboxylate (147)



A solution containing crotyl-2-bromotryptamine **144** (280 mg, 0.59 mmol), di-*tert*-butyl dicarbonate (192 mg, 0.88 mmol), and DMAP (14 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was heated to 40 °C for 3 h. The reaction was quenched by addition of H_2O (10 mL) and the reaction mixture extracted with CH_2Cl_2 (3 × 5mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:4 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (149 mg, 0.26 mmol, 44%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.99 (m, 1H, ArH), 7.92 (ddd, J = 1.1 and 1.5 and 7.3 Hz, 1H, ArH), 7.44-7.57 (m, 4H, ArH), 7.18-7.29 (m, 2H, ArH), 5.72 (m, 1H, CH_2CH=$CHCH_3$), 5.41 (m, 1H, CH_2CH=$CHCH_3$), 3.99 (d, J = 6.9 Hz, 2H, CH_2CH=$CHCH_3$), 3.43 (m, 2H, CH_2CH_2NH), 2.99 (m, 2H, CH_2CH_2NH), 1.67 (s, 12H, CH_2CH=$CHCH_3$ and Boc-*t*Bu); ^{13}C NMR (67.5MHz, $CDCl_3$, δ) 149.1, 136.5, 134.0, 133.7, 133.4, 131.7, 131.6, 130.8, 128.6, 125.5, 124.7, 124.2, 123.2, 119.7, 118.2, 115.4, 109.6, 85.1, 50.1, 45.1, 28.3, 24.8, 17.9; HRMS-ESI (*m/z*) $[C_{25}H_{28}N_3O_6SBr + H]^+$ calcd 578.0955, found 578.0967.

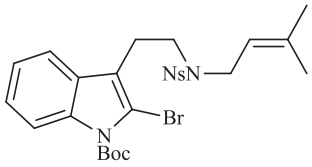
***N*-(2-(2-bromo-1*H*-indol-3-yl)ethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzenesulfonamide (145)**



A solution containing nosyl-2-bromotryptamine **141** (295 mg, 0.70 mmol), dimethylallyl bromide (115 mg, 0.76 mmol), and K_2CO_3 (145 mg, 1.05 mmol) in acetonitrile (5 mL) was stirred at 60 °C for 3 h. After this time the solvent was removed and the crude dissolved in EtOAC (10 mL) and washed with H_2O (10 mL) then brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (302 mg, 0.61 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.13 (brs, 1H, indole-NH), 7.92 (m, 1H, ArH), 7.44-7.58 (m, 4H, ArH), 7.22 (m, 1H,

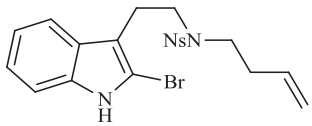
ArH), 7.11 (dquin, *J* = 1.4 and 7.0 Hz, 2H, ArH), 5.14 (tt, *J* = 1.4 and 7.3 Hz, 1H, CH_2CH=$C(CH_3)_2$), 4.05 (d, *J* = 7.2 Hz, 2H, CH_2CH=$C(CH_3)_2$), 3.45 (m, 2H, CH_2CH_2NH), 2.97 (m, 2H, CH_2CH_2NH), 1.71 (d, *J* = 0.9 Hz, 3H, CH_2CH=$C(CH_3)_2$), 1.67 (d, *J* = 0.8 Hz, 3H, CH_2CH=$C(CH_3)_2$); ^{13}C NMR (67.5MHz, $CDCl_3$, δ) 138.0, 136.1, 133.8, 131.6, 130.7, 129.5, 127.5, 124.2, 122.5, 120.3, 119.2, 118.1, 112.0, 110.6, 108.6, 46.5, 45.7, 26.0, 24.7, 18.0; HRMS-ESI (*m/z*) $[C_{21}H_{22}N_3O_4SBr - H]^-$ calcd 490.0442, found 490.0429.

tert-butyl 2-bromo-3-(2-(*N*-(3-methylbut-2-en-1-yl)-2-nitrophenylsulfonamido)ethyl)-1*H*-indole-1-carboxylate (148)



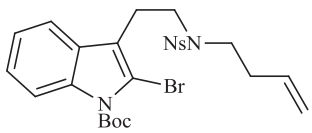
A solution containing dimethylallyl-2-bromotryptamine **145** (300 mg, 0.61 mmol), di-*tert*-butyl dicarbonate (199 mg, 0.92 mmol), and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was heated to 40 °C for 3 h. The reaction was quenched by addition of H_2O (10 mL) and the reaction mixture extracted with CH_2Cl_2 (3 × 5mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:2 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (173 mg, 0.29 mmol, 48%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.99 (m, 1H, ArH), 7.92 (m, 1H, ArH), 7.53-7.59 (m, 3H, ArH), 7.46-7.49 (m, 1H, ArH), 7.19-7.29 (m, 2H, ArH), 5.14 (tt, *J* = 2.8 and 7.3 Hz, 1H, CH_2CH=$C(CH_3)_2$), 4.04 (d, *J* = 7.3 Hz, 2H, CH_2CH=$C(CH_3)_2$), 3.42 (m, 2H, CH_2CH_2NH), 3.00 (m, 2H, CH_2CH_2NH), 1.71 (d, *J* = 0.9 Hz, 3H, CH_2CH=$C(CH_3)_2$), 1.67 (s, 12H, CH_2CH=$C(CH_3)_2$ and Boc-*t*Bu); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 149.1, 138.0, 136.5, 133.7, 133.3, 131.5, 130.8, 128.6, 124.7, 124.2, 123.2, 119.7, 119.2, 118.2, 115.4, 109.5, 85.1, 45.9, 45.7, 28.3, 26.0, 25.3, 14.2; HRMS-ESI (*m/z*) $[C_{26}H_{30}N_3O_6SBr + H]^+$ calcd 592.1111, found 592.1107.

_N_-(2-(2-bromo-1*H*-indol-3-yl)ethyl)-_N_-(but-3-en-1-yl)-2-nitrobenzenesulfonamide (163)



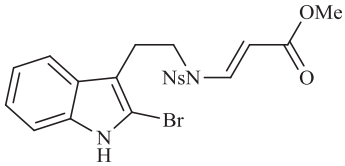
To a cooled (0 °C) solution of nosyl-2-bromotryptamine **141** (214 mg, 0.50 mmol), 3-buten-1-ol (40 mg, 0.55 mmol) and triphenylphosphine (262 mg, 1.0 mmol) in toluene (10 mL) was added diethylazodicarboxylate (139 mg, 0.80 mmol). The reaction was stirred at room temperature for 16 h. The solvent was removed and purification by column chromatography (1:3 EtOAc:Pet Sp.) afforded the title compound as a yellow oil (136 mg, 0.28 mmol, 57%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.03 (brs, 1H, indole-NH), 7.96 (m, 1H, ArH), 7.57-7.65 (m, 3H, ArH), 7.47 (d, *J* = 8.4 Hz, 1H, ArH), 7.24 (m, 1H, ArH), 7.14 (dtd, *J* = 1.4 and 7.0 and 16.7 Hz, 2H, ArH), 5.75 (m, 1H, CH_2CH_2CH=CH_2), 5.07 (t, *J* = 17.2 Hz, 2H, CH_2CH_2CH=CH_2), 3.53 (t, *J* = 7.7 Hz, 4H, CH_2CH_2CH=CH_2 and CH_2CH_2NH), 2.99 (m, 2H, CH_2CH_2NH), 2.40 (q, *J* = 7.7 Hz, 2H, CH_2CH_2CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 136.0, 134.3, 133.7, 133.3, 133.2, 131.5, 130.7, 127.3, 124.1, 122.5, 120.4, 118.0, 117.5, 111.8, 110.5, 108.5, 47.1, 46.7, 32.8, 24.3; HRMS-ESI (*m/z*) $[C_{20}H_{20}N_3O_4SBr - H]^-$ calcd 476.0285, found 476.0299.

tert-butyl 2-bromo-3-(2-(_N_-(but-3-en-1-yl)-2-nitrophenylsulfonamido)ethyl)-1_H_-indole-1-carboxylate (164)



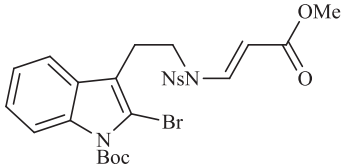
A solution containing butene-2-bromotryptamine **163** (169 mg, 0.35 mmol), di-*tert*-butyl dicarbonate (116 mg, 0.53 mmol) and DMAP (9 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) was stirred at 40 ^oC for 2 h. The reaction was quenched by the addition of H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:1 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (179 mg, 0.31 mmol, 88%). ^1H NMR (300 MHz, $CDCl_3$, δ) 8.04 (d, *J* = 8.1 Hz, 1H, ArH), 7.95 (d, *J* = 7.7 Hz, 1H, ArH), 7.59 (m, 3H, ArH), 7.46 (d, *J* = 8.2 Hz, 1H, ArH), 7.26 (m, 2H, ArH), 5.75 (m, 1H, $CH_2CH_2CH=CH_2$), 5.08 (t, *J* = 11.2 Hz, 2H, $CH_2CH_2CH=CH_2$), 3.53 (m, 4H, $CH_2CH_2CH=CH_2$ and CH_2CH_2NH), 3.02 (t, *J* = 7.2 Hz, 2H, CH_2CH_2NH), 2.44 (q, *J* = 7.2 Hz, 2H, $CH_2CH_2CH=CH_2$), 1.68 (s, 9H, Boc-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 149.3, 136.2, 134.4, 133.7, 133.3, 133.1, 132.5, 130.5, 127.3, 124.1, 122.6, 120.3, 118.0, 117.8, 111.8, 110.5, 108.5, 84.8, 47.3, 46.8, 33.1, 28.3, 24.1; HRMS-ESI (*m/z*) $[C_{25}H_{28}N_3O_6SBr + H]^+$ calcd 578.0955, found 578.0953.

(_E_)-tert-butyl 2-bromo-3-(2-(_N_-(3-methoxy-3-oxoprop-1-en-1-yl)-2-nitrophenyl sulfonamido)ethyl)-1_H_-indole-1-carboxylate (175)



To a solution containing nosyl-2-bromotryptamine **141** (373 mg, 0.88 mmol) and methyl propiolate (96 mg, 1.1 mmol) in acetonitrile (10 mL) at 0 ^oC was added *N,N*-dicyclohexylmethylamine (223 mg, 1.1 mmol) dropwise over 10 mins. After stirring at 0 ^oC for 2 h. the solvent was removed. The reaction mixture was dissolved in EtOAc and washed with HCl (0.1 M, 4 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (383 mg, 0.75 mmol, 86%). ^1H NMR (270 MHz, $CDCl_3$, δ) 8.55 (brs, 1H, indole-NH), 8.10 (d, *J* = 14.1 Hz, 1H, $CH=CHCO_2Me$), 7.97 (d, *J* = 7.4 Hz, 1H, ArH), 7.64 (m, 3H, ArH), 7.46 (m, 1H, ArH), 7.22 (m, 1H, ArH), 7.10-7.17 (m, 2H, ArH), 5.52 (d, *J* = 14.1 Hz, 1H, $CH=CHCO_2Me$), 3.78 (s, 3H, CO_2Me), 3.70 (m, 2H, CH_2CH_2NH), 3.05 (m, 2H, CH_2CH_2NH); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 163.7, 141.2, 137.6, 134.5, 133.7, 133.5, 132.8, 131.0, 128.4, 125.5, 124.0, 122.9, 121.0, 118.0, 113.6, 110.4, 110.3, 53.0, 43.1, 25.8; HRMS-ESI (*m/z*) $[C_{20}H_{18}N_3O_6SBr + H]^+$ calcd 508.0172, found 508.0183.

(_E_)-tert-butyl 2-bromo-3-(2-(_N_-(3-methoxy-3-oxoprop-1-en-1-yl)-2-nitrophenyl sulfonamido)ethyl)-1_H_-indole-1-carboxylate (176)

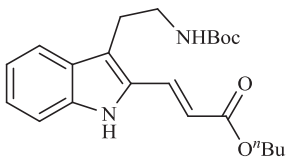


A solution containing acrylate-2-bromotryptamine **175** (383 mg, 0.75 mmol), di-*tert*-butyl dicarbonate (247 mg, 1.13 mmol) and DMAP (18 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. The reaction was quenched by the addition of H_2O (10 mL) and the reaction mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:2 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (304 mg, 0.50 mmol, 66%). ^1H NMR (270

MHz, $CDCl_3$, δ) 8.09 (d, *J* = 14.1 Hz, 1H, C<u>H</u>=CHCO$_2$Me), 8.00 (m, 1H, Ar<u>H</u>), 7.94 (m, 1H, Ar<u>H</u>), 7.62-7.69 (m, 3H, Ar<u>H</u>), 7.48 (m, 1H, Ar<u>H</u>), 7.26 (m, 2H, Ar<u>H</u>), 5.55 (d, *J* = 14.1 Hz, 1H, CH=C<u>H</u>CO$_2$Me), 3.77 (s, 3H, CO$_2$<u>Me</u>), 3.71 (m, 2H, CH$_2$C<u>H$_2$</u>NH), 3.10 (m, 2H, C<u>H$_2$</u>CH$_2$NH), 1.68 (s, 9H, Boc-<u>*t*Bu</u>); ^{13}C NMR (270 MHz, $CDCl_3$, δ) 167.2, 148.9, 147.8, 141.2, 136.5, 134.9, 132.3, 131.3, 131.2, 128.3, 125.1, 124.9, 123.4, 118.6, 117.9, 115.5, 110.0, 98.9, 85.4, 51.7, 45.1, 28.3, 23.1; HRMS-ESI (*m/z*) [$C_{25}H_{26}N_3O_8SBr$ + H]$^+$ calcd 608.0697, found 608.0711.

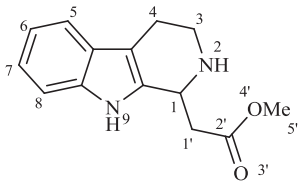
7.2.2 Chapter Three

(*E*)-butyl 3-(3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-indol-2-yl)acrylate (207)



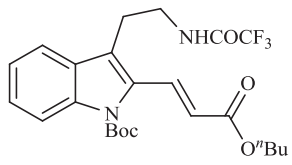
A sealed tube containing N_{10}-Boc-2-bromotryptamine **206** (200 mg, 0.59 mmol), potassium carbonate (246 mg, 1.77 mmol), butyl acrylate (226 mg, 1.77 mmol), tetrakis(triphenylphosphine) palladium (136.0 mg, 10 mol%) and toluene (2 ml) was heated to 120 ^{o}C for 16 h.. The solvent was concentrated, then the crude reaction mixture taken up in EtOAc (5 ml) and enough silica added so that a dry powder was formed when the solvent was concentrated. Purification by column chromatography (1:7 EtOAc/Pet Sp.) afforded the title compound as a pale yellow oil (143 mg, 0.37 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.46 (brs, 1H, indole-N<u>H</u>). 7.74 (d, *J* = 15.7 Hz, 1H, C<u>H</u>=CHCO$_2$*n*Bu), 7.61 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.31 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.26 (dt, *J* = 1.1 and 8.0 Hz, 1H, Ar<u>H</u>), 7.09 (dt, *J* = 1.1 and 8.0 Hz, 1H, Ar<u>H</u>), 6.20 (d, *J* = 15.7 Hz, 1H, CH=C<u>H</u>CO$_2$*n*Bu), 4.56 (t, *J* = 5.8 Hz, 1H, N<u>H</u>Boc), 4.21 (m, 2H, CO$_2$<u>*n*Bu</u>), 3.39 (q, *J* = 6.2 Hz, 2H, CH$_2$C<u>H$_2$</u>NH), 3.07 (t, *J* = 6.6 Hz, 2H, C<u>H$_2$</u>CH$_2$NH), 1.70 (m, 2H, CO$_2$<u>*n*Bu</u>), 1.45 (m, 2H, CO$_2$<u>*n*Bu</u>), 1.42 (s, 9H, Boc-<u>*t*Bu</u>), 0.96 (m, 3H, CO$_2$<u>*n*Bu</u>); ^{13}C NMR (100 MHz, $CDCl_3$ δ) 167.1, 155.9, 137.5, 131.7, 130.6, 128.5, 125.2, 120.3, 120.1, 119.8, 114.9, 111.1, 79.3, 64.6, 41.5, 30.9, 28.5, 25.0, 19.3, 13.9; HRMS-ESI (*m/z*) [$C_{22}H_{30}N_2O_4$ + H]$^+$ calcd 387.2278, found 387.2275.

(*R,S*)-methyl 2,3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (210)



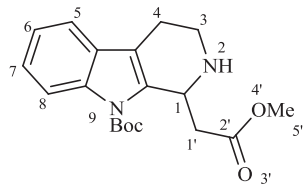
To a solution of N_{10}-Boc-2-acrylatetryptamine **207** (140 mg, 0.36 mmol) in CH_2Cl_2 (9 mL) was added TFA (1 mL). After stirring at room temperature for 1 h. additional TFA (1 mL) was added and stirring continued for 1 h. After this time the solvent was removed and the reaction mixture dissolved in methanol (5 mL) and sodium methoxide added (158 mg, 2.92 mmol). The resultant mixture was stirred at room temperature for 16 h. after which time the reaction mixture was concentrated and purified by column chromatography (1:8 MeOH:EtOAc) to afford the title compound as a clear oil (24 mg, 0.10 mmol, 27% over 2 steps). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.57 (brs, 1H, N<u>H9</u>), 7.49 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.32 (d, *J* = 7.8 Hz, 1H, Ar<u>H</u>), 7.15 (dt, *J* = 1.1 and 7.1 Hz, 1H, Ar<u>H</u>) 7.07 (dt, *J* = 1.3 and 7.6 Hz, 1H, Ar<u>H</u>), 4.50 (t, *J* = 6.6 Hz, 1H, <u>H1</u>), 3.75 (s, 3H, CO$_2$<u>Me</u>), 3.23 (m, 1H, <u>H3a</u>), 3.10 (m, 1H, <u>H3b</u>), 2.86 (d, *J* = 6.8 Hz, 2H, <u>H4</u>), 2.74 (t, *J* = 5.6 Hz, 2H, <u>H1'</u>), 2.53 (brs, 1H, N<u>H2</u>); ^{13}C NMR (67.5 MHz, $CDCl_3$ δ) 173.7, 135.6, 134.7, 127.2, 121.9, 119.4, 118.2, 111.1, 109.1, 52.2, 48.8, 41.9, 40.5, 22.5; HRMS-ESI (*m/z*) [$C_{14}H_{16}N_2O_2$ + H]$^+$ calcd 245.1285, found 245.1292.

(*E*)-*tert*-butyl 2-(3-butoxy-3-oxoprop-1-en-1-yl)-3-(2-(trifluoroacetamido)ethyl)-1*H*-indole-1-carboxylate (211)



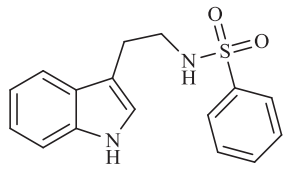
A sealed tube containing trifluoroacetate-2-bromoindole **60** (170 mg, 0.39 mmol), $Pd(PPh_3)_4$ (45 mg, 10 mol%), Na_2CO_3 (124 mg, 1.17 mmol) and butyl acrylate (75 mg, 0.59 mmol) in toluene (2 mL) was heated at 120 °C for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:9 EtOAc:Pet Sp) to afford the title compound as a clear oil (110 mg, 0.23 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.17 (d, *J* = 8.4 Hz, 1H, ArH), 7.94 (d, *J* = 16.2 Hz, 1H, CH=CHCO$_2$*n*Bu), 7.62 (d, *J* = 7.8 Hz, 1H, ArH), 7.37 (t, *J* = 8.0 Hz, 1H, ArH), 7.27 (t, *J* = 7.8 Hz, 1H, ArH), 6.56 (brs, 1H, NH), 6.11 (d, *J* = 16.2 Hz, 1H, CH=CHCO$_2$*n*Bu), 4.21 (t, *J* = 6.7 Hz, 2H, CO$_2$*n*Bu), 3.65 (q, *J* = 6.7 Hz, 2H, CH$_2$CH$_2$NH), 3.12 (t, *J* = 7.6 Hz, 2H, CH$_2$CH$_2$NH), 1.69 (m, 2H, CO$_2$*n*Bu), 1.65 (s, 9H, Boc-*t*Bu), 1.43 (m, 2H, CO$_2$*n*Bu), 0.96 (t, *J* = 7.5 Hz, 3H, CO$_2$*n*Bu); HRMS-ESI (*m/z*) $[C_{24}H_{29}N_2O_5F_3 + H]^+$ calcd 483.2101, found 483.2107.

(*R,S*)-methyl 2-(9-*tert*-butoxycarbonyl)-2,3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (213)



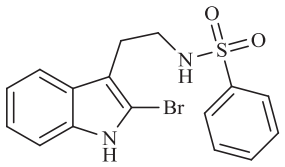
A solution containing 2-acrylatetryptamine **211** (122 mg, 0.25 mmol) and K_2CO_3 (70 mg, 0.51 mmol) in methanol/H_2O (7:3, 10 mL) was heated at 60 °C for 2 h. The volatiles were removed, and EtOAc (30 mL) was added and the reaction mixture washed with H_2O (10 mL) then brine. The organic phase was separated, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:1 EtOAc: Pet Sp.) afforded the title compound as a pale yellow oil (50 mg, 0.15 mmol, 57%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.12 (d, *J* = 7.6 Hz, 1H, ArH), 7.42 (dd, *J* = 1.5 and 6.7 Hz, 1H, ArH), 7.20-7.32 (m, 2H, ArH), 5.06 (d, *J* = 9.1, 1H, H1), 3.75 (s, 3H, CO$_2$Me), 3.20 (m, 2H, H3), 3.00 (dd, *J* = 2.8 and 16.1 Hz, 1H, H4a), 2.74 (m, 3H, H4b and H1'), 2.15 (brs, 1H, NH2), 1.67 (s, 9H, Boc-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$ δ) 172.3, 150.1, 135.9, 135.2, 129.2, 124.4, 122.8, 118.0, 116.2, 115.8, 84.3, 51.8, 49.7, 38.0, 37.4, 28.2, 22.0; HRMS-ESI (*m/z*) $[C_{19}H_{24}N_2O_4 + H]^+$ calcd 345.1809, found 345.1802.

3-(2-(benzenesulfonamido)ethyl)indole (461)



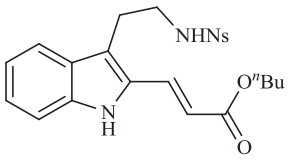
To a solution of tryptamine (500 mg, 3.12 mmol) and triethylamine (474 mg, 4.68 mmol) in CH_2Cl_2 (20 mL) was added benzenesulfonyl chloride (606 mg, 3.43 mmol). After stirring at room temperature for 16 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a pale orange oil (865 mg, 2.88 mmol, 93%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.29 (brs, 1H, indole-NH), 7.78 (d, *J* = 7.5 Hz, 2H, ArH), 7.31-7.53 (m, 5H, ArH), 7.18 (t, *J* = 6.9 Hz, 1H, ArH), 7.07 (t, *J* = 7.3 Hz, 1H, ArH), 6.87 (s, 1H, indole-C2-ArH), 4.94 (brt, 1H, CH$_2$CH$_2$NH), 3.27 (q, *J* = 6.1 Hz, 2H, CH$_2$CH$_2$NH), 2.89 (t, *J* = 6.3 Hz, 2H, CH$_2$CH$_2$NH); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 139.8, 136.5, 132.8, 129.2, 127.1, 127.0, 123.0, 122.2, 119.5, 118.6, 111.7, 111.5, 43.4, 25.6; HRMS-ESI (*m/z*) $[C_{16}H_{16}N_2O_2S + H]^+$ calcd 393.0279, found 393.0289.

2-bromo-3-(2-(benzenesulfonamido)ethyl)indole (462)



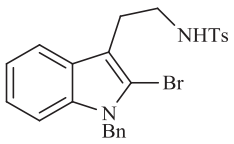
To a cooled solution of benzenesulfonyltryptamine **461** (1683 mg, 5.60 mmol) in THF:$CHCl_3$ (1:1, 100 mL) was added pyridinium tribromide (1970 mg, 6.16 mmol) portionwise over 90 mins. Saturated aqueous sodium sulphite (10 mL) was added, and following a colour change, saturated aqueous $NaHCO_3$ (10 mL) was also added. The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was subjected to column chromatography (1:4 EtOAc:Pet Spirits) to afford the title compound as a clear colourless oil (1753 mg, 4.62 mmol, 83%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.40 (brs, 1H, indole-NH), 7.77 (d, *J* = 7.5 Hz, 2H, ArH), 7.33-7.49 (m, 4H, ArH), 7.23 (d, *J* = 7.9 Hz, 1H, ArH), 7.13 (t, *J* = 7.1 Hz, 1H, ArH), 7.04 (t, *J* = 7.7 Hz, 1H, ArH), 4.71 (t, *J* = 5.9 Hz, 1H, CH_2CH_2NH), 3.24 (q, *J* = 6.5 Hz, 2H, CH_2CH_2NH), 2.87 (t, *J* = 6.8 Hz, 2H, CH_2CH_2NH); ^{13}C NMR – due to rapid degradation of the compound a clean spectrum was not obtained. HRMS-ESI (*m/z*) $[C_{16}H_{15}N_2O_2SBr + H]^+$ calcd 379.0110, found 379.0093.

(*E*)-butyl 3-(3-(2-(2-nitrophenylsulfonamido)ethyl)-1*H*-indol-2-yl)acrylate (220)



A sealed tube containing nosyl-2-bromotryptamine **141** (550 mg, 1.3 mmol), $Pd(PPh_3)_4$ (150 mg, 10 mol%), K_2CO_3 (540 mg, 3.9 mmol) and butyl acrylate (183 mg, 1.43 mmol) in toluene (5 mL) was heated at 120 °C for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:2 EtOAc:Pet Sp) to afford the title compound as a clear oil (306 mg, 0.65 mmol, 50%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.53 (brs, 1H, indole-NH), 7.96 (m, 1H, CH=$CHCO_2n$Bu), 7.70 (m, 2H, ArH), 7.58 (m, 2H, ArH), 7.44 (d, *J* = 7.9 Hz, 1H, ArH), 7.20-7.27 (m, 2H, ArH), 6.97-7.03 (m, 1H, ArH), 6.19 (d, *J* = 15.9 Hz, 1H, CH=CHCO_2nBu), 5.46 (t, *J* = 5.8 Hz, 1H, CH, NsNH), 4.18 (t, *J* = 6.7 Hz, 2H, CO_2nBu), 3.43 (q, *J* = 6.0 Hz, 2H, CH_2CH_2NH), 3.09 (t, *J* = 6.8 Hz, 2H, CH_2CH_2NH), 1.68 (m, 2H, CO_2nBu), 1.43 (m, 2H, CO_2nBu), 0.95 (t, *J* = 7.3 Hz, 3H, CO_2nBu); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 166.0, 146.1, 136.2, 132.3, 132.1, 131.5, 130.0, 129.7, 129.2, 126.5, 124.1, 123.8, 119.0, 118.0, 116.1, 114.1, 110.2, 63.4, 43.1, 29.5, 23.5, 179, 12.5; HRMS-ESI (*m/z*) $[C_{23}H_{25}N_3O_6S + Na]^+$ calcd 494.1356, found 494.1372.

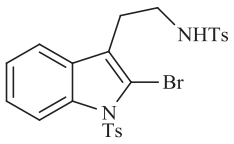
N_1-Benzyl-2-bromo-3-(2-(*p*-toluenesulfonylamido)ethyl)indole (222)



A solution containing 2-bromoindole **132** (230 mg, 0.58 mmol), and NaH (42 mg, 1.7 mmol) in THF (10 mL) was stirred at 0 °C for 30 mins. After this time, benzyl bromide (110 mg, 0.64 mmol) was added and the reaction mixture stirred at ambient temperature for 16 hrs. The reaction was treated with water (10 mL) and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (1:4 EtOAc/Pet Sp) to afford the title compound as a clear colourless oil (110 mg, 0.23 mmol, 39%). FT-IR (ν, cm^{-1}, KBr) 1598, 1454, 1327, 1157, 1092, 813, 739; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.68 (d, *J* = 8.2 Hz, 2H, ArH), 7.43 (d, *J* = 7.9 Hz, 1H, ArH), 7.06-7.29 (m, 10H, ArH), 5.37 (s, 2H, CH_2Ph), 4.58 (brt, 1H, $TsNH_2$), 3.29 (q, *J* = 6.5 Hz, 2H, CH_2CH_2NH),

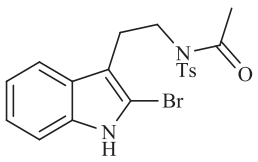
2.98 (t, *J* = 6.9 Hz, 2H, C$\underline{H_2}$CH$_2$NH), 2.40 (s, 3H, Ts$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 143.2, 136.9, 136.6, 129.6, 128.8, 127.6, 127.2, 127.0, 126.4, 122.4, 120.2, 118.0, 113.7, 111.0, 110.0, 48.3, 42.8, 26.0, 21.5; HRMS-ESI (*m/z*) $[C_{24}H_{23}BrN_2O_2S + H]^+$ calcd 483.0747, found 483.0752.

N_1-(*p*-toluenesulfonyl)-2-bromo-3-(2-(*p*-toluenesulfonylamido)ethyl)indole (224)



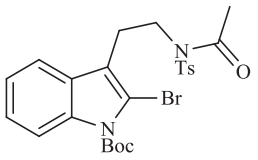
A solution containing 2-bromoindole **132** (218 mg, 0.55 mmol), DMAP (14 mg, 0.11 mmol), DIPEA (86 mg, 0.66 mmol) and tosyl chloride (116 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) was stirred at ambient temperature for 4 hrs. The ensuing mixture was treated with water (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by column chromatography (1:4 EtOAc/Pet Sp) to afford the title compound as a clear colourless oil (97 mg, 0.18 mmol, 32%). FT-IR (ν, cm^{-1}, KBr) 1596, 1444, 1379, 1326, 1156, 1088, 813, 748, 670, 571; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.23 (d, *J* = 9.0 Hz, 1H, ArH), 7.72 (d, *J* = 9.0 Hz, 2H, ArH), 7.55 (d, *J* = 9.0 Hz, 2H, ArH), 7.16-7.33 (m, 7H, ArH), 4.47 (brs, 1H, TsNH), 3.17 (q, *J* = 6.0 Hz, 2H, $CH_2C\underline{H_2}NH$), 2.82 (t, *J* = 6.0 Hz, 2H, C$\underline{H_2}CH_2$NH), 2.39 (s, 3H, Ts$\underline{CH_3}$), 2.34 (s, 3H, Ts$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 145.4, 143.4, 137.3, 136.6, 135.1, 129.8, 129.6, 129.1, 127.0, 126.8, 125.2, 124.0, 121.3, 118.2, 115.4, 109.9, 41.7, 26.0, 21.6, 21.5; HRMS-ESI (*m/z*) $[C_{24}H_{23}BrN_2O_4S_2 + H]^+$ calcd 547.0355, found 547.0338.

N-(2-(2-bromo-1*H*-indol-3-yl)ethyl)-*N*-tosylacetamide (229)



To a solution of tosyl-2-bromotryptamine **132** (801 mg, 2.04 mmol) in THF (40 mL) at 0 °C was added sodium hydride (49 mg, 2.04 mmol). After 30 mins. acetyl chloride (160 mg, 2.04 mmol) was added and the resultant mixture stirred at room temperature for 16 h. To reaction was quenched by addition of H_2O (10 mL) and extracted EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound as a pale pink amorphous solid (779 mg, 1.79 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.20 (brs, 1H, indole-NH), 7.78 (d, *J* = 8.3 Hz, 2H, ArH), 7.68 (m, 1H, ArH), 7.30 (d, *J* = 8.1 Hz, 2H, ArH), 7.26 (m, 1H, ArH), 7.12-7.19 (m, 2H, ArH), 3.94 (m, 2H, $CH_2C\underline{H_2}NH$), 3.12 (m, 2H, C$\underline{H_2}CH_2$NH), 2.41 (s, 3H, $TsCH_3$), 2.37 (s, 3H, CO$\underline{Me}$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 170.3, 145.0, 136.8, 136.2, 130.1, 130.0, 127.7, 127.6, 127.4, 122.6, 120.5, 118.5, 112.0, 110.5, 108.8, 46.6, 25.4, 25.2, 21.7; HRMS-ESI (*m/z*) $[C_{19}H_{19}BrN_2O_3S + H]^+$ calcd 435.0373, found 435.0382.

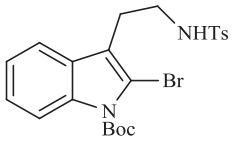
***tert*-butyl 2-bromo-3-(2-(*N*-tosylacetamido)ethyl)-1*H*-indole-1-carboxylate (230)**



To a solution of tosyl-2-bromotryptamine **132** (564 mg, 1.43 mmol) in THF (20 mL) at 0 °C was added sodium hydride (52 mg, 2.15 mmol). After 20 mins. acetyl chloride (124 mg, 1.58 mmol) was added and the resultant mixture stirred at room temperature for 1 h. To this solution was then added DMAP (18 mg, 0.14 mmol) and di-*tert*-butyl dicarbonate (344 mg, 1.58 mmol) and reaction mixture heated at 40 °C for 30 mins. After cooling to room temperature, H_2O (10 mL) was added and extracted with EtOAc (2 × 10 mL). The

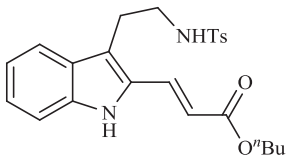
combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:4 EtOAc:Pet Sp.) afforded the title compound as a clear oil (503 mg, 0.94 mmol, 66%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.05 (m, 1H, ArH), 7.72 (d, *J* = 8.4 Hz, 2H, ArH), 7.68 (m, 1H, ArH), 7.25-7.30 (m, 4H, ArH), 3.91 (m, 2H, CH_2CH_2NH), 3.14 (m, 2H, CH_2CH_2NH), 2.42 (s, 3H, $TsCH_3$), 2.35 (s, 3H, COMe), 1.69 (s, 9H, Boc-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.2, 149.1, 145.0, 136.7, 136.4, 129.9, 128.6, 127.6, 127.4, 124.6, 123.2, 119.5, 118.4, 115.3, 109.8, 85.0, 45.5, 28.2, 25.7, 25.2, 21.6; HRMS-ESI (*m/z*) $[C_{24}H_{27}BrN_2O_5S + H]^+$ calcd 535.0897, found 535.0888.

tert-butyl 2-bromo-3-(2-(_p_-toluenesulfonamido)ethyl)-1_H_-indole-1-carboxylate (133)



To a solution of *N*-tosylacetamido-2-bromotryptamine **230** (503 mg, 0.94 mmol) in THF (10 mL) was added hydrazine monohydrate (79 mg, 1.58 mmol) and the reaction mixture stirred for 3 h. at room temperature. The reaction was quenched by the addition of H_2O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound as a clear oil (343 mg, 0.70 mmol, 74%). The characterisation data obtained for this compound was identical to that previously reported in Section 7.2.1.

(_E_)-butyl 3-(3-(2-(_p_-toluenesulfonylamido)ethyl)-1_H_-indol-2-yl)acrylate (216)

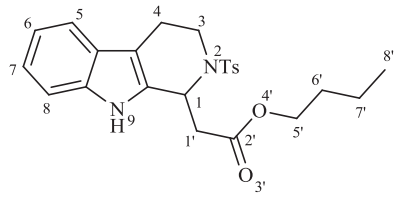


A sealed tube containing 2-bromoindole **132** (92 mg, 0.23 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), Na_2CO_3 (74 mg, 0.70 mmol) and butyl acrylate (33 mg, 0.26 mmol) in toluene (2 mL) was heated at 120 °C for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product purified by column chromatography (1:4 EtOAc:Pet Sp) to afford the title compound as an orange oil (102 mg, 99%). FT-IR (ν, cm^{-1}, KBr) 3345, 1692s, 1623, 1454, 1321, 1181, 1156, 744; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.58 (brs, 1H, indole-NH), 7.69 (d, *J* = 16.0 Hz, 1H, CH=CHCO$_2$*n*Bu), 7.65 (d, *J* = 8.2 Hz, 2H, ArH), 7.46 (d, *J* = 8.0 Hz, 1H, ArH), 7.30 (d, *J* = 8.2 Hz, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 2H, ArH), 7.06 (t, *J* = 8.0 Hz, 2H, ArH), 6.20 (d, *J* = 16.0 Hz, 1H, CH=CHCO$_2$*n*Bu), 4.70 (t, *J* = 6.0 Hz, 1H, TsNH), 4.11 (t, *J* = 6.8 Hz, 2H, CO$_2$*n*Bu), 3.23 (q, *J* = 6.6 Hz, 2H, CH_2CH_2NH), 3.05 (t, *J* = 6.8 Hz, 2H, CH_2CH_2NH), 2.38 (s, 3H, $TsCH_3$), 1.63 (m, *J* = 8.0 Hz, 2H, CO$_2$*n*Bu), 1.42 (m, *J* = 7.5 Hz, 2H, CO$_2$*n*Bu), 0.95 (t, *J* = 7.5 Hz, 3H, CO$_2$*n*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 165.8, 142.1, 136.1, 135.6, 130.1, 129.5, 128.4, 126.7, 125.7, 123.9, 119.1, 118.3, 116.7, 114.0, 110.0, 63.3, 42.4, 29.5, 23.7, 20.2, 17.9, 12.5; HRMS-ESI (*m/z*) $[C_{24}H_{28}N_2O_4S + H]^+$ calcd 441.1843, found 441.1827.

General procedure A for the synthesis of tetrahydro-_β_-carbolines:

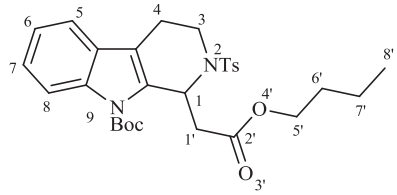
A sealed tube containing a 2-bromoindole (1.0 eq), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 eq) and butyl acrylate (1.1 eq) in toluene was heated at 120 °C for 16 hrs. The reaction mixture was cooled to room temperature, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-butyl 2-(2-(*p*-toluenesulfonyl)-3,4,9-tetrahydro-1*H*-carbolin-1-yl)acetate (215)



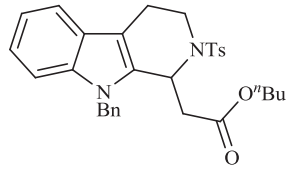
General procedure A was followed using 2-bromoindole **132** (92 mg, 0.23 mmol), $Pd(PPh_3)_4$ (27 mg, 10 mol%), K_2CO_3 (97 mg, 0.70 mmol) and butyl acrylate (33 mg, 0.26 mmol) in toluene (2 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (31 mg, 0.07 mmol, 30%). FT-IR (ν, cm^{-1}, KBr) 3395, 1726s, 1455, 1337, 1158, 743; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.77 (brs, 1H, NH9), 7.65 (d, *J* = 8.3 Hz, 2H, ArH), 7.33 (d, *J* = 8.0 Hz, 1H, ArH), 7.29 (d, *J* = 8.1 Hz, 1H, ArH), 7.12-7.16 (m, 3H, ArH), 7.04 (dt, *J* = 1.0 and 7.0 Hz, 1H, ArH), 5.49 (dd, *J* = 3.0 and 10.6 Hz, 1H, H1), 4.19 (m, 3H, H5' and H3a), 3.34 (m, 1H, H3b), 3.15 (dd, *J* = 3.3 and 17.3 Hz, 1H, H4a), 3.00 (dd, *J* = 10.7 and 17.3 Hz, 1H, H4b), 2.50 (m, 2H, H1'), 2.28 (s, 3H, TsCH_3), 1.63 (m, *J* = 7.9 Hz, 2H, H6'), 1.37 (m, *J* = 7.6 Hz, 2H, H7'), 0.93 (t, *J* = 7.4 Hz, 3H, H8'); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 171.9, 142.2, 136.6, 134.3, 130.8, 128.5, 125.4, 125.0, 121.0, 118.1, 116.9, 109.9, 106.4, 64.0, 47.6, 40.0, 39.1, 29.3, 20.2, 19.0, 17.8, 12.4; HRMS-ESI (*m/z*) $[C_{24}H_{28}N_2O_4S + H]^+$ calcd 441.1843, found 441.1832.

(*R*,*S*)-butyl 2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (214)



General procedure A was followed using 2-bromoindole **133** (100 mg, 0.20 mmol), $Pd(PPh_3)_4$ (23 mg, 10 mol%), K_2CO_3 (84 mg, 0.61 mmol) and butyl acrylate (29 mg, 0.22 mmol) in toluene (4 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (91 mg, 0.17 mmol, 83%). FT-IR (ν, cm^{-1}, KBr) 1730vs, 1457, 1374, 1324, 1159, 747; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.10 (d, *J* = 8.2 Hz, 1H, ArH), 7.62 (d, *J* = 8.3 Hz, 2H, ArH), 7.14-7.28 (m, 4H, ArH), 7.03 (d, *J* = 8.6 Hz, 1H, ArH), 6.12 (dd, *J* = 3.6 and 10.6 Hz, 1H, H1), 4.05 (m, 3H, H5' and H3a), 3.50 (m, 1H, H3b), 3.00 (dd, *J* = 3.7 and 14.3 Hz, 1H, H4a), 2.70 (dd, *J* = 10.6 and 14.3 Hz, 1H, H4b), 2.39-2.60 (m, 2H, H1'), 2.18 (s, 3H, $TsCH_3$), 1.75 (s, 9H, Boc-*t*Bu), 1.60 (m, *J* = 7.8 Hz, 2H, H6'), 1.34 (m, *J* = 7.6 Hz, 2H, H7'), 0.92 (t, *J* = 7.5 Hz, 3H, H8'); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 169.8, 149.9, 143.4, 137.5, 135.9, 133.0, 129.2, 128.6, 127.1, 124.8, 122.9, 118.0, 115.7, 114.9, 85.0, 64.9, 51.1, 40.3, 37.9, 30.6, 28.4, 21.4, 19.7, 19.2, 13.8; HRMS-ESI (*m/z*) $[C_{29}H_{36}N_2O_6S - H]^-$ calcd 539.2221, found 539.2219.

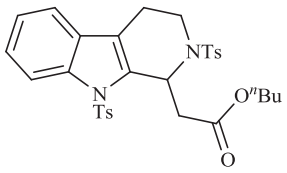
(*R*,*S*)-butyl 2-(9-benzyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (234)



General procedure A was followed using 2-bromoindole **222** (190 mg, 0.39 mmol), $Pd(PPh_3)_4$ (45 mg, 10 mol%), K_2CO_3 (163 mg, 1.2 mmol) and butyl acrylate (55 mg, 0.43 mmol) in toluene (5 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (113 mg, 0.21 mmol, 54%). FT-IR (ν, cm^{-1}, KBr) 1733s, 1458, 1342, 1158, 741, 721; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.99-7.43 (m, 13H, ArH), 5.60 (d, *J* = 7.1 Hz, 1H, CH), 5.33 (q, *J* = 16.8 Hz, 2H, CH_2Ph), 4.11 (m, 3H), 3.48 (m, 1H), 2.60-2.80 (m, 4H), 2.26 (s, 3H), 1.61 (m, *J* = 8.0 Hz,

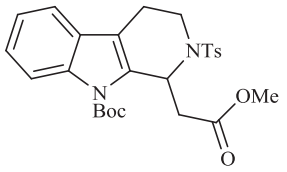
2H), 1.36 (m, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 170.0, 143.2, 137.8, 137.29, 137.27, 133.1, 129.4, 129.0, 127.8, 127.0, 126.6, 126.4, 122.4, 119.7, 118.5, 109.9, 108.4, 65.2, 49.6, 46.9, 41.1, 39.0, 30.6, 21.5, 20.0, 19.2, 13.8; HRMS-ESI (*m/z*) $[C_{31}H_{34}N_2O_4S + H]^+$ calcd 531.2312, found 531.2314.

(*R,S*)-butyl 2-(9-(*p*-toluenesulfonyl)-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (235)



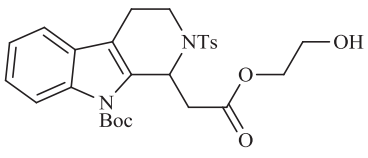
General procedure A was followed using 2-bromoindole **224** (200 mg, 0.36 mmol), $Pd(PPh_3)_4$ (42 mg, 10 mol%), K_2CO_3 (151 mg, 1.1 mmol) and butyl acrylate (52 mg, 0.40 mmol) in toluene (5 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale orange oil (118 mg, 0.20 mmol, 54%). FT-IR (ν, cm^{-1}, KBr) 1732s, 1598, 1452, 1375, 1335, 1174, 750, 666, 582, 545; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.15 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.18-7.30 (m, 5H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.27 (d, *J* = 7.9 Hz, 1H, C<u>H</u>), 3.94 (m, 3H), 3.32 (dd, *J* = 2.9 and 15.2 Hz, 2H), 2.70 (m, 2H), 2.50 (dd, *J* = 2.8 and 18.2 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.54 (m, *J* = 7.0 Hz, 2H), 1.37 (m, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.7, 145.1, 143.3, 137.6, 136.3, 134.6, 133.4, 129.9, 129.6, 129.3, 127.3, 127.0, 125.2, 123.9, 118.6, 118.4, 115.0, 64.7, 50.7, 40.6, 37.6, 30.5, 21.5, 21.4, 20.5, 19.0, 13.7; HRMS-ESI (*m/z*) $[C_{31}H_{34}N_2O_6S_2 + H]^+$ calcd 595.1931, found 595.1919.

(*R,S*)-methyl 2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (236)



General procedure A was followed using 2-bromoindole **133** (250 mg, 0.51 mmol), $Pd(PPh_3)_4$ (59 mg, 10 mol%), K_2CO_3 (210 mg, 1.5 mmol) and methyl acrylate (73 mg, 0.56 mmol) in toluene (5 mL). Purification by column chromatography (1:19 acetone:toluene) afforded the title compound as a pale yellow oil (200 mg, 0.40 mmol, 79%). FT-IR (ν, cm^{-1}, KBr) 1731vs, 1456, 1373, 1323, 1159, 720; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.06 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.16-7.25 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.10 (dd, *J* = 3.6 and 10.7 Hz, 1H, CH), 4.12 (dd, *J* = 6.5 and 15.1 Hz, 1H), 3.65 (s, 3H, CO_2<u>Me</u>), 3.46 (m, 1H), 3.03 (dd, *J* = 3.7 and 14.4 Hz, 1H), 2.68 (dd, *J* = 10.7 and 14.3Hz, 1H), 2.46-2.59 (m, 2H), 2.19 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 170.0, 149.8, 143.3, 137.4, 135.8, 132.8, 129.2, 128.5, 127.0, 124.7, 122.8, 117.9, 115.7, 114.9, 85.0, 51.9, 51.0, 39.9, 37.8, 28.2, 21.3, 19.6; HRMS-ESI (*m/z*) $[C_{26}H_{30}N_2O_6S + H]^+$ calcd 499.1897, found 499.1915.

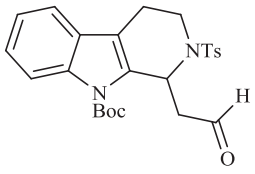
(*R,S*)-(2-hydroxyethyl) 2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetate (237)



General procedure A was followed using 2-bromoindole **133** (280 mg, 0.57 mmol), $Pd(PPh_3)_4$ (66 mg, 10 mol%), K_2CO_3 (235 mg, 1.7 mmol) and 2-hydroxyethyl acrylate (73 mg, 0.62 mmol) in toluene (6 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (192 mg, 0.36 mmol, 64%). FT-IR (ν, cm^{-1}, KBr) 3524,

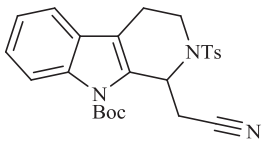
1738vs, 1457, 1377, 1325, 1245, 1157, 716; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.05 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.13-7.25 (m, 3H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.18 (dd, *J* = 3.6 and 10.8 Hz, 1H, C<u>H</u>), 4.50 (m, 1H, O<u>H</u>), 4.12 (m, 2H), 3.87 (t, *J* = 4.3 Hz, 2H), 3.56 (m, 1H), 3.12 (dd, *J* = 3.7 and 14.8 Hz, 1H), 2.74 (dd, *J* = 10.8 and 14.7 Hz, 1H), 2.36 (m, 2H), 2.10 (s, 3H), 1.76 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 169.5, 149.9, 143.9, 136.6, 135.8, 132.5, 129.3, 128.4, 126.9, 124.9, 123.0, 118.0, 115.7, 114.7, 85.3, 67.4, 60.9, 51.2, 40.5, 37.8, 28.4, 21.3, 18.9; HRMS-ESI (*m/z*) $[C_{27}H_{32}N_2O_7S - H]^-$ calcd 527.1857, found 527.1846.

(*R,S*)-2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetaldehyde (238)



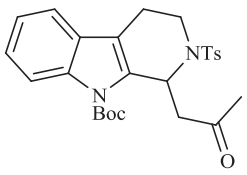
General procedure A was followed using 2-bromoindole **133** (200 mg, 0.40 mmol), $Pd(PPh_3)_4$ (47 mg, 10 mol%), K_2CO_3 (168 mg, 1.2 mmol) and acrolein (25 mg, 0.45 mmol) in toluene (5 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale orange oil (122 mg, 0.26 mmol, 64%). FT-IR (ν, cm^{-1}, KBr) 2977, 1727vs, 1456, 1373, 1320, 1160, 749; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.81 (dd, *J* = 1.2 and 4.2 Hz, 1H, C<u>H</u>O), 8.00 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.16-7.29 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.29 (d, *J* = 10.1 Hz, 1H, C<u>H</u>), 4.16 (dd, *J* = 6.4 and 16.0 Hz, 1H), 3.35 (m, 1H), 2.98 (d, *J* = 4.6 Hz, 1H), 2.39-2.69 (m, 3H), 2.21 (s, 3H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 199.2, 148.8, 142.5, 135.7, 134.2, 131.3, 128.2, 127.2, 125.7, 123.5, 121.6, 116.8, 114.4, 113.7, 83.7, 48.0, 46.2, 36.6, 27.0, 20.0, 18.2; HRMS-ESI (*m/z*) $[C_{25}H_{28}N_2O_5S + H]^+$ calcd 469.1792, found 469.1773.

(*R,S*)-2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acrylonitrile (240)



General procedure A was followed using 2-bromoindole **133** (100 mg, 0.20 mmol), $Pd(PPh_3)_4$ (24 mg, 10 mol%), K_2CO_3 (84 mg, 0.61 mmol) and acrylonitrile (12 mg, 0.22 mmol) in toluene (4 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (63 mg, 0.14 mmol, 67%). FT-IR (ν, cm^{-1}, KBr) 2251, 1727, 1456, 1374, 1320, 1160, 913, 750, 561; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.02 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.17-7.33 (m, 5H), 5.99 (m, 1H, C<u>H</u>), 4.10 (m, 1H), 3.65 (m, 1H), 3.06 (m, 2H), 2.66 (m, 2H), 2.30 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 150.1, 143.9, 136.7, 135.7, 130.6, 129.6, 128.3, 127.3, 125.2, 123.1, 118.4, 117.3, 116.7, 115.9, 85.3, 49.7, 38.4, 28.3, 24.3, 21.4, 19.9; HRMS-ESI (*m/z*) $[C_{25}H_{27}N_3O_4S + H]^+$ calcd 466.1795, found 466.1775.

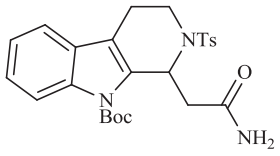
(*R,S*)-2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)propan-2-one (241)



General procedure A was followed using 2-bromoindole **133** (300 mg, 0.61 mmol,), $Pd(PPh_3)_4$ (70 mg, 10 mol%), K_2CO_3 (252 mg, 1.82 mmol) and 3-buten-2-one (51 mg, 0.73 mmol) in toluene (3 mL) Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded tetrahydro-*β*-carboline **17** as a pale yellow oil (228 mg, 0.47 mmol,

78%) FT-IR (ν, cm-1, KBr) 1716vs, 1465, 1386, 1327, 1159, 698; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.96 (dt, *J* = 0.9, 8.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.12-7.27 (m, 3H), 7.00 (dd, *J* = 0.6, 8.6 Hz, 2H), 6.23 (dd, *J* = 3.3, 10.6 Hz, 1H, C<u>H</u>), 4.05 (dd, *J* = 6.5, 15.3 Hz, 1H), 3.38-3.50 (m, 1H), 3.08 (dd, *J* = 3.5, 14.2 Hz, 1H), 2.70 (dd, *J* = 10.6, 14.2 Hz, 1H), 2.41-2.58 (m, 2H), 2.35 (s, 3H), 2.14 (s, 3H, CO<u>CH$_3$</u>), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.0, 150.1, 143.5, 136.8, 135.2, 133.5, 129.1, 128.5, 127.0, 124.5, 122.8, 117.9, 115.6, 114.5, 84.8, 50.5, 48.8, 37.7, 29.2, 28.3, 21.2, 19.2; HRMS-ESI (*m/z*) $[C_{26}H_{30}N_2O_5S + Na]^+$ calcd 505.1768, found 505.1789.

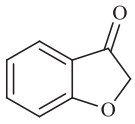
(*R*,*S*)-2-(9-*tert*-butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)acetamide (239)



General procedure A was followed using 2-bromoindole **133** (180 mg, 0.36 mmol), $Pd(PPh_3)_4$ (42 mg, 10 mol%), K_2CO_3 (151 mg, 1.1 mmol) and acrylamide (29 mg, 0.40 mmol) in toluene (5 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded a pale yellow oil. Partial indole deprotection during the domino procedure resulted in an inseparable mixture of indole protected tetrahydro-*β*-carboline and indole deprotected tetrahydro-*β*-carboline (142 mg, approx 80%). Indole-*N*-Boc = HRMS-ESI (*m/z*) $[C_{25}H_{29}N_3O_5S + H]^+$ calcd 484.1901, found 484.1905. Indole-*N*H = HRMS-ESI (*m/z*) $[C_{20}H_{21}N_3O_3S + H]^+$ calcd 384.1376, found 384.1379.

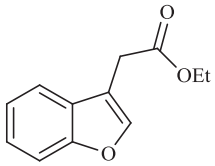
7.2.3 Chapter Four

benzofuran-3(2*H*)-one (261)



A solution of 2-hydroxyacetophenone (1.0 g, 7.35 mmol) in $CHCl_3$ (7 mL) was added to a refluxing solution of $CuBr_2$ (3.28 g, 14.7 mmol) in EtOAc (15 mL) and the resultant mixture refluxed for 16 h. The reaction mixture was cooled to room temperature, washed with H_2O (4 x 10 mL) then brine. The organic phase was dried over $MgSO_4$, and concentrated. The crude mixture was dissolved in acetonitrile (10 mL) and triethylamine (3.0 mL, 21.5 mmol) was added and the reaction mixture stirred at 60^{o}C for 2 hours. The solvent was concentrated and the crude mixture taken up in EtOAc, washed with HCl (1M, 2 × 20 mL), $NaHCO_3$ (saturated aqueous, 20 mL) and brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography to afford the title compound as a bright orange oil (857 mg, 6.39 mmol, 87% over 2 steps). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.69 (dd, *J* = 0.7, 1.5 Hz, 1H, Ar<u>H</u>), 7.66 (dd, *J* = 0.7, 1.5 Hz, 1H, Ar<u>H</u>), 7.64 (d, *J* = 1.5 Hz, 1H, Ar<u>H</u>), 7.61 (d, *J* = 1.3 Hz, 1H, Ar<u>H</u>), 7.58 (d, *J* = 1.5 Hz, 1H, Ar<u>H</u>), 4.62 (s, 2H, C<u>H$_2$</u>); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 199.9, 173.9, 137.9, 124.0, 122.0, 121.1, 113.6, 74.7; HRMS-ESI (*m/z*) $[C_8H_6O_2 + H]^+$ calcd 135.0441, found 135.0438.

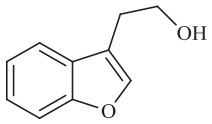
ethyl 2-(benzo[*b*]furan-3-yl)acetate (259)



A solution containing benzofuranone **261** (300 mg, 2.24 mmol) and (carboxymethylene)triphenylphosphorane (1.169 mg, 3.36 mmol) in toluene (5 mL) was refluxed at 120 ^{o}C for 48 h. The reaction mixture was allowed to cool to room temperature, concentrated and the crude purified by column chromatography (1:49 EtOAc:Pet. Sp.) to afford the

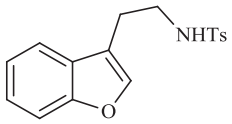
title compound as a bright yellow oil (353 mg, 1.73 mmol, 77%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (s, 1H, benzofuran-C2-ArH), 7.59 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.28 (dquin, J = 1.6, 7.3 Hz, 2H, ArH), 4.20 (q, J = 7.2 Hz, 2H, CO_2Et), 3.69 (s, 2H, CH_2CO_2Et), 1.26 (t, J = 7.1 Hz, 3H, CO_2Et); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.7, 155.2, 142.8, 127.6, 124.4, 122.6, 119.7, 113.2, 111.5, 61.1, 29.8, 14.2; HRMS-ESI (*m/z*) $[C_{12}H_{12}O_3 + H]^+$ calcd 205.0859, found 205.0845.

2-(benzo[*b*]furan-3-yl)ethanol (262)



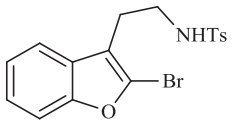
To a solution of $LiAlH_4$ (195 mg, 5.13 mmol) in THF (5 mL) at 0^{o}C was added dropwise benzofuran methyl ester **259** (350 mg, 1.71 mmoL) in THF (5 mL). After stirring at room temperature for 16 h. the reaction mixture was cooled to 0^{o}C and quenched by the careful addition of H_2O. After dilution with EtOAC (20 mL) the reaction mixture was washed with H_2O (2 × 10 mL) and brine. The organic phase was separated, dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (250 mg, 1.54 mmol, 90%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.53-7.57 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.46 (m, 1H, ArH), 7.20-7.32 (m, 2H, ArH), 3.88 (t, J = 6.4 Hz, 2H, CH_2CH_2OH), 2.90 (dt, J = 1.0, 6.4 Hz, 2H, CH_2CH_2OH), 2.03 (brs, 1H, CH_2CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 155.4, 142.1, 128.0, 124.4, 122.5, 119.5, 116.8, 111.6, 61.7, 27.1; HRMS-ESI (*m/z*) $[C_{10}H_{10}O_2 + H]^+$ calcd 163.0754, found 163.0749.

***N*-(2-(benzo[*b*]furan-3-yl)ethyl)-*p*-toluenesulfonamide (263)**



To a solution of benzofuran alcohol **262** (869 mg, 5.36 mmol) and triethylamine (1.12 mL, 8.04 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C was added *p*-toluenesulfonyl chloride (1.532 g, 8.04 mmol) in one portion. After stirring for 3 hrs, the reaction mixture was diluted with CH_2Cl_2, washed 1M HCl (2 x 10 mL), 5% Aqueous NaOH (2 x 10 mL), and brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude was then taken up in acetonitrile (20 mL). *p*-toluenesulfonamide and potassium carbonate were added and the resultant mixture was refluxed at 85 ^{o}C for 16 hrs. After cooling to room temperature the solvent was concentrated. The crude was then taken up in ethyl acetate and washed 1M HCl (2 x 10 mL), 5% Aqueous NaOH (2 x 10 mL), and brine. The organic layer was separated, dried over $MgSO_4$ and concentrated to afford the title compound (939 mg, 2.98 mmol, 56% over 2 steps) ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.67 (d, J = 8.3 Hz, 2H, ArH), 7.40-7.44 (m, 2H, ArH), 7.37 (s, 1H, benzofuran-C2-ArH), 7.14-7.29 (m, 4H, ArH), 4.89 (t, J = 6.2 Hz, 1H, NHTs), 3.25 (q, J = 6.5 Hz, 2H, CH_2CH_2NH), 2.83 (t, J = 7.2 Hz, 2H, CH_2CH_2NH), 2.37 (s, 3H, $TsCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 155.4, 143.6, 142.3, 136.8, 129.8, 127.5, 127.1, 124.5, 122.6, 119.4, 116.3, 111.7, 42.4, 24.2, 21.6; HRMS-ESI (*m/z*) $[C_{17}H_{17}NO_3S + Na]^+$ calcd 338.0821, found 338.0807.

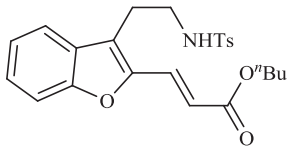
***N*-(2-(2-bromobenzo[*b*]furan-3-yl)ethyl)-*p*-toluenesulfonamide (264)**



A solution of *N*-bromosuccinimide (81 mg, 0.45 mmol) in acetonitrile (5 mL) was added dropwise to a stirred solution of benzofuran sulfonamide **263** (130 mg, 0.41 mmol) in chloroform (5 mL) at 0 ^{o}C. After stirring at room temperature for 1 h. the reaction mixture was poured into water and extracted with chloroform (3 × 10 mL). The combined organic phases

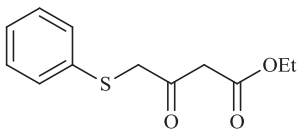
were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography to afford the title compound as a pale yellow oil (154 mg, 0.39 mmol, 95%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.64 (d, *J* = 8.4 Hz, 2H, ArH), 7.34-7.37 (m, 2H, ArH), 7.22-7.25 (m, 1H, ArH), 7.14-7.20 (m, 3H, ArH), 4.84 (t, *J* = 6.2 Hz, 1H, NHTs), 3.25 (q, *J* = 6.9 Hz, 2H, CH_2CH_2NH), 2.80 (t, *J* = 6.9 Hz, 2H, CH_2CH_2NH), 2.36 (s, 3H, $TsCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 155.2, 143.4, 136.7, 129.6, 128.1, 127.4, 126.9, 124.4, 123.3, 118.6, 115.7, 111.0, 41.9, 25.0, 21.5; HRMS-ESI (*m/z*) $[C_{17}H_{16}BrNO_3S + H]^+$ calcd 394.0107, found 394.0094.

(*E*)-butyl 3-(3-(2-(*p*-toluenylsulfonamido)ethyl)benzo[*b*]furan-2-yl)acrylate (265)



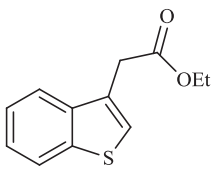
To a sealed tube containing toluene (3 mL) was added sequentially 2-bromobenzofuran sulfonamide **264** (100 mg, 0.25 mmol), Na_2CO_3 (81 mg, 0.76 mmol), $Pd(PPh_3)_4$ (29 mg, 10 mol%) and butyl acrylate (39 mg, 0.30 mmol). The resultant mixture was heated to 120 °C for 16 h. After cooling to room temperature the reaction mixture was filtered, concentrated and the crude purified by column chromatography (1:4 EtOAc: Pet. Sp.) to afford the title compound as a pale yellow oil (68 mg, 0.15 mmol, 61%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.5 Hz, 2H, ArH), 7.50 (d, *J* = 15.5 Hz, 1H, CH=CHCO$_2$*n*Bu), 7.30-7.44 (m, 3H, ArH), 7.15-7.21 (m, 3H, ArH), 6.54 (d, *J* = 15.5 Hz, 1H, CH=CHCO$_2$*n*Bu), 4.95 (t, *J* = 6.4 Hz, 1H, NHTs), 4.16 (t, *J* = 6.6 Hz, 2H, CO$_2$*n*Bu), 3.28 (q, *J* = 7.0 Hz, 2H, CH_2CH_2NH), 2.96 (t, *J* = 6.8 Hz, 2H, CH_2CH_2NH), 2.37 (s, 3H, $TsCH_3$), 1.61-1.73 (m, 2H, CO$_2$*n*Bu), 1.32-1.48 (m, 2H, CO$_2$*n*Bu), 0.94 (t, *J* = 7.3 Hz, 3H, CO$_2$*n*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 167.1, 154.9, 149.3, 143.5, 136.8, 129.7, 128.7, 128.6, 127.1, 126.9, 123.3, 120.6, 120.2, 118.7, 111.5, 64.7, 42.9, 30.8, 24.6, 21.6, 19.3, 13.8; HRMS-ESI (*m/z*) $[C_{24}H_{27}NO_5S + H]^+$ calcd 442.1683, found 442.1662.

ethyl 3-oxo-4-(phenylthio)butanoate (271)



To a stirred solution of thiophenol (5.00 g, 45.4 mmol) and triethylamine (5.51 g, 54.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added ethyl-4-chloroacetoacetate (8.17 g, 49.6 mmol). After stirring for 4 h. at ambient temperature, the reaction mixture was washed with NaOH (5%. Aq w/w, 2 × 20 mL), HCl (1M. aq. 2 × 20 mL) and brine. The organic phase was separated, dried over $MgSO_4$ and concentrated to afford the title compound as an orange oil (10.23 g, 42.9 mmol, 95%) ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.20-7.34 (m, 5H, ArH), 4.16 (q, *J* = 7.2 Hz, 2H, CO_2Et), 3.79 (s, 2H, CH_2CO_2Et), 3.61 (s, 2H, SCH_2), 1.23 (t, *J* = 7.2 Hz, 3H, CO_2Et); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 198.0, 167.0, 134.1, 129.7, 129.2, 127.1, 61.5, 46.6, 43.9, 14.1; HRMS-ESI (*m/z*) $[C_{12}H_{14}O_3S + H]^+$ calcd 253.0767, found 253.0779.

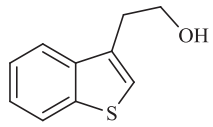
ethyl 2-(benzo[*b*]thiophen-3-yl)acetate (272)



A solution containing polyphosphoric acid (20 g), Celite (10 g) and phosphorous pentoxide (1.80 g, 12.6 mmol) in toluene (150 mL) was refluxed for 1 h. After this time phenylthiobutanoate **271** (3.80 g, 15.95 mmol) was added and refluxing continued for 16 h. After cooling to room temperature the reaction mixture was filtered, washed with K_2CO_3 (Sat. Aq. 3 × 20 mL) and brine. The organic phase was dried over $MgSO_4$and concentrated.

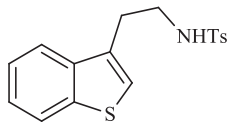
Purification by column chromatography (1:9 EtOAc:Pet Sp.) afforded the title compound as a yellow oil (2834 mg, 12.87 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.89 (d, *J* = 7.05, 1H, ArH), 7.78 (d, *J* = 7.0 Hz, 1H, ArH), 7.38 (m, 3H, ArH), 4.21 (q, *J* = 6.4 Hz, 2H, CO_2Et), 3.88 (s, 2H, CH_2CO_2Et), 1.27 (t, *J* = 6.4 Hz, 3H, CO_2Et); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.7, 140.2, 138.6, 128.4, 124.5, 124.4, 124.2, 122.8, 121.8, 61.1, 34.6, 14.2; HRMS-ESI (*m/z*) $[C_{12}H_{12}O_2S + H]^+$ calcd 221.0631, found 221.0628.

2-(benzo[*b*]thiophen-3-yl)ethanol (273)



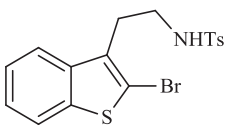
To a cooled solution (0 °C) of lithium aluminium hydride (639 mg, 16.83 mmol) in THF (30 mL) was added dropwise benzothiopheneacetate **272** (1236 mg, 5.61 mmol) and the reaction mixture stirred at room temperature for 16 h. After cooling to 0 °C, the reaction was quenched by the careful addition of H_2O (10 mL). The reaction mixture was filtered, diluted with EtOAc (20 mL) and washed with H_2O (2 × 10 mL) then brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (876 mg, 4.91 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.89 (d, *J* = 7.7, 1H, ArH), 7.78 (d, *J* = 7.0 Hz, 1H, ArH), 7.38 (quin, *J* = 6.5 Hz, 2H, ArH), 7.23 (s, 1H, ArH), 3.99 (q, *J* = 6.2 Hz, 2H, CH_2CH_2OH), 3.14 (t, *J* = 6.4 Hz, 2H, CH_2CH_2OH), 1.45 (t, *J* = 5.7 Hz, 1H, CH_2CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 139.9, 138.5, 128.4, 124.3, 124.0, 123.0, 122.9, 121.6, 61.9, 31.9; HRMS-ESI (*m/z*) $[C_{10}H_{10}OS + Na]^+$ calcd 201.0345, found 201.0349.

***N*-(2-(benzo[*b*]thiophen-3-yl)ethyl)-*p*-toluenesulfonamide (274)**



To a solution containing benzothiophene ethanol **273** (330 mg, 1.85 mmol) and triethylamine (282 mg, 2.79 mmol) in CH_2Cl_2 was added *p*-toluenesulfonyl chloride (532 mg, 2.79 mmol). After stirring for 3 h. the reaction mixture was diluted with CH_2Cl_2, washed 1M HCl (2 x 10 mL), 5% Aqueous NaOH (2 x 10 mL), and brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude was then taken up in acetonitrile (20 mL) and *p*-toluenesulfonamide (288 mg, 1.68 mmol) and K_2CO_3 (232 mg, 1.68 mmol) were added and the resultant mixture was refluxed at 90 °C for 16 h. After cooling to room temperature the solvent was concentrated. Purification by column chromatography (1:4 EtOAc:Pet Sp.) afforded the title compound as a pale oil (185 mg, 0.56 mmol, 30% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.85 (m, 1H, ArH), 7.68 (d, *J* = 8.2 Hz, 2H, ArH), 7.60 (m, 2H, ArH), 7.35 (m, 2H, ArH), 7.25 (d, *J* = 8.1 Hz, 1H, ArH), 7.10 (s, 1H, benzothiophene-C2- ArH), 4.46 (t, *J* = 7.1 Hz, 1H, NHTs), 3.34 (q, *J* = 6.5 Hz, 2H, CH_2CH_2NH), 3.04 (t, *J* = 6.7 Hz, 2H, CH_2CH_2OH), 2.40 (s, 3H, TsCH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 143.6, 140.7, 138.3, 136.8, 132.2, 129.8, 127.1, 124.5, 124.2, 123.3, 123.1, 121.4, 42.5, 29.0, 21.6; HRMS-ESI (*m/z*) $[C_{17}H_{17}NO_2S_2 + H]^+$ calcd 332.0773 found 332.0783.

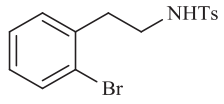
***N*-(2-(2-bromobenzo[*b*]thiophen-3-yl)ethyl)-*p*-toluenesulfonamide (275)**



To a solution of benzothiophene sulfonamide **274** (180 mg, 0.54 mmol) in CH_2Cl_2 at 0 °C was added *N*-bromosuccinimide (106 mg, 0.60 mmol). After stirring at this temperature for 1 h. the reaction mixture was concentrated and purification by column chromatography afforded the title compound as a clear oil (60 mg, 0.15 mmol, 27%). ^{1}H

NMR (270 MHz, $CDCl_3$, δ) 7.77 (m, 1H, ArH), 7.66 (d, *J* = 7.5 Hz, 2H, ArH), 7.56 (m, 2H, ArH), 7.31 (m, 2H, ArH), 7.19 (d, *J* = 7.9 Hz, 1H, ArH), 4.60 (brs, 1H, NHTs), 3.23 (q, *J* = 5.9 Hz, 2H, CH_2CH_2NH), 3.04 (t, *J* = 7.3 Hz, 2H, CH_2CH_2NH), 2.36 (s, 3H, $TsCH_3$); ^{13}C NMR – due to rapid degradation of the compound a clean spectrum was not obtained.; HRMS-ESI (*m/z*) $[C_{17}H_{16}NO_2S_2Br + H]^+$ calcd 409.9879 found 409.9885.

_N_-(2-bromophenethyl)-_p_-toluenesulfonamide (279)

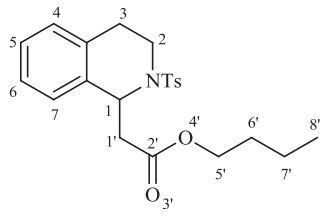


To a cooled solution (0 °C) of 2-bromophenethylamine (400mg, 2.0 mmol) and triethylamine (242 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (420 mg, 2.2 mmol) in one portion. The reaction mixture was stirred for 2 h. at ambient temperature. The reaction mixture was then washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a colourless oil (624 mg, 1.76 mmol, 88%). ^1H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (dd, *J* = 1.2, 7.9 Hz, 1H, ArH), 7.26 (d, *J* = 8.1 Hz, 2H, ArH) 7.03-7.20 (m, 3H, ArH), 4.57 (brt, *J* = 6.2 Hz, 1H, NHTs), 3.21 (q, *J* = 6.9 Hz, 2H, CH_2CH_2NH), 2.90 (t, *J* = 7.2 Hz, 2H, CH_2CH_2NH), 2.40 (s, 3H, $TsCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 143.4, 137.1, 133.0, 131.1, 129.7, 129.0, 128.2, 127.7, 127.1, 124.4, 42.5, 36.3, 21.5; HRMS-ESI (*m/z*) $[C_{15}H_{16}BrNO_2S + Na]^+$ calcd 375.9977, found 375.9979.

General Procedure B for Tetrahydroisoquinoline Formation:

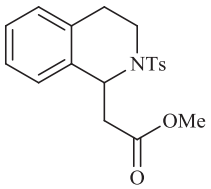
A sealed tube containing a 2-bromophenethylamine **279** (1.0 eq), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), K_2CO_3 (3.0 eq) and alkene (1.2 eq) in toluene (3 mL) was flushed with argon, then heated at 120 °C for 16 hrs. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-butyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (280)



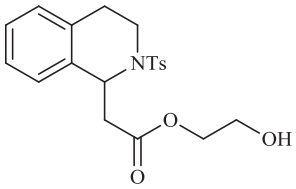
General procedure B was followed using 2-bromophenethylamine **279** (100 mg, 0.28 mmol), butyl acrylate (44 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (90 mg, 0.22 mmol, 80%). ^1H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 7.14 (d, *J* = 7.9 Hz, 2H, ArH), 7.08-7.10 (m, 3H, ArH), 6.95 (m, 1H, ArH), 5.46 (t, *J* = 6.9 Hz, 1H, H1), 4.04 (dt, *J* = 3.5, 6.7 Hz, 2H, H5'), 3.71-3.80 (m, 1H, H2a), 3.47-3.58 (m, 1H, H2b), 2.88 (dd, *J* = 7.2, 14.6 Hz, 1H, H3a), 2.63-2.74 (m, 3H, H3b and H1'), 2.32 (s, 3H, $TsCH_3$), 1.58 (m, 2H, H6'), 1.32 (m, 2H, H7'), 0.90 (t, *J* = 7.4 Hz, 3H, H8'); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ); 170.4, 143.3, 137.2, 135.5, 133.1, 129.5, 129.0, 127.3, 127.2, 126.7, 126.5, 64.8, 53.4, 43.6, 39.7, 30.6, 27.0, 21.5, 19.1, 13.8; HRMS-ESI (*m/z*) $[C_{22}H_{27}NO_4S + H]^+$ calcd 402.1734, found 402.1734.

(*R*,*S*)-methyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (283)



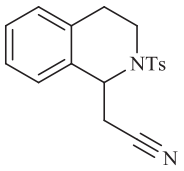
General procedure B was followed using 2-bromophenethylamine **279** (200 mg, 0.56 mmol), methyl acrylate (58 mg, 0.67 mmol), $Pd(OAc)_2$ (12 mg, 10 mol%), PPh_3 (14 mg, 10 mol%), potassium carbonate (232 mg, 1.68 mmol) and toluene (3 mL). Purification by column chromatography (1:9 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (168 mg, 0.47 mmol, 83%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.64 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.08-7.10 (m, 3H), 6.95 (m, 1H), 5.47 (t, *J* = 7.2 Hz, 1H, C<u>H</u>), 3.77 (m, 1H), 3.65 (s, 3H, CO_2<u>Me</u>), 3.53 (m, 1H), 2.90 (dd, *J* = 7.6 and 14.6 Hz, 1H), 2.62-2.75 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ); 170.7, 143.3, 137.2, 135.3, 133.1, 129.5, 129.1, 127.3, 127.2, 126.6, 126.5, 53.5, 52.0, 43.4, 39.7, 26.9, 21.5; HRMS-ESI (*m/z*) $[C_{19}H_{21}NO_4S + Na]^+$ calcd 382.1084, found 382.1081.

(*R*,*S*)-2-hydroxyethyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (284)



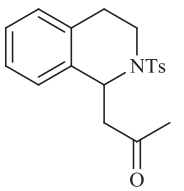
General procedure B was followed using 2-bromophenethylamine **279** (100 mg, 0.28 mmol), 2-hydroxyethyl acrylate (39 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (2:3 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (83 mg, 0.21 mmol, 76%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.61 (d, *J* = 8.4 Hz, 2H), 7.06-7.15 (m, 5H), 6.91 (m, 1H), 5.47 (t, *J* = 5.9 Hz, 1H, C<u>H</u>), 4.21-4.31 (m, 2H), 3.71-3.78 (m, 2H), 3.50-3.59 (m, 2H), 2.91 (ddd, *J* = 1.5 and 8.2 and 14.8 Hz, 1H), 2.78 (dd, *J* = 5.7 and 14.8 Hz, 1H), 2.60-2.65 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 170.0, 143.2, 137.1, 135.2, 133.0, 129.5, 129.0, 127.2, 127.1, 126.7, 126.6, 126.4, 62.5, 53.4, 43.3, 39.6, 26.7, 21.4; HRMS-ESI (*m/z*) $[C_{20}H_{23}NO_5S + Na]^+$ calcd 412.1189, found 412.1178.

(*R*,*S*)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (285)



General procedure B was followed using 2-bromophenethylamine **279** (100 mg, 0.28 mmol), acrylonitrile (18 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1:9 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (75 mg, 0.23 mmol, 82%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, *J* = 8.4 Hz, 2H), 7.13-7.22 (m, 5H), 7.07 (m, 1H), 5.17 (t, *J* = 5.7 Hz, 1H, C<u>H</u>), 3.64-3.74 (m, 1H), 3.48-3.57 (m, 1H), 2.98 (dd, *J* = 4.0 and 5.9 Hz, 2H), 2.64-2.92 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 144.1, 135.8, 134.1, 132.7, 130.0, 129.2, 128.2, 127.4, 127.1, 126.9, 117.3, 52.8, 41.1, 28.0, 27.7, 21.6; HRMS-ESI (*m/z*) $[C_{18}H_{18}N_2O_2S - H]^-$ calcd 325.1016, found 325.1009.

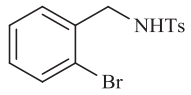
(*R*,*S*)-1-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (286)



General procedure B was followed using 2-bromophenethylamine **279** (100 mg, 0.28 mmol), 3-buten-2-one (24 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1:9 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (76 mg, 0.22 mmol, 79%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2

Hz, 2H), 7.07-7.09 (m, 3H), 6.94 (m, 1H), 5.50 (t, *J* = 6.2 Hz, 1H, CH), 3.67-3.74 (m, 1H), 3.46-3.56 (m, 1H), 3.05 (dd, *J* = 5.9 and 16 Hz, 1H), 2.82 (dd, *J* = 6.4 and 16 Hz, 1H), 2.64-2.69 (m, 2H), 2.32 (s, 3H), 2.15 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 205.4, 143.4, 136.7, 136.2, 132.8, 129.5, 128.8, 127.2, 127.0, 126.7, 126.6, 52.7, 52.1, 40.1, 30.4, 27.2, 21.5; HRMS-ESI (*m/z*) $[C_{19}H_{21}NO_3S + Na]^+$ calcd 366.1134, found 366.1135.

_N_-(2-bromobenzyl)-_p_-toluenesulfonamide (199)

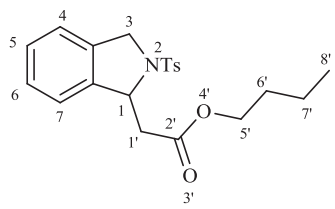


To a cooled solution (0 °C) of 2-bromobenzylamine hydrochloride (400 mg, 1.80 mmol) and triethylamine (401 mg, 3.96 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (378 mg, 1.98 mmol) in one portion. The reaction mixture was stirred for 2 h. at ambient temperature. The reaction mixture was then washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound as a colourless oil (610 mg, 1.79 mmol, 99%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, *J* = 8.4 Hz, 2H, ArH), 7.43 (dd, *J* = 1.2, 7.9 Hz, 1H, ArH), 7.19-7.30 (m, 4H, ArH), 7.07 (dt, *J* = 1.7 and 7.7 Hz, 1H, ArH), 5.11 (brt, *J* = 5.9 Hz, 1H, NHTs), 4.21 (d, *J* = 6.2 Hz, 2H, CH_2NH), 2.39 (s, 3H, TsCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 143.5, 136.9, 135.5, 132.8, 130.5, 129.6, 129.5, 127.7, 127.1, 123.5, 47.5, 21.5; HRMS-ESI (*m/z*) $[C_{14}H_{14}BrNO_2S - H]^-$ calcd 337.9856, found 337.9862.

General Procedure C for Isoindoline Formation:

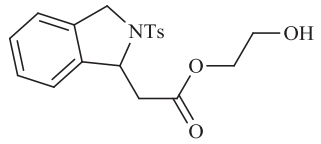
A sealed tube containing 2-bromobenzylamine **199** (1.0 eq), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), triethylamine (3.0 eq) and alkene (1.2 eq) in DMF was flushed with argon, then heated at 120 °C for 16 hrs. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-butyl 2-(2-tosylisoindolin-1-yl)acetate (292)



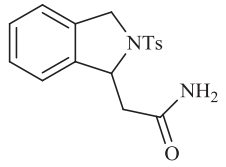
General procedure C was followed using 2-bromobenzylamine **199** (100 mg, 0.29 mmol), butyl acrylate (45 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1:9 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (86 mg, 0.22 mmol, 77%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, *J* = 8.2 Hz, 2H, ArH), 7.18-7.27 (m, 5H, ArH), 7.10-7.13 (m, 1H, ArH), 5.27 (m, *J* = 3.0 and 3.7 Hz, 1H, H1), 4.73 (dd, *J* = 2.5 and 13.8 Hz, 1H, H3a), 4.53 (d, *J* = 13.8 Hz, 1H, H3a), 4.09 (t, *J* = 6.7 Hz, 2H, H5'), 3.30 (dd, *J* = 3.9 and 16.5 Hz, 1H, H1a'), 2.86 (dd, *J* = 7.9 and 16.5 Hz, 1H, H1a'), 2.36 (s, 3H, $TsCH_3$), 1.53-1.63 (m, 2H), 1.23-1.40 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.0, 143.7, 139.6, 135.5, 134.0, 129.8, 128.1, 127.9, 127.6, 122.7, 122.4, 64.6, 62.1, 53.9, 42.8, 30.6, 21.5, 19.1, 13.7; HRMS-ESI (*m/z*) $[C_{21}H_{25}NO_4S + Na]^+$ calcd 410.1396, found 410.1380.

(*R*,*S*)-2-hydroxyethyl 2-(2-tosylisoindolin-1-yl)acetate (296)



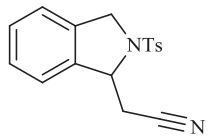
General procedure C was followed using 2-bromobenzylamine **199** (100 mg, 0.29 mmol), 2-hydroxyethyl acrylate (40 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (2:3 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (91 mg, 0.24 mmol, 84 %). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, *J* = 8.2 Hz, 2H), 7.19-7.28 (m, 5H), 7.09-7.16 (m, 1H), 5.31 (m, 1H, C<u>H</u>), 4.73 (dd, *J* = 2.5 and 14.1 Hz, 1H), 4.50 (d, *J* = 13.8 Hz, 1H), 4.32 (m, 1H), 4.19 (m, 1H), 3.81 (m, 2H), 3.17 (dd, *J* = 4.9 and 15.8 Hz, 1H), 2.99 (dd, *J* = 5.9 and 16.0 Hz, 1H), 2.36 (s, 3H), 2.33 (brt, 1H, O<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.1, 144.0, 139.3, 135.5, 133.8, 129.9, 128.3, 128.0, 127.6, 122.6, 122.5, 66.6, 62.3, 61.0, 53.9, 43.0, 21.5; HRMS-ESI (*m/z*) $[C_{19}H_{21}NO_5S + Na]^+$ calcd 398.1032, found 398.1024.

(*R*,*S*)-2-(2-tosylisoindolin-1-yl)acetamide (297)



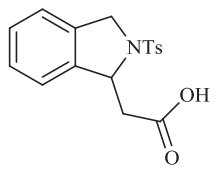
General procedure C was followed using 2-bromobenzylamine **199** (100 mg, 0.29 mmol), acrylamide (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1:1 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (68 mg, 0.21 mmol, 71%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, *J* = 8.2 Hz, 2H), 7.18-7.29 (m, 5H), 7.10-7.14 (m, 1H), 5.86 (brs, 1H, N<u>Ha</u>), 5.40 (brs, 1H, N<u>Hb</u>), 5.18 (m, *J* = 3.2 and 3.9 Hz, 1H, C<u>H</u>), 4.73(dd, *J* = 2.0 and 13.8 Hz, 1H), 4.53 (d, *J* = 13.8 Hz, 1H), 3.15 (dd, *J* = 3.7 and 15.0 Hz, 1H), 2.90 (dd, *J* = 7.1 and 15.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 172.0, 144.2, 139.2, 135.0, 133.2, 130.1, 128.3, 128.2, 127.8, 123.3, 122.4, 62.6, 54.2, 43.7, 21.6; HRMS-ESI (*m/z*) $[C_{17}H_{18}N_2O_3S + H]^+$ calcd 331.1111, found 331.1126.

(*R*,*S*)-2-(2-tosylisoindolin-1-yl)acetonitrile (298)



General procedure C was followed using 2-bromobenzylamine **199** (100 mg, 0.29 mmol), acrylonitrile (18 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1:6 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (62 mg, 0.20 mmol, 68%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.76 (d, *J* = 8.2 Hz, 2H), 7.18-7.33 (m, 6H), 5.11 (m, 1H, C<u>H</u>), 4.80 (dd, *J* = 2.7 and 13.8 Hz, 1H), 4.55 (d, *J* = 13.8 Hz, 1H), 3.16 (s, 1H), 3.14 (d, *J* = 1.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 144.4, 136.7, 135.8, 133.8, 130.1, 129.1, 128.4, 127.5, 122.9, 122.6, 116.7, 61.5, 53.9, 26.9, 21.5; HRMS-ESI (*m/z*) $[C_{17}H_{16}N_2O_2S + H]^+$ calcd 313.1005, found 313.1013.

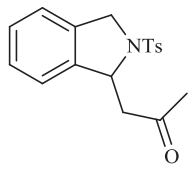
(*R*,*S*)-2-(2-tosylisoindolin-1-yl)acetic acid (299)



General procedure C was followed using 2-bromobenzylamine **199** (100 mg. 0.29 mmol), acrylic acid (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (3:1 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (82 mg, 0.25 mmol, 85%). H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.18-

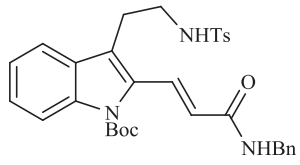
7.22 (m, 3H), 7.10-7.13 (m, 1H), 5.28 (m, 1H, CH), 4.73 (dd, *J* = 2.2 and 13.9 Hz, 1H), 4.53 (d, *J* = 13.9 Hz, 1H), 3.39 (dd, *J* = 3.9 and 16.5 Hz, 1H), 2.91 (dd, *J* = 7.9 and 16.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 176.5, 143.9, 139.2, 135.4, 133.8, 129.9, 128.3, 128.1, 127.6, 122.7, 122.5, 61.8, 53.9, 42.7, 21.5; HRMS-ESI (*m/z*) $[C_{17}H_{17}NO_4S + Na]^+$ calcd 354.0771, found 354.0759.

(*R*,*S*)-1-(2-tosylisoindolin-1-yl)propan-2-one (300)



General procedure C was followed using 2-bromobenzylamine **199** (100 mg, 0.29 mmol), 3-buten-2-one (24 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1:4 EtOAc:Pet Sp) afforded the title compound as a pale yellow oil (82 mg, 0.25 mmol, 86%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.16-7.20 (m, 3H), 7.07-7.12 (m, 1H), 5.30 (m, 1H, CH), 4.75 (dd, *J* = 2.4 and 13.9 Hz, 1H), 4.50 (d, *J* = 13.9 Hz, 1H), 3.50 (dd, *J* = 3.4 and 17.8 Hz, 1H), 2.99 (dd, *J* = 7.7 and 18.0 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.5, 143.8, 140.2, 135.1, 133.5, 129.9, 128.7, 128.0, 127.7, 122.9, 122.3, 61.1, 53.9, 52.2, 30.8, 21.5; HRMS-ESI (*m/z*) $[C_{18}H_{19}NO_3S + Na]^+$ calcd 352.0978, found 352.0993.

(*E*)-tert-butyl 2-(3-(benzylamino)-3-oxoprop-1-en-1-yl)-3-(2-(*p*-toluenesulfonamido)ethyl)-1*H*-indole-1-carboxylate (309)



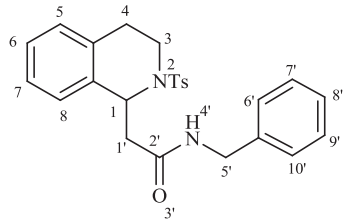
To a solution containing benzylamine (32 mg, 0.36 mmol), and triethylamine (39 mg, 0.39 mmol) in toluene (3 mL) was added acryloyl chloride (38 mg, 0.36 mmol) and the resultant mixture stirred at room temperature for 1 h. After this time, $Pd(PPh_3)_4$ (37 mg, 10 mol%), potassium carbonate (134 mg, 0.97 mmol) and 2-bromoindolesulfonamide **133** (160 mg, 0.32 mmol, in 1 mL toluene) were added. The pressure vessel was purged with nitrogen, sealed and then heated to 120 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was filtered, and the solvent concentrated. Purification by flash chromatography (EtOAc:Pet Sp 1:1) afforded the title compound as a pale yellow oil (149 mg, 0.26 mmol, 80%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.16 (d, *J* = 8.3 Hz, 1H, ArH), 7.93 (d, *J* = 15.8 Hz, 1H, CH=CHCONHBn), 7.61 (d, *J* = 8.3 Hz, 2H, ArH), 7.15-7.38 (m, 10H, ArH), 6.80 (t, *J* = 5.8 Hz, 1H, NHBn), 6.50 (d, *J* = 15.8 Hz, 1H, CH=CHCONHBn), 5.00 (t, *J* = 6.6 Hz, 1H, NHTs), 4.58 (d, *J* = 5.8 Hz, 2H, CH_2Ph), 3.29 (m, 2H, CH_2CH_2NH), 3.05 (m, 2H, CH_2CH_2NH), 2.36 (s, 3H, TsCH_3), 1.65 (s, 9H, Boc-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 165.5, 150.0, 143.6, 138.4, 137.0, 136.3, 133.4, 131.8, 129.7, 129.2, 128.6, 127.8, 127.3, 126.7, 125.5, 123.5, 122.9, 118.6, 118.2, 115.7, 84.8, 43.6, 43.0, 31.0, 28.2, 26.8, 21.5; HRMS-ESI (*m/z*) $[C_{32}H_{35}N_3O_5S + H]^+$ calcd 574.2370, found 574.2372.

General Procedure D for the three-component domino Heck-aza-Michael reaction

To a pressure vessel containing a solution of potassium carbonate (116 mg, 0.84 mmol), amine (0.34 mmol) and toluene (2 mL + a few drops of DMF when necessary) was added acryloyl chloride (30 mg, 0.34 mmol) and the resultant mixture stirred for 1 hour at room temperature. After this time, $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%) and 2-bromophenethylsulfonamide **279** (100 mg, 0.28 mmol, in 1 mL toluene) were added. The

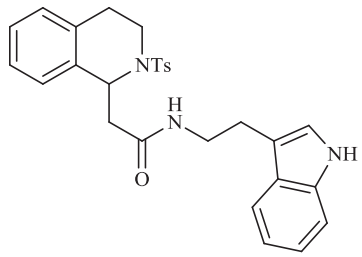
pressure vessel was purged with nitrogen, sealed and then heated to 120 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was filtered, and the solvent concentrated. Purification by flash chromatography (EtOAc:Pet Sp 2:3) afforded the desired tetrahydroisoquinoline.

***(R,S)-N*-benzyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (314)**



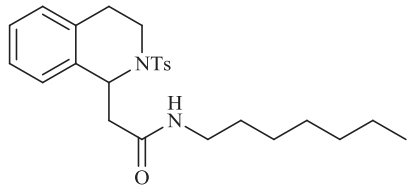
General procedure D was followed using benzylamine (36 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (118 mg, 0.27 mmol, 97%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.62 (d, *J* = 8.3 Hz, 2H, ArH), 7.25-7.34 (m, 5H, ArH), 7.03-7.13 (m, 5H, ArH), 6.87-6.90 (m, 1H, ArH), 6.25 (brs, 1H, NH4'), 5.40 (t, *J* = 6.4 Hz, 1H, H1), 4.42 (d, *J* = 5.7 Hz, 2H, H5'), 3.76 (dt, *J* = 4.5 and 13.6 Hz, 1H, H3a), 3.43-3.53 (m, 1H, H3b), 2.88 (dd, *J* = 7.3 and 14.9 Hz, 1H, H4a), 2.56-2.68 (m, 3H, H4b and H1'), 2.30 (s, 3H, TsCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.2, 143.5, 138.0, 136.6, 135.2, 132.7, 129.5, 128.9, 128.6, 128.0, 127.4, 127.2, 127.1, 126.9, 126.5, 53.6, 45.4, 43.8, 39.8, 26.7, 21.5; HRMS-ESI (*m/z*) $[C_{25}H_{26}N_2O_3S + Na]^+$ calcd 457.1556, found 457.1568.

***(R,S)-N*-(2-(1*H*-indol-3-yl)ethyl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (315)**



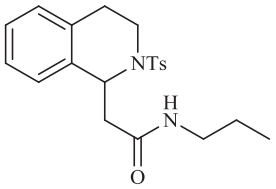
General procedure D was followed using tryptamine (54 mg, 0.34 mmol). The title compound was isolated as an orange oil (126 mg, 0.26 mmol, 92%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.31 (brs, 1H), 7.52-7.58 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17 (dt, *J* = 1.2 and 7.0 Hz, 1H), 7.00-7.10 (m, 7H), 6.84-6.87 (m, 1H), 6.02 (brt, *J* = 5.6 Hz, 1H, NH) 5.36 (t, *J* = 6.5 Hz, 1H, CH), 3.76 (dt, *J* = 4.7 and 13.6 Hz, 1H), 3.55 (q, *J* = 5.7 Hz, 2H), 3.36-3.46 (m, 1H), 2.94 (dt, *J* = 1.8 and 6.5 Hz, 2H), 2.71 (dd, *J* = 7.4 and 14.9 Hz, 1H), 2.46-2.59 (m, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.4, 143.5, 136.6, 136.4, 135.2, 132.7, 129.5, 128.8, 127.4, 127.1, 127.0, 126.9, 126.5, 122.4, 122.0, 119.3, 118.7, 112.8, 111.3, 53.7, 45.4, 39.9, 39.7, 26.6, 25.1, 21.4; HRMS-ESI (*m/z*) $[C_{28}H_{29}N_3O_3S + H]^+$ calcd 488.2002, found 488.1997.

***(R,S)-N*-heptyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (316)**



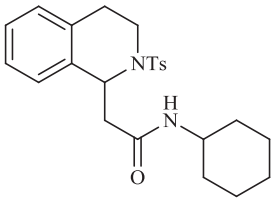
General procedure D was followed using heptylamine (39 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (110 mg, 0.25 mmol, 89%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.60 (d, *J* = 8.3 Hz, 2H), 7.03-7.12 (m, 5H), 6.86-6.88 (d, *J* = 6.4 Hz, 1H), 6.10 (brt, 1H), 5.37 (t, *J* = 6.9 Hz, 1H, CH), 3.78 (dt, *J* = 4.7 and 13.6 Hz, 1H), 3.43-3.54 (m, 1H), 3.22 (q, *J* = 6.5 Hz, 2H), 2.82 (dd, *J* = 7.6 and 15.2 Hz, 1H), 2.55-2.62 (m, 3H), 2.30 (s, 3H), 1.47 (m, 2H), 1.25 (m, 8H), 0.85 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.3, 143.5, 136.6, 135.2, 132.6, 129.5, 128.9, 127.2, 127.1, 126.9, 126.5, 53.6, 46.2, 39.8, 39.6, 31.8, 29.3, 29.0, 26.9, 26.5, 22.6, 21.5, 14.1; HRMS-ESI (*m/z*) $[C_{25}H_{34}N_2O_3S + H]^+$ calcd 443.2327, found 443.2341.

(*R,S*)-*N*-propyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (317)



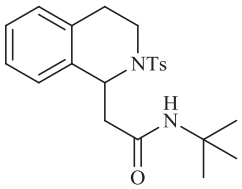
General procedure D was followed using propylamine (20 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (45 mg, 0.12 mmol, 42%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.60 (d, *J* = 8.3 Hz, 2H), 7.02-7.12 (m, 5H), 6.86-6.88 (d, *J* = 6.7 Hz, 1H), 6.11 (brs, 1H), 5.37 (t, *J* = 5.9 Hz, 1H, CH), 3.76 (dtd, *J* = 0.9 and 4.7 and 13.6 Hz, 1H), 3.44-3.55 (m, 1H), 3.17-3.24 (m, 2H), 2.82 (dd, *J* = 7.7 and 15.2 Hz, 1H), 2.54-2.64 (m, 3H), 2.30 (s, 3H), 1.52 (t, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.3, 143.5, 136.7, 135.2, 132.6, 129.5, 128.9, 127.2, 127.1, 126.9, 126.5, 53.6, 45.2, 41.5, 39.5, 26.4, 22.6, 21.4, 11.4; HRMS-ESI (*m/z*) $[C_{21}H_{26}N_2O_3S + Na]^+$ calcd 409.1556, found 409.1549.

(*R,S*)-*N*-cyclohexyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (318)



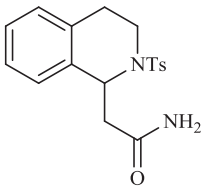
General procedure D was followed using cyclohexylamine (33 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (92 mg, 0.22 mmol, 77%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.60 (d, *J* = 8.3 Hz, 2H), 7.05-7.12 (m, 5H), 6.87 (d, *J* = 6.4 Hz, 1H), 5.95 (d, *J* = 7.9 Hz, 1H), 5.37 (t, *J* = 6.4 Hz, 1H, CH), 3.67-3.83 (m, 2H), 3.49 (dt, *J* = 8.1 and 16.4 Hz, 1H), 2.79 (dd, *J* = 7.6 and 15.1 Hz, 1H), 2.52-2.62 (m, 3H), 2.30 (s, 3H), 1.86-1.90 (m, 2H), 1.55-1.70 (m, 4H), 1.05-1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.3, 143.5, 136.8, 135.2, 132.6, 129.5, 128.9, 127.1, 127.0, 126.9, 126.4, 53.7, 48.5, 45.3, 39.5, 32.9, 26.4, 25.5, 24.9, 21.4; HRMS-ESI (*m/z*) $[C_{24}H_{30}N_2O_3S - H]^-$ calcd 425.1904, found 425.1898.

(*R,S*)-*N*-(*tert*-butyl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (319)



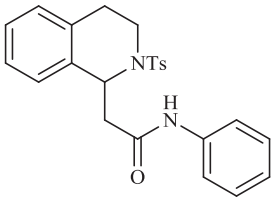
General procedure D was followed using *tert*-butylamine (25 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (104 mg, 0.26 mmol, 93%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.62 (d, *J* = 8.3 Hz, 2H), 7.02-7.12 (m, 5H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.72 (brs, 1H), 5.35 (t, *J* = 6.5 Hz, 1H, CH), 3.76 (dt, *J* = 4.7 and 14.2 Hz, 1H), 3.45-3.56 (m, 1H), 2.76 (dd, *J* = 7.1 and 14.9 Hz, 1H), 2.46-2.58 (m, 3H), 2.30 (s, 3H), 1.33 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.7, 143.5, 136.9, 135.5, 132.7, 129.6, 128.9, 127.2, 127.1, 127.0, 126.5, 53.9, 51.5, 46.4, 39.7, 28.7, 26.6, 21.5; HRMS-ESI (*m/z*) $[C_{22}H_{28}N_2O_3S + H]^+$ calcd 401.1893, found 401.1903.

(*R,S*)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (320)



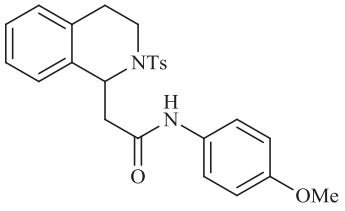
General procedure D was followed using 2-nitrobenzylamine hydrochloride (63 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (31 mg, 0.09 mmol, 32%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.62 (d, *J* = 8.3 Hz, 2H), 7.03-7.12 (m, 5H), 6.87 (d, *J* = 7.0 Hz, 1H), 6.25 (brs, 1H, NHa), 5.49 (brs, 1H, NHb), 5.39 (dd, *J* = 5.6 and 7.7 Hz, 1H, CH), 3.82 (dtd, *J* = 0.7 and 4.7 and 14.2 Hz, 1H), 3.46-3.57 (m, 1H), 2.89 (dd, *J* = 8.0 and 15.6 Hz, 1H), 2.69 (dd, *J* = 5.4 and 15.6 Hz, 1H), 2.56-2.61 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.8, 143.8, 136.6, 135.1, 132.6, 129.6, 129.0, 127.3, 127.2, 126.9, 126.7, 53.6, 44.8, 39.6, 26.4, 21.5; HRMS-ESI (*m/z*) $[C_{18}H_{20}N_2O_3S + H]^+$ calcd 345.1267, found 345.1257.

(*R,S*)-*N*-phenyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (325)



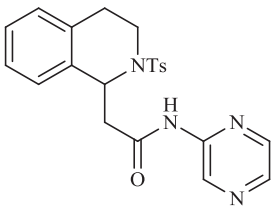
General procedure D was followed using aniline (31 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (98 mg, 0.23 mmol, 83%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.02 (brs, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.07-7.13 (m, 6H), 6.90 (d, *J* = 6.4 Hz, 1H), 5.46 (dd, *J* = 5.1 and 7.5 Hz, 1H, C<u>H</u>), 3.82 (dt, *J* = 4.6 and 14.1 Hz, 1H), 3.47-3.58 (m, 1H), 3.00 (dd, *J* = 7.7 and 15.5 Hz, 1H), 2.82 (dd, *J* = 5.2 and 15.6 Hz, 1H), 2.59-2.65 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 167.8, 143.7, 138.0, 136.3, 134.9, 132.7, 129.6, 129.0, 128.9, 127.2, 127.1, 126.8, 126.6, 124.3, 120.1, 53.5, 46.1, 39.6, 26.5, 21.5; HRMS-ESI (*m/z*) $[C_{24}H_{24}N_2O_3S + H]^+$ calcd 421.1580, found 421.1599.

(*R,S*)-*N*-(4-methoxyphenyl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (326)



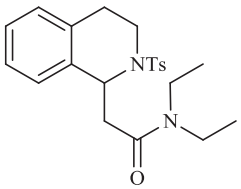
General procedure D was followed using *p*-anisidine (41 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (100 mg, 0.22 mmol, 79%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.05 (brs, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H) 7.05-7.10 (m, 5H), 6.89 (d, *J* = 5.7 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.40 (dd, *J* = 5.5 and 7.7 Hz, 1H, C<u>H</u>), 3.78 (m, 1H), 3.76 (s, 3H, O<u>Me</u>), 3.43-3.56 (m, 1H), 2.97 (dd, *J* = 7.9 and 15.4 Hz, 1H), 2.75 (dd, *J* = 5.3 and 15.4 Hz, 1H), 2.56-2.63 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 167.6, 156.4, 143.8, 136.5, 135.1, 132.7, 131.2, 129.6, 129.1, 127.3, 127.2, 127.0, 126.7, 122.0, 114.1, 55.5, 53.7, 46.0, 39.7, 26.5, 21.5; HRMS-ESI (*m/z*) $[C_{25}H_{26}N_2O_4S + Na]^+$ calcd 473.1505, found 473.1484.

(*R,S*)-*N*-(pyrazin-2-yl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (327)



General procedure D was followed using aminopyrazine (32 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (33 mg, 0.08 mmol, 28%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 9.48 (s, 1H), 8.33 (d, *J* = 2.5 Hz, 1H), 8.22-8.25 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.08-7.14 (m, 5H), 6.96 (d, *J* = 4.7 Hz, 1H), 5.50 (t, *J* = 6.3 Hz, 1H, C<u>H</u>), 3.80 (dt, *J* = 5.1 and 13.6 Hz, 1H), 3.50-3.60 (m, 1H), 3.04 (dd, *J* = 7.3, 14.9 Hz, 1H), 2.88 (dd, *J* = 5.6 and 15.0 Hz, 1H), 2.66-2.73 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.1, 147.9, 143.7, 142.1, 140.3, 137.2, 136.4, 134.9, 133.0, 129.6, 129.0, 127.4, 127.2, 127.1, 126.8, 53.5, 46.6, 40.1, 27.1, 21.5; HRMS-ESI (*m/z*) $[C_{22}H_{22}N_4O_3S + H]^+$ calcd 423.1485, found 423.1505.

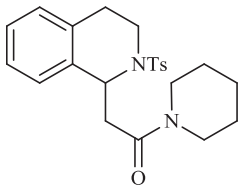
(*R,S*)-*N,N*-diethyl-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamide (329)



General procedure D was followed using diethylamine (25 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (64 mg, 0.16 mmol, 57%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.66 (d, *J* = 8.3 Hz, 2H), 7.05-7.17 (m, 5H), 6.93-6.96 (m, 1H), 5.54 (dd, *J* = 5.1 and 7.4 Hz, 1H, C<u>H</u>), 3.52-3.71 (m, 2H), 3.26-3.42 (m, 2H), 3.06-3.22 (m, 2H), 2.88 (dd, *J* = 5.1 and 14.6 Hz, 1H), 2.67-2.75 (m, 3H), 2.32 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.8,

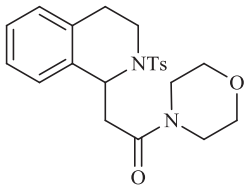
143.1, 136.8, 136.3, 133.0, 129.5, 128.5, 127.3, 127.2, 126.9, 126.4, 53.7, 42.4, 42.1, 40.8, 40.4, 27.7, 21.4, 14.3, 13.0; HRMS-ESI (*m/z*) $[C_{22}H_{28}N_2O_3S + H]^+$ calcd 401.1893, found 401.1878.

(*R,S*)-1-(piperidin-1-yl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone (333)



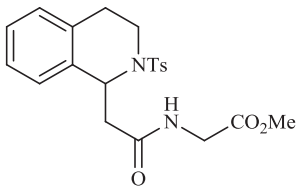
General procedure D was followed using piperidine (29 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (102 mg, 0.25 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.62 (d, *J* = 8.3 Hz, 2H), 7.06-7.18 (m, 5H), 6.93-6.96 (m, 1H), 5.48 (dd, *J* = 5.9 and 6.9 Hz, 1H, C<u>H</u>), 3.23-3.71 (m, 6H), 2.98 (dd, *J* = 7.9 and 16.7 Hz, 1H), 2.67-2.80 (m, 3H), 2.32 (s, 3H), 1.40-1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 167.8, 143.2, 136.8, 136.1, 133.0, 129.5, 128.6, 127.2, 127.1, 127.0, 126.4, 53.6, 47.0, 42.8, 42.4, 40.5, 27.4, 26.3, 25.4, 24.5, 21.4; HRMS-ESI (*m/z*) $[C_{23}H_{28}N_2O_3S + H]^+$ calcd 413.1893, found 413.1914.

(*R,S*)-1-morpholino-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone (334)



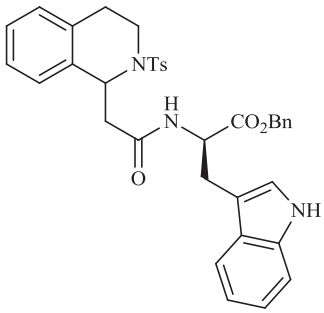
General procedure D was followed using morpoholine (29 mg, 0.34 mmol). The title compound was isolated as a pale yellow oil (91 mg, 0.22 mmol, 78%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.4 Hz, 2H), 7.08-7.18 (m, 5H), 6.94-6.97 (m, 1H), 5.48 (t, *J* = 6.3 Hz, 1H, C<u>H</u>), 3.28-3.68 (m, 8H), 3.00 (dd, *J* = 5.9 and 14.5 Hz, 1H), 2.76 (dd, *J* = 7.3 and 14.5 Hz, 3H), 2.68 (t, *J* = 6.2 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.5, 143.4, 136.7, 135.8, 133.1, 129.7, 128.8, 127.3, 127.2, 127.1, 126.6, 66.8, 66.5, 53.8, 46.4, 42.2, 42.1, 40.7, 27.4, 21.5; HRMS-ESI (*m/z*) $[C_{22}H_{26}N_2O_4S + H]^+$ calcd 415.1686, found 415.1707.

(*R,S*)-methyl 2-(2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamido)acetate (339)



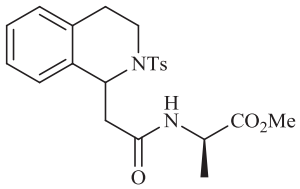
General procedure D was followed using glycine methyl ester hydrochloride (54 mg, 0.34 mmol). The title compound was isolated as an orange oil (84 mg, 0.20 mmol, 72%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.3 Hz, 2H), 7.05-7.14 (m, 5H), 6.90 (d, *J* = 6.0 Hz, 1H), 6.54 (brt, 1H, N<u>H</u>) 5.41 (t, *J* = 6.5 Hz, 1H, C<u>H</u>), 4.02 (t, *J* = 5.0 Hz, 2H), 3.76 (m, 1H), 3.74 (s, 3H, CO_2<u>Me</u>), 3.55 (m, 1H), 2.89 (dd, *J* = 7.4 and 14.9 Hz, 1H), 2.59-2.71 (m, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.3, 169.7, 143.5, 136.7, 135.1, 132.7, 129.5, 128.9, 127.2, 127.1, 126.9, 126.6, 53.6, 52.4, 45.2, 41.4, 39.8, 26.7, 21.5; HRMS-ESI (*m/z*) $[C_{21}H_{24}N_2O_5S + H]^+$ calcd 417.1479, found 417.1496.

(2*R*)-benzyl 3-(1*H*-indol-3-yl)-2-(2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamido) propanoate (340)



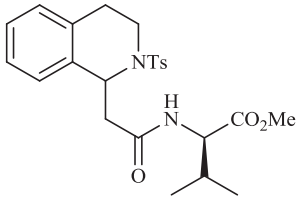
General procedure D was followed using L-tryptophan benzyl ester hydrochloride (99 mg, 0.34 mmol). The title compound was isolated as an orange oil (167 mg, 0.27 mmol, 96%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.23 (brs, 0.5H), 8.14 (brs, 0.5H), 7.60 (dd, *J* = 1.5 and 8.2 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 0.5H), 6.93-7.36 (m, 14H), 6.88 (d, *J* = 2.2 Hz, 0.5H), 6.84 (m, 0.5H), 6.67 (d, *J* = 2.2 Hz, 0.5H), 6.29 (t, *J* = 10.0 Hz, 1H), 5.40 (t, *J* = 6.4 Hz, 1H, C<u>H</u>), 5.05 (d, *J* = 2.5 Hz, 2H), 4.97 (m, 1H), 3.68 (m, 1H), 3.15-3.46 (m, 3H), 2.47-2.81 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.7, 171.6, 169.2, 169.1, 143.4, 136.8, 136.5, 136.1, 136.0, 135.4, 135.34, 135.32, 135.2, 132.9, 132.6, 129.5, 129.4, 128.8, 128.7, 128.56, 128.55, 128.46, 128.41, 128.38, 128.35, 127.6, 127.5, 127.2, 127.0, 126.9, 126.49, 126.48, 123.4, 123.3, 122.0, 119.6, 119.5, 118.5, 111.3, 111.2, 109.6, 109.5, 67.15, 67.11, 53.5, 53.4, 53.1, 53.0, 45.3, 40.0, 39.7, 27.6, 27.5, 27.0, 26.6, 21.4; HRMS-ESI (*m/z*) $[C_{36}H_{35}N_3O_5S - H]^-$ calcd 620.2225, found 620.2197. (Diastereomeric ratio approx. 1:1 by ^{1}H and ^{13}C NMR)

(2*R*)-methyl 2-(2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamido)propanoate (341)



General procedure D was followed using L-alanine methyl ester hydrochloride (47 mg, 0.34 mmol). The title compound was isolated as an orange oil (65 mg, 0.15 mmol, 54%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.61 (d, *J* = 8.3 Hz, 2H), 7.09-7.13 (m, 5H), 6.89 (m, 1H), 6.59 (d, *J* = 7.0 Hz, 0.5H), 6.45 (d, *J* = 7.3 Hz, 0.5H), 5.43 (dt, *J* = 2.4 and 7.0 Hz, 1H, C<u>H</u>), 4.57 (m, 1H), 3.77 (m, 1H), 3.74 (s, 1.5H), 3.72 (s, 1.5H), 3.54 (m, 1H), 2.84 (m, 1H), 2.66 (m, 3H, CO_2<u>Me</u>), 2.31 (s, 3H), 1.41 (d, *J* = 7.3 Hz, 1.5H), 1.39 (d, *J* = 7.3 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 173.4, 173.3, 169.0, 168.9, 143.45, 143.43, 136.8, 136.7, 135.2, 135.1, 132.6, 129.5, 128.9, 128.8, 127.16, 127.14, 127.12 ,127.0, 126.9, 126.8, 126.5, 126.4, 53.6, 53.5, 52.44, 52.40, 48.3, 48.2, 45.1, 39.7, 39.6, 26.6, 26.5, 21.5, 18.2, 18.1; HRMS-ESI (*m/z*) $[C_{22}H_{26}N_2O_5S + H]^+$ calcd 431.1635, found 431.1619. (Diastereomeric ratio approx. 1:1 by ^{1}H and ^{13}C NMR)

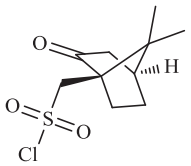
(2*R*)-methyl 3-methyl-2-(2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetamido)butanoate (342)



General procedure D was followed using L-valine methyl ester hydrochloride (56 mg, 0.34 mmol). The title compound was isolated as an orange oil (94 mg, 0.20 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.66 (d, *J* = 5.9 Hz, 2H), 7.04-7.14 (m, 5H), 6.92 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 0.25H), 6.31 (d, *J* = 8.5 Hz, 0.75H), 5.43 (t, *J* = 6.3 Hz, 1H, C<u>H</u>), 4.54 (dd, *J* = 5.0 and 8.6 Hz, 1H), 3.82 (m, 1H), 3.72 (s, 3H), 3.57 (m, 1H), 2.89 (m, 1H), 2.61-2.70 (m, 3H), 2.32 (s, 3H), 2.13 (m, 1H), 0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 127.2, 169.4, 143.4, 136.7, 135.3, 132.7, 129.5, 128.9, 127.2, 127.1, 127.0, 126.9, 126.5, 57.5, 53.6, 53.5, 52.1,

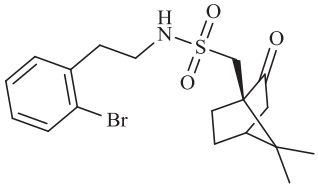
52.0, 45.6, 45.4, 40.0, 39.8, 31.1, 31.0, 26.9, 26.7, 21.5, 18.8, 18.0; HRMS-ESI (*m/z*) $[C_{24}H_{30}N_2O_5S + H]^+$ calcd 459.1948, found 459.1931. HPLC: t_r = 16.99 min [major], t_r = 27.35 min [minor] (Chiralpak AD column, flow rate 1.0 mL/min, n-hexane/*i*PrOH = 80:20, λ = 278 nm, 25 °C) *de* = 40%.

(1*R*)-(-)-10-camphorsulfonyl chloride (347)



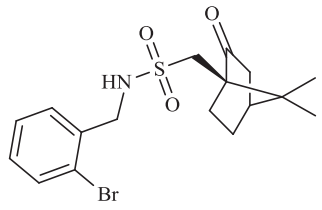
A solution of (1*R*)-(-)-10-camphorsulfonic acid (1.0 g, 4.30 mmol) in $SOCl_2$ (1534 mg, 12.9 mmol) was stirred at room temperature for 1 h., heated at 40 °C for 6 h. then stirred at ambient temperature for 16 h. The reaction mixture was diluted with ether (10 mL), quenched with H_2O over ice then extracted with ether (2 × 5 mL). The combined organic phases were washed with H_2O, and $NaHCO_3$ (sat. aq., 4 × 10 mL), dried over $MgSO_4$ then concentrated to afford the title compound as a clear oil (970 mg, 3.87 mmol, 90%) ^{1}H NMR (270 MHz, $CDCl_3$, δ) 4.31 (d, *J* = 14.6 Hz, 1H, C<u>H</u>), 3.73 (d, *J* = 14.6, 1H, C<u>H</u>), 2.36-2.44 (m, 2H), 2.06-2.16 (m, 2H), 1.95 (d, *J* = 18.6 Hz, 1H), 1.70-1.80 (m, 1H), 1.45-1.51 (m, 1H), 1.11 (s, 3H, C<u>H</u>$_3$), 0.90 (m, 3H, C<u>H</u>$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 212.9, 64.4, 59.8, 48.3, 42.9, 42.4, 27.0, 25.4, 19.8, 19.7; HRMS-ESI (*m/z*) $[C_{10}H_{15}ClO_3S + H]^+$ calcd 251.0503, found 251.0496.

***N*-(2-bromophenethyl)-1-((1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide (348)**



To a solution of 2-bromophenethylamine (262 mg, 1.31 mmol) and triethylamine (331 mg, 3.28 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of (1*R*)-(-)-10-camphorsulfonyl chloride **347** (330 g, 1.31 mmol) in CH_2Cl_2 (5 mL). After stirring at ambient temperature for 2 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a white amorphous solid (433 mg, 1.04 mmol, 80%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.50 (d, *J* = 0.9, 7.9 Hz, 1H, Ar<u>H</u>), 7.12-7.30 (m, 2H, Ar<u>H</u>), 7.04-7.10 (m, 1H, Ar<u>H</u>), 5.23 (brs, 1H, N<u>H</u>SO_2), 3.40 (t, *J* = 6.9 Hz, 2H, CH_2C<u>H</u>$_2$NH), 3.36 (d, *J* = 15.0 Hz, 1H), 3.03 (dt, *J* = 1.5, 6.7 Hz, 2H, C<u>H</u>$_2$$CH_2$NH), 2.88 (d, *J* = 15.0 Hz, 1H), 2.29-2.38 (m, 1H), 1.81-2.21 (m, 5H), 1.41 (m, 1H), 0.98 (s, 3H, C<u>H</u>$_3$), 0.85 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 216.7, 137.5, 133.0, 131.3, 128.5, 127.7, 124.5, 59.1, 49.4, 48.7, 43.2, 42.9, 42.7, 36.9, 27.0, 26.5, 19.9, 19.5; HRMS-ESI (*m/z*) $[C_{18}H_{24}BrNO_3S + H]^+$ calcd 414.0733, found 414.0748.

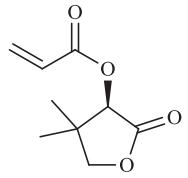
***N*-(2-bromobenzyl)-1-((1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide (350)**



To a solution of 2-bromobenzylamine hydrochloride (291 mg, 1.31 mmol) and triethylamine (331 mg, 3.28 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of (1*R*)-(-)-10-camphorsulfonyl chloride (330 g, 1.31 mmol) in CH_2Cl_2 (5 mL). After stirring at ambient temperature for 2 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$

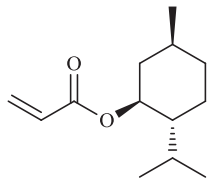
and concentrated under reduced pressure to afford the title compound as a white amorphous solid (436 mg, 1.09 mmol, 83%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.51 (dt, *J* = 1.2 and 7.9 Hz, 2H, ArH), 7.29 (dt, *J* = 1.2 and 7.5 Hz, 1H, ArH), 7.14 (dt, *J* = 1.8 and 7.5 Hz, 1H, ArH), 5.93 (t, *J* = 6.6 Hz, 1H, $NHSO_2$), 4.43 (dd, *J* = 3.1 and 6.6 Hz, 2H, CH_2NH), 3.15 (d, *J* = 15.0 Hz, 1H), 2.83 (d, *J* = 15.6 Hz, 1H), 1.99-2.38 (m, 5H), 1.96 (d, *J* = 18.5 Hz, 1H), 1.39 (m, 1H), 0.92 (s, 3H, CH_3), 0.73 (s, 3H, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 216.7, 136.5, 133.0, 130.8, 129.7, 127.9, 123.9, 59.4, 51.3, 48.8, 47.9, 43.0, 42.8, 27.1, 27.0, 19.9, 19.5; HRMS-ESI (*m/z*) $[C_{17}H_{22}BrNO_3S + H]^+$ calcd 400.0577, found 400.0589.

(*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl acrylate (357)



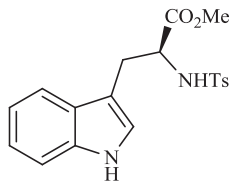
To a cooled solution (0 °C) of (*R*)-(-)-pantolactone (100 mg, 0.77 mmol) in THF (5 mL) was sequentially added acryloyl chloride (70 mg, 0.77 mmol) then triethylamine (117 mg, 1.15 mmol). After stirring at room temperature for 3 h. the reaction mixture was concentrated, re-dissolved in EtOAc (10 mL) then washed with HCl (1M, 10 mL), $NaHCO_3$ (Sat. Aq. 10 mL) and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a white amorphous solid (116 mg, 0.63 mmol, 82%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.52 (dd, *J* = 1.3 and 17.3 Hz, 1H, CH_2=CH), 6.20 (dd, *J* = 10.4 and 17.3 Hz, 1H, CH_2=CH), 5.95 (dd, *J* = 1.3 and 10.4 Hz, 1H, CH_2=CH), 5.40 (s, 1H, CH), 4.03 (s, 2H, CH_2), 1.21 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 172.4, 164.9, 133.0, 127.1, 76.3, 75.2, 40.4, 23.1, 20.0; HRMS-ESI (*m/z*) $[C_9H_{12}O_4 + H]^+$ calcd 185.0808, found 185.0806.

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl acrylate (359)



To a cooled solution (0 °C) of (+)-menthol (100 mg, 0.64 mmol) in THF (5 mL) was sequentially added acryloyl chloride (58 mg, 0.64 mmol) then triethylamine (97 mg, 0.96 mmol). After stirring at room temperature for 3 h. the reaction mixture was concentrated, re-dissolved in EtOAc (10 mL) then washed with HCl (1M, 10 mL), $NaHCO_3$ (Sat. Aq. 10 mL) and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound as a white amorphous solid (104 mg, 0.49 mmol, 77%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.38 (dd, *J* = 1.6 and 17.3 Hz, 1H, CH_2=CH), 6.08 (dd, *J* = 10.3 and 17.3 Hz, 1H, CH_2=CH), 5.75 (dd, *J* = 1.6 and 10.3 Hz, 1H, CH_2=CH), 4.73 (dt, *J* = 4.4 and 10.8 Hz, 1H, CH), 1.99 (m, 1H, CH), 1.84 (m, 1H, CH), 1.66 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 1.01 (m, 2H, CH_2), 0.95 (m, 1H, CH), 0.88 (d, *J* = 6.5 Hz, 3H, CH_3), 0.84 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 165.9, 130.3, 129.1, 74.4, 47.1, 40.9, 34.3, 31.4, 26.4, 23.6, 22.1, 20.8, 16.5; HRMS-ESI (*m/z*) $[C_{13}H_{22}O_2 + H]^+$ calcd 211.1693, found 211.1698.

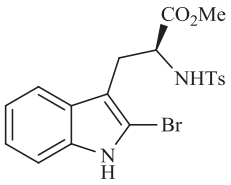
(*S*)-methyl 3-(1*H*-indol-3-yl)-2-(*p*-toluenylsulfonamido)propanoate (463)



To a solution of L-tryptophan methyl ester hydrochloride (400 mg, 1.57 mmol) and triethylamine (477 mg, 4.71 mmol) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonyl chloride (449 mg, 2.36 mmol). After stirring at room temperature for 16 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under

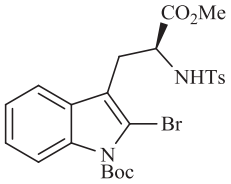
reduced pressure to afford the title compound as a clear oil (514 mg, 1.38 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.39 (brs, 1H, indole-NH), 7.56 (d, *J* = 8.3 Hz, 2H, ArH), 7.41 (d, *J* = 7.9 Hz, 1H, ArH), 7.29 (d, *J* = 8.0 Hz, 1H, ArH), 7.13 (dt, *J* = 1.1 and 7.0 Hz, 1H, ArH), 7.09 (d, *J* = 8.3 Hz, 2H, ArH), 7.00 (m, 1H, ArH), 6.94 (d, *J* = 2.4 Hz, 1H, indole-C2-ArH), 5.49 (d, *J* = 8.7 Hz, 1H, NHTs), 4.23 (m, 1H, CH_2CH), 3.43 (s, 3H, CO_2Me), 3.19 (dd, *J* = 2.8 and 5.3 Hz, 2H, CH_2CH), 2.31 (s, 3H, $TsCH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 172.0, 143.6, 136.4, 136.3, 129.6, 127.2, 127.1, 123.9, 122.0, 119.5, 118.4, 111.6, 108.7, 56.2, 52.6, 29.2, 21.6; HRMS-ESI (*m/z*) $[C_{19}H_{20}N_2O_4S + H]^+$ calcd 373.1217, found 373.1228.

(*S*)-methyl 3-(2-bromo-1*H*-indol-3-yl)-2-(*p*-toluenylsulfonamido)propanoate (464)



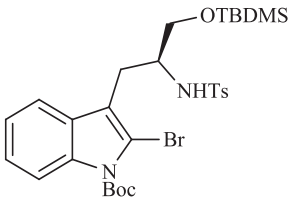
A solution of tosyl-tryptophan **463** (850 mg, 2.28 mmol) in THF:$CHCl_3$ (1:1, 300 mL) was stirred at 0 °C for 15 mins. Pyridinium tribromide (803 mg, 2.51 mmol) was then added portion-wise over 1 h. Saturated aqueous sodium sulphite (10 mL) was added, and following a colour change, saturated aqueous $NaHCO_3$ (10 mL) was also added. The aqueous phase was extracted with $CHCl_3$ (2 × 5 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was subjected to column chromatography (1:3 EtOAc:Pet Spirits) to afford the title compound as a clear colourless oil (710 mg, 1.57 mmol, 69%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.50 (brs, 1H, indole-NH), 7.51 (d, *J* = 8.3 Hz, 2H, ArH), 7.38 (d, *J* = 7.5 Hz, 1H, ArH), 7.15 (m, 1H, ArH), 7.06-7.11 (m, 2H, ArH), 7.05 (d, *J* = 7.9 Hz, 2H, ArH), 5.30 (d, *J* = 9.5 Hz, 1H, NHTs), 4.20 (m, 1H, CH_2CH), 3.49 (s, 3H, CO_2Me), 3.12 (ddd, *J* = 6.1 and 14.5 and 26.9 Hz, 2H, CH_2CH), 2.29 (s, 3H, $TsCH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.9, 143.5, 136.4, 136.1, 129.4, 127.4, 127.0, 122.5, 120.4, 117.9, 110.8, 109.8, 109.0, 55.9, 52.8, 29.3, 21.6; HRMS-ESI (*m/z*) $[C_{19}H_{19}N_2O_4SBr + H]^+$ calcd 451.0322, found 451.0313.

(*S*)-tert-butyl 2-bromo-3-(3-methoxy-2-(*p*-toluenylsulfonamido)-3-oxopropyl)-1*H*-indole-1-carboxylate (371)



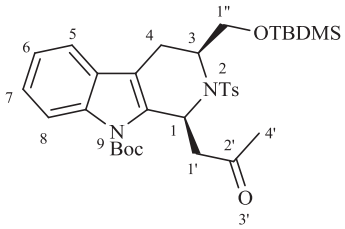
To a solution (359 mg, 1.64 mmol) containing tosyl-2-bromotryptophan **464** (742 mg, 1.64 mmol) and DMAP (10 mg, 0.08 mmol) in CH_2Cl_2 (20 mL) was added di-*tert*-butyl dicarbonate. After stirring for 2 h. at ambient temperature, water (10 mL) was added. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (1:4 EtOAc:Pet Spirits) to afford the title compound as a clear colourless oil (787 mg, 1.43 mmol, 87%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.98 (d, *J* = 7.5 Hz, 1H, ArH), 7.40 (d, *J* = 8.4 Hz, 2H, ArH), 7.33 (m, 1H, ArH), 7.16-7.23 (m, 2H, ArH), 6.95 (d, *J* = 8.4 Hz, 2H, ArH), 5.36 (d, *J* = 9.6 Hz, 1H, NHTs), 4.22 (m, 1H, CH), 3.56 (s, 3H, CO_2Me), 3.06 (ddd, *J* = 6.0 and 14.3 and 22.9 Hz, 2H, CH_2), 2.28 (s, 3H, $TsCH_3$), 1.68 (s, 9H, Boc-*t*Bu); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.8, 148.8, 143.3, 136.4, 129.2, 128.7, 128.3, 126.7, 124.6, 123.2, 117.9, 117.3, 115.3, 110.7, 85.3, 55.2, 52.9, 29.6, 28.3, 21.6; HRMS-ESI (*m/z*) $[C_{24}H_{27}N_2O_6SBr + Na]^+$ calcd 573.0665, found 573.0692.

(*S*)-tert-butyl 2-bromo-3-(3-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-toluenylsulfonamido)propyl)-1*H*-indole-1-carboxylate (373)



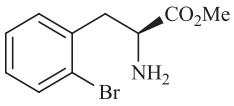
To a cooled solution (0 °C) containing Boc 2-bromotryptophan **371** (787 mg, 1.43mmol) in THF/EtOH (2:3, 20 mL) was added $NaBH_4$ (162 mg, 4.28 mmol). After stirring at room temperature for 16 h. the reaction was quenched by the addition of H_2O (10 mL) and the volatiles removed *in vacuo*. Aqueous NaOH (25% w/w, 1 mL) was added and the reaction mixture extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was then taken up in DMF (10 mL) and imidazole (183 mg, 2.69 mmol) and *tert*-butyldimethylsilyl chloride (194 mg, 1.29 mmol) were added and the resultant mixture stirred at room temperature for 16 h. The crude reaction mixture was concentrated, and following the addition of NH_4Cl (saturated aqueous, 10 mL) extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated and purified by column chromatography (1:9 EtOAc:Pet Sp.) to afford the title compound as a clear oil (590 mg, 0.93 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.95 (d, *J* = 8.5 Hz, 1H, ArH), 7.36 (d, *J* = 8.2 Hz, 2H, ArH), 7.30 (d, *J* = 7.8 Hz, 1H, ArH), 7.22 (m, 1H, ArH), 7.14 (m, 1H, ArH), 6.82 (d, *J* = 8.1 Hz, 2H, ArH), 4.83 (d, *J* = 7.6 Hz, 1H, NHTs), 3.73 (dd, *J* = 2.9 and 9.7 Hz, 1H, CH), 3.59 (dd, *J* = 5.8 and 9.7 Hz, 1H, CH_2-Si), 3.52 (m, 1H, CH_2-Si), 2.94 (dd, *J* = 5.5 and 14.5 Hz, 1H, ArCH_2), 2.79 (dd, J = 9.0 and 14.5 Hz, 1H, ArCH_2), 2.25 (s, 3H, TsCH_3), 1.70 (s, 9H, Boc-*t*Bu), 0.93 (s, 9H, Si-*t*Bu), 0.09 (s, 3H, Si-Me), 0.07 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 148.9, 142.9, 136.7, 136.4, 129.0, 128.5, 126.4, 124.4, 123.0, 119.2, 117.9, 115.3, 109.8, 85.1, 65.4, 54.9, 28.3, 26.0, 21.6, -5.2, -5.4 HRMS-ESI (*m/z*) $[C_{29}H_{41}O_5N_2SSiBr + H]^+$ calcd 637.1762, found 637.1743.

(1*S*,3*S*)-tert-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(2-oxopropyl)-2-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (374)



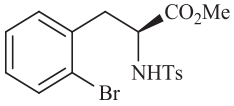
A sealed tube containing 2-bromoindole **373** (100 mg, 0.16 mmol), $Pd(PPh_3)_4$ (18 mg, 0.016 mmol), K_2CO_3 (65 mg, 0.47 mmol) and 3-buten-2-one (13 mg, 0.19 mmol) in toluene (3 mL) was heated at 110 °C for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product purified by column chromatography (1:7 EtOAc:Pet Sp) to afford the title compound as a yellow oil (81 mg, 0.13 mmol, 81%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.95 (d, *J* = 8.2 Hz, 1H, ArH), 7.64 (d, *J* = 8.3 Hz, 2H, ArH), 7.17-7.29 (m, 3H, ArH), 7.04 (d, *J* = 8.1 Hz, 2H, ArH), 6.33 (dd, *J* = 3.2 and 9.5 Hz, 1H, H1), 4.24 (m, 1H, H3), 3.83 (dd, *J* = 4.9 and 9.7 Hz, 1H, H1a"), 3.68 (t, *J* = 9.4 Hz, 1H, H1b"), 2.99 (dd, *J* = 3.9 Hz, 1H, H1a'), 2.59-2.74 (m, 3H, H1b' and H4), 2.40 (s, 3H, COMe), 2.22 (s, 3H, TsCH_3), 1.71 (s, 9H, Boc-*t*Bu), 0.83 (s, 9H, Si-*t*Bu), 0.00 (s, 6H, Si-$(Me)_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 206.1, 150.3, 143.5, 136.7, 135.8, 132.9, 129.5, 128.9, 128.7, 127.3, 127.2, 126.7, 124.6, 122.9, 118.2, 115.7, 113.7, 84.8, 65.8, 53.1, 51.3, 50.0, 29.5, 28.3, 26.0, 21.4, 20.2, 18.3, -5.3; HRMS-ESI (*m/z*) $[C_{33}H_{46}O_6N_2SSi + H]^+$ calcd 627.2919, found 627.2931. HPLC: t_r = 4.98 min [minor], t_r = 5.30 min [major] (Chiralpak AD column, flow rate 1.0 mL/min, n-hexane/*i*PrOH = 90:10, λ = 256 nm, 25 °C); *de* = 60%.

L-2-bromophenylalanine methyl ester (376)



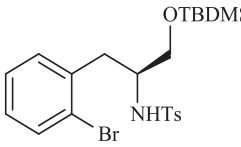
A solution containing L-phenylalanine methyl ester hydrochloride (100 mg, 4.64 mmol) and $Pd(OAc)_2$ (1040 mg, 4.63 mmol) in acetonitrile (60 mL) was stirred at room temperature for 6 days. After this time the reaction mixture was filtered through a plug of $MgSO_4$ and the filtrate concentrated. The residue was then dissolved in CH_2Cl_2 (5 mL) and Et_2O (30 mL) added to precipitate an orange solid which was filtered, washed with Et_2O (2 × 5 mL) and air dried (1255 mg, 1.96 mmol). The solid was taken up in CH_2Cl_2 (50 mL) and Br_2 (627 mg, 3.92 mmol) added and the solution stirred at room temperature for 16 h. After this time the reaction mixture was filtered through a plug of Celite and the filtrate concentrated. The residue was then dissolved in CH_2Cl_2 (20 mL) and following the addition of 1,10-phenanthroline monohydrate (328 mg, 1.65 mmol), the solution was stirred at room temperature for 3 h. The yellow solid was filtered off, and the filtrate was concentrated. Et_2O was added and the resulting suspension filtered through a plug of Celite. The filtrate was concentrated to afford the title compound as a yellow oil (594 mg, 2.30 mmol, 50% yield over 3 steps). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.50 (d, *J* = 8.5 Hz, 1H, ArH), 7.15-7.19 (m, 2H, ArH), 7.01-7.07 (m, 1H, ArH), 3.78 (dd, *J* = 5.7 and 8.6 Hz, 1H, CH), 3.63 (s, 3H, CO_2Me), 3.17 (dd, *J* = 5.6 and 13.6 Hz, 1H, CH_2), 2.85 (dd, *J* = 8.7 and 13.6 Hz, 1H, CH_2), 1.52 (brs, 2H, NH_2); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 175.4, 137.1, 133.1, 131.7, 128.6, 127.5, 124.9, 54.5, 52.1, 41.6; HRMS-ESI (*m/z*) $[C_{10}H_{12}O_2NBr + H]^+$ calcd 258.0124, found 258.0121.

(*S*)-methyl 3-(2-bromophenyl)-2-(*p*-toluenylsulfonamido)propanoate (383)



To a solution of 2-bromo-L-phenylalanine methyl ester **376** (1800 mg, 6.97 mmol) and triethylamine (1058 mg, 10.46 mmol) in CH_2Cl_2 (50 mL) was added *p*-toluenesulfonyl chloride (1462 mg, 7.67 mmol). After stirring at room temperature for 16 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a clear oil (2651 mg, 6.43 mmol, 92%). M.p. 103.1-104.8 ^{o}C ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.92 (d, *J* = 8.4 Hz, 1H, ArH), 7.57 (d, *J* = 8.3 Hz, 2H, ArH), 7.44 (dd, *J* = 1.2 and 7.9 Hz, 1H, ArH), 7.14 (d, *J* = 8.0 Hz, 2H, ArH), 7.08 (m, 1H, ArH), 7.02-7.06 (m, 1H, ArH), 5.21 (d, *J* = 9.8 Hz, 1H, NHTs), 4.24 (m, 1H, CH), 3.49 (s, 3H, CO_2Me), 2.98-3.17 (m, 2H, CH_2), 2.37 (s, 3H, $TsCH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.7, 143.6, 135.0, 133.0, 131.8, 130.3, 129.6, 128.9, 127.6, 127.2, 124.8, 55.5, 52.6, 39.6, 21.6; HRMS-ESI (*m/z*) $[C_{17}H_{18}O_4NSBr + Na]^+$ calcd 434.0032, found 434.0033.

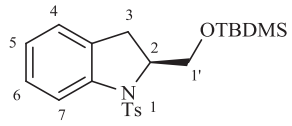
(*S*)-*N*-(1-(2-bromophenyl)-3-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-*p*-toluenesulfonamide (385)



To a cooled solution (0 ^{o}C) containing 2-bromophenylalanine **383** (1131 mg, 2.74 mmol) in THF/EtOH (2:3, 20 mL) was added $NaBH_4$ (311 mg, 8.22 mmol). After stirring at room temperature for 16 h. the reaction was quenched by the addition of H_2O (10 mL) and the volatiles removed *in vacuo*. Aqueous NaOH (25% w/w, 1 mL) was added and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was then taken

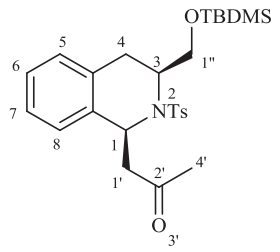
up in DMF (10 mL) and imidazole (560 mg, 8.22 mmol) and *tert*-butyldimethylsilyl chloride (1239 mg, 8.22 mmol) were added and the resultant mixture stirred at room temperature for 16 h. The crude reaction mixture was concentrated, and following the addition of NH_4Cl (saturated aqueous, 10 mL) extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated and purified by column chromatography (1:19 EtOAc:Pet Sp.) to afford the title compound as a clear oil (878 mg, 1.76 mmol, 64%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.54 (dt, *J* = 2.0 and 8.5 Hz, 2H, ArH), 7.37 (dd, *J* = 1.2 and 7.8 Hz, 1H, ArH), 7.12 (m, 2H, ArH), 6.95-7.06 (m, 3H, ArH), 4.85 (d, *J* = 8.3 Hz, 1H, NHTs), 3.59 (m, 1H, CH), 3.50 (m, 2H, CH_2-Si), 2.89 (t, *J* = 7.7 Hz, 2H, ArCH_2CH), 2.36 (s, 3H, TsCH_3), 0.88 (s, 9H, Si-*t*Bu), 0.02 (s, 3H, Si-Me), 0.01 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 143.0, 137.3, 133.0, 131.9, 129.5, 128.6, 128.2, 127.4, 127.0, 124.7, 64.5, 54.9, 38.7, 26.1, 21.5, 18.2, -5.5; HRMS-ESI (*m/z*) $[C_{22}H_{32}O_3NSSiBr + H]^+$ calcd 498.1128, found 498.1146.

(*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-tosylindoline (387)



A sealed tube containing 2-bromophenyl sulfonamide **385** (100 mg, 0.20 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), P(*t*Bu)$_3$.HBF_4 (6 mg, 0.02 mmol), K_2CO_3 (83 mg, 0.6 mmol) and 3-buten-2-one (42 mg, 0.60 mmol) in toluene (3 mL) was heated at 110 ^{o}C for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product purified by column chromatography (1:9 EtOAc:Pet Sp) to afford the title compound as a clear oil (81 mg, 0.19 mmol, 97%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, *J* = 8.1 Hz, 1H, ArH), 7.54 (d, *J* = 8.3 Hz, 2H, ArH), 7.19 (m, 1H, ArH), 7.16 (d, *J* = 8.2 Hz, 2H, ArH), 7.00 (m, 2H, ArH), 4.24 (m, 1H, H2), 3.90 (dd, *J* = 4.2 and 10.0 Hz, 1H, H1a'), 3.62 (dd, *J* = 7.9 Hz, 1H, H1b'), 2.86 (dd, *J* = 2.6 and 16.4 Hz, 1H, H3a), 2.73 (dd, *J* = 9.4 and 16.3 Hz, 1H, H3b), 2.33 (s, 3H, TsCH_3), 0.79 (s, 9H, Si-*t*Bu), 0.05 (s, 3H, Si-Me), 0.00 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 143.9, 141.9, 135.2, 132.3, 129.6, 127.5, 127.1, 125.2, 124.6, 117.0, 65.7, 62.9, 31.1, 25.8, 21.6, 18.2, -5.3, -5.4; HRMS-ESI (*m/z*) $[C_{22}H_{31}O_3NSSi + H]^+$ calcd 418.1867, found 418.1859.

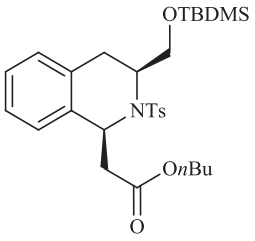
1-((1*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (386)



A sealed tube containing 2-bromophenyl sulfonamide **385** (150 mg, 0.30 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (8 mg, 0.03 mmol), K_2CO_3 (207 mg, 1.5 mmol) and 3-buten-2-one (42 mg, 0.60 mmol) in toluene (3 mL) was heated at 110 ^{o}C for 16 h. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:19 EtOAc:Pet Sp) to afford the title compound as a yellow oil (99 mg, 0.20 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.49 (d, *J* = 8.2 Hz, 2H, ArH), 7.04 (d, *J* = 8.5 Hz, 2H, ArH), 7.01 (m, 1H, ArH), 6.95 (m, 3H, ArH), 5.38 (dd, *J* = 3.6 and 8.5 Hz, 1H, H1), 3.88 (m, 1H, H3), 3.81 (m, 2H, H1"), 3.19 (dd, *J* = 3.8 and 17.6 Hz, 1H, H1a'), 2.90 (d, *J* = 8.4 Hz, 1H, H4a), 2.84 (dd, *J* = 3.2 and 8.6 Hz, 1H, H4b), 2.75 (dd, *J* = 6.4 and 16.1 Hz, 1H, H1b'), 2.27 (s, 3H, TsCH_3), 2.12 (s, 3H, H4'), 0.92 (s, 9H, Si-*t*Bu), 0.098 (s, 3H, Si-Me), 0.096 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 205.4, 143.1, 136.7, 136.1, 132.4, 129.4, 128.2, 127.3, 127.2, 126.9, 126.3, 66.5, 55.0, 53.2, 52.1, 30.4, 29.3, 26.0, 21.5, 18.4, -5.2, -5.3; HRMS-ESI (*m/z*) $[C_{26}H_{37}O_4NSSi +$

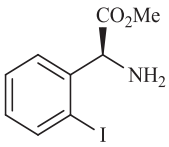
H]$^+$ calcd 488.2285, found 488.2287. HPLC: t_r = 10.42 min [major], t_r = 11.38 min [minor] (Chiralpak AD-H column, flow rate 1.0 mL/min, n-hexane/*i*PrOH = 98:2, λ = 256 nm, 25 °C) *de* = 85%.

butyl 2-((1*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (388)



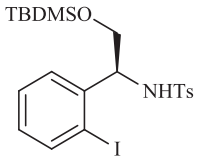
A sealed tube containing 2-bromophenyl sulfonamide **385** (150 mg, 0.30 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (8 mg, 0.03 mmol), K_2CO_3 (207 mg, 1.5 mmol) and butyl acrylate (77 mg, 0.60 mmol) in toluene (3 mL) was heated at 110 ^oC for 16 hrs. The resulting mixture was cooled to room temperature and concentrated. The crude product was purified by column chromatography (1:7 EtOAc:Pet Sp) to afford the title compound as a clear oil (120 mg, 0.22 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.47 (d, *J* = 8.2 Hz, 2H, ArH), 6.91-7.04 (m, 6H, ArH), 5.31 (dd, *J* = 5.4 and 8.8 Hz, 1H, ArC1H), 3.81-4.09 (m, 5H, C3H, CH_2-Si and CO_2*n*Bu), 2.70-2.97 (m, 4H, ArCH_2 and CH_2CO_2*n*Bu), 2.26 (s, 3H, TsCH_3), 1.56 (m, 2H, CO_2*n*Bu), 1.31 (m, 2H, CO_2*n*Bu), 0.91 (s, 9H, Si-*t*Bu), 0.88 (m, 3H, CO_2*n*Bu), 0.09 (s, 6H, Si-$(Me)_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 207.1, 170.7, 143.1, 136.1,, 132.8, 129.3, 128.2, 127.5, 127.3, 126.8, 126.1, 67.2, 64.7, 55.4, 54.2, 43.3, 31.0, 30.6, 29.4, 26.0, 21.4, 19.2, 13.8, -5.3; HRMS-ESI (*m/z*) [$C_{29}H_{43}O_5NSSi$ + H]$^+$ calcd 546.2704, found 546.2698. HPLC: t_r = 8.68 min [major], t_r = 11.68 min [minor] (Chiralpak AD-H column, flow rate 1.0 mL/min, n-hexane/*i*PrOH = 98:2, λ = 256 nm, 25 °C); *de* = 92%.

(*S*)-methyl 2-amino-2-(2-iodophenyl)acetate (391)



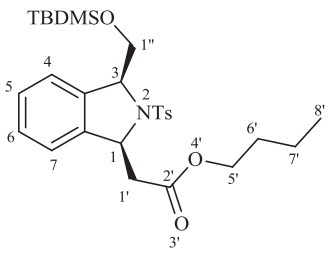
A solution containing (*S*)-(+)-2-phenylglycine methyl ester hydrochloride (1888 mg, 9.36 mmol) and $Pd(OAc)_2$ (2000 mg, 8.91 mmol) in acetone was refluxed for 16 h. After cooling to room temperature the reaction mixture was filtered through a plug of $MgSO_4$ and the filtrate concentrated. The residue was then dissolved in CH_2Cl_2 (5 mL) and Et_2O (30 mL) added to precipitate an orange solid which was filtered, washed with Et_2O (2 × 5 mL) and air dried (2.569 mg, 4.20 mmol). The solid was taken up in CH_2Cl_2 (75 mL) and I_2 (2072 mg, 8.16 mmol) added and the solution stirred at room temperature for 16 h. After this time the reaction mixture was filtered through a plug of Celite and the filtrate concentrated. The residue was then dissolved in CH_2Cl_2 (20 mL) and following the addition of 1,10-phenanthroline monohydrate (607 mg, 3.06 mmol), the solution was stirred at room temperature for 3 h. The yellow solid was filtered off, and the filtrate was concentrated. Et_2O (30 mL) was added and the resulting suspension filtered through a plug of Celite. The filtrate was concentrated to afford the title compound as a yellow oil (813 mg, 2.79 mmol, 30% over 3 steps). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.86 (d, *J* = 7.8 Hz, 1H, ArH), 7.33-7.36 (m, 2H, ArH), 6.97 (m, 1H, ArH), 5.02 (s, 1H, CH_2), 3.73 (s, 3H, CO_2Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 174.2, 140.1, 130.2, 129.8, 129.0, 127.6, 100.0, 62.7, 52.8; HRMS-ESI (*m/z*) [$C_9H_{10}O_2NI$ + H]$^+$ calcd 291.9829, found 291.9826.

(*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-(2-iodophenyl)ethyl)-*p*-toluenesulfonamide (392)



To a solution of 2-iodophenylglycine methyl ester **391** (800 mg, 2.75 mmol) and triethylamine (417 mg, 4.13 mmol) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonyl chloride (629 mg, 3.30 mmol). After stirring at room temperature for 16 h. the reaction mixture was washed with HCl (1M, 2 × 10 mL), NaOH (Aq 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a yellow oil (955 mg, 2.14 mmol, 78%). To a cooled solution (0 ^oC) containing 2-iodophenylglycine (950 mg, 2.13 mmol) in THF/EtOH (2:3, 30 mL) was added $NaBH_4$ (242 mg, 6.39 mmol). After stirring at room temperature for 16 h. the reaction was quenched by the addition of H_2O (10 mL) and the volatiles removed *in vacuo*. Aqueous NaOH (25% w/w, 1 mL) was added and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was then taken up in DMF (10 mL) and imidazole (435 mg, 6.39 mmol) and *tert*-butyldimethylsilyl chloride (963 mg, 6.39 mmol) were added and the resultant mixture stirred at room temperature for 16 h. The crude reaction mixture was concentrated, and following the addition of NH_4Cl (saturated aqueous, 10 mL) extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated and purified by column chromatography (1:9 EtOAc:Pet Sp.) to afford the title compound as a clear oil (132 mg, 0.25 mmol, 12%). ^1H NMR (270 MHz, $CDCl_3$, δ) 7.74 (dd, *J* = 1.24 and 7.9 Hz, 1H, ArH), 7.67 (d, *J* = 8.5 Hz, 2H, ArH), 7.36 (dd, *J* = 1.6 and 7.7 Hz, 1H, ArH), 7.18-7.24 (m, 3H, ArH), 6.90 (dt, *J* = 1.9 and 7.9 Hz, 1H, ArH), 5.37 (d, *J* = 3.9 Hz, 1H, NHTs), 4.52 (dt, *J* = 4.1 and 7.3 Hz, 1H, CH), 3.67 (dd, *J* = 4.1 and 10.5 Hz, 1H, CH_2), 3.37 (dd, *J* = 7.3 and 10.5 Hz, 1H, CH_2), 2.37 (s, 3H, TsCH_3), 0.77 (s, 9H, Si-*t*Bu), -0.12 (s, 3H, Si-Me), -0.15 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 143.5, 139.9, 139.4, 136.3, 129.6, 129.5, 129.3, 128.2, 127.6, 127.1, 98.3, 65.0, 42.1, 25.8, 21.6, -5.50, -5.51; HRMS-ESI (*m/z*) $[C_{21}H_{30}O_3NSSiI + H]^+$ calcd 532.0833, found 532.0847. HPLC: t_r = 5.41 min [major], t_r = 5.81 min [minor] (Chiralpak AD-H column, flow rate 1.0 mL/min, *n*-hexane/*i*PrOH = 98:2, λ = 210 nm, 25 °C); *de* = 86%.

butyl 2-((1*S*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-tosylisoindolin-1-yl)acetate (393)

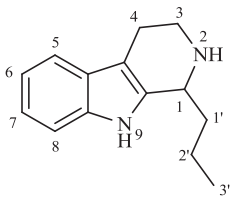


A sealed tube containing 2-iodophenylsulfonamide **392** (60 mg, 0.11 mmol), $Pd(OAc)_2$ (3 mg, 0.006 mmol), PPh_3 (3 mg, 0.006 mmol), triethylamine (33 mg, 0.33 mmol) and butyl acrylate (18 mg, 0.14 mmol) in DMF (2 mL) was heated at 110 ^oC for 16 hrs. The resulting mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product purified by column chromatography (1:19 EtOAc:Pet Sp) to afford the title compound as a clear oil (47 mg, 0.09 mmol, 79%). ^1H NMR (270 MHz, $CDCl_3$, δ) 7.70 (d, *J* = 8.3 Hz, 2H, ArH), 7.11-7.23 (m, 6H, ArH), 5.25 (dd, *J* = 4.1 and 8.9 Hz, 1H, H1), 4.78 (dd, *J* = 3.2 and 6.5 Hz, 1H, H3), 4.14 (m, 3H, H5' and H1a'), 3.77 (dd, *J* = 6.8 and 9.9 Hz, 1H, H1b'), 3.23 (dd, *J* = 4.2 and 16.1 Hz, 1H, H1a"), 2.77 (dd, *J* = 9.0 and 16.1 Hz, 1H, H1b"), 2.33 (s, 3H, TsCH_3), 1.64 (m, 2H, H6'), 1.35 (m, 2H, H7'), 0.92 (t, *J* = 7.3 Hz, 3H, H8'), 0.82 (s, 9H, Si-*t*Bu), 0.02 (s, 3H, Si-Me), -0.01 (s, 3H, Si-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.3, 143.8, 139.8, 138.2, 134.5,

129.9, 128.1, 127.9, 127.5, 123.6, 122.7, 67.7, 66.6, 64.6, 62.1, 44.3, 31.0, 30.7, 25.9, 25.5, 21.6, 19.2, 18.4, 13.8, -5.3, -5.5; HRMS-ESI (*m/z*) $[C_{13}H_{22}O_2 + H]^+$ calcd 211.1693, found 211.1698. HRMS-ESI (*m/z*) $[C_{28}H_{41}O_5NSSi + H]^+$ calcd 532.2547, found 532.2561. HPLC: t_r = 7.98 min [major], t_r = 9.01 min [minor] (Chiralpak AD-H column, flow rate 1.0 mL/min, *n*-hexane/*i*PrOH = 98:2, λ = 256 nm, 25 °C); *de* = 87%.

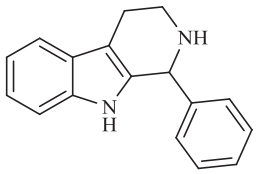
7.2.4 Chapter Five

1-propyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (405)



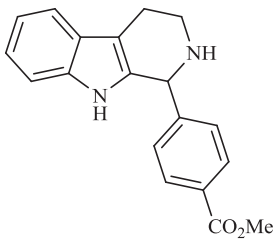
Method A: To a solution of tryptamine (1000 mg, 6.24 mmol) and butyraldehyde (450 mg, 6.24 mmol) in H_2O (22.5 mL) at room temperature was added trifluoroacetic acid (2.5 mL). After stirring for 16 h. at ambient temperature, $NaHCO_3$ (5% aq. w/w, 10 mL) was added to quench the reaction. The reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as an orange amorphous solid (1061 mg, 4.95 mmol, 79%) *Method B:* To a solution of tryptamine (500 mg, 3.12 mmol) and butyraldehyde (247 mg, 3.43 mmol) in CH_2Cl_2 (9 mL) at room temperature was added trifluoroacetic acid (1 mL). After stirring for 16 h. at ambient temperature $NaHCO_3$ (5% aq. w/w, 10 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as an orange amorphous solid (664 mg, 3.10 mmol, 99%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.88 (brs, 1H, indole-NH), 7.48 (dd, *J* = 1.6 and 7.3 Hz, 1H, ArH), 7.27-7.31 (m, 1H, ArH), 7.11 (dqn, *J* = 1.5 and 7.1 Hz, 2H, ArH), 4.06 (m, 1H, H1), 3.35 (dt, *J* = 4.5 and 12.6 Hz, 1H, H3a), 2.97-3.07 (m, 1H, H3b), 2.74 (m, 2H, H4), 1.46-1.87 (m, 6H, H1' and H2'), 0.99 (t, *J* = 7.5 Hz, 3H, H3'); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 136.5, 135.7, 127.7, 121.5, 119.4, 118.1, 110.8, 109.0, 52.6, 42.7, 37.4, 22.9, 19.2, 14.3; HRMS-ESI (*m/z*) $[C_{14}H_{18}N_2 + H]^+$ calcd 215.1543, found 215.1539.

1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (406)



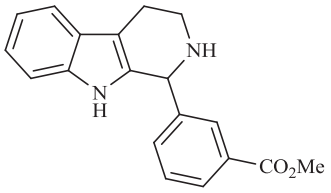
To a solution of tryptamine (100 mg, 0.62 mmol) and benzaldehyde (73 mg, 0.69 mmol) in H_2O (4.5 mL) at room temperature was added trifluoroacetic acid (0.5 mL). After stirring for 16 h. the reaction was quenched by the addition of $NaHCO_3$ (5% Aq, w/w). The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with H_2O (2 × 20 mL) then brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography (1:8, MeOH:EtOAc) to afford the title compound as a pale yellow amorphous solid (137 mg, 0.55 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.67 (brs, 1H), 7.53 (m, 1H), 7.27-7.33 (m, 5H), 7.10-7.17 (m, 3H,), 5.17 (s, 1H, CH), 3.34 (dt, *J* = 4.3 and 12.5 Hz, 1H), 3.07-3.16 (m, 1H), 2.78-2.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 141.5, 136.0, 134.2, 129.0, 128.9, 128.7, 128.6, 128.4, 127.4, 121.9, 119.5, 118.3, 110.9, 110.3, 58.2, 42.9, 22.4; HRMS-ESI (*m/z*) $[C_{17}H_{16}N_2 + H]^+$ calcd 249.1386, found 249.1398.

methyl 4-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzoate (411)



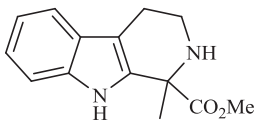
To a solution of tryptamine (500 mg, 3.12 mmol) and methyl-4-formylbenzoate (564 mg, 3.43 mmol) in CH_2Cl_2 (19 mL) at room temperature was added trifluoroacetic acid (1 mL). After stirring for 16 h. at ambient temperature the reaction mixture was concentrated. K_2CO_3 (5% aq. w/w, 30 mL) was added and the crude extracted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:49 MeOH:CH_2Cl_2) afforded the title compound as a pale brown amorphous solid (655 mg, 2.14 mmol, 69%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.00 (d, J = 8.0 Hz, 2H), 7.54 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.08-7.24 (m, 3H), 5.20 (s, 1H, C<u>H</u>), 3.90 (s, 3H, CO_2<u>Me</u>), 3.35 (dt, J = 4.7 and 12.3 Hz, 1H), 3.09-3.19 (m, 1H), 2.78-2.96 (m, 2H), 1.83 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 166.7, 146.9, 135.9, 133.6, 130.1, 130.0, 128.5, 127.3, 121.9, 119.5, 118.3, 110.9, 110.5, 57.8, 52.2, 42.7, 22.5; HRMS-ESI (*m/z*) $[C_{19}H_{18}N_2O_2 + H]^+$ calcd. 307.1441, found 307.1427.

methyl 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzoate (412)



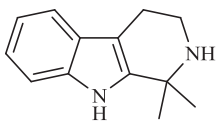
To a solution of tryptamine (500 mg, 3.12 mmol) and methyl-3-formylbenzoate (564 mg, 3.43 mmol) in CH_2Cl_2 (19 mL) at room temperature was added trifluoroacetic acid (1 mL). After stirring for 16 h. at ambient temperature the reaction mixture was concentrated. K_2CO_3 (5% aq. w/w, 30 mL) was added and the crude extracted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:49 MeOH:CH_2Cl_2) afforded the title compound as a pale brown amorphous solid (828 mg, 2.70 mmol, 87%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.95-7.99 (m, 2H), 7.65 (brs, 1H), 7.53 (m, 1H), 7.50 (dt, J = 1.5 and 7.7 Hz, 1H), 7.36-7.42 (m, 1H), 7.10-7.22 (m, 3H), 5.18 (s, 1H, C<u>H</u>), 3.86 (s, 3H, CO_2<u>Me</u>), 3.35 (dt, J = 4.0 and 12.3 Hz, 1H), 3.08-3.18 (m, 1H), 2.78-2.94 (m, 2H), 1.85 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 166.8, 142.4, 136.0, 133.9, 133.1, 130.7, 130.5, 129.4, 128.9, 127.4, 121.8, 119.5, 118.3, 110.9, 110.4, 57.9, 52.2, 42.9, 22.5; HRMS-ESI (*m/z*) $[C_{19}H_{18}N_2O_2 + H]^+$ calcd. 307.1441, found 307.1448.

methyl 1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylate (413)



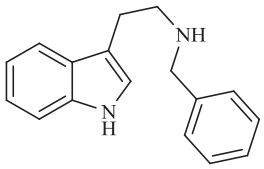
To a solution of tryptamine (200 mg, 1.25 mmol) and methyl pyruvate (153 mg, 1.49 mmol) in methanol (9.5 mL) at room temperature was added trifluoroacetic acid (0.5 mL). After refluxing at 67 ^{o}C for 72 h. the reaction mixture was cooled to room temperature and the volatiles removed. The crude was dissolved in EtOAc (10 mL) and washed with $NaHCO_3$ (sat. aq. 20 mL) and brine. The organic phase was separated, dried over $MgSO_4$ and concentrated to afford the title compound as a pale brown amorphous solid (303 mg, 1.24 mmol, 99%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.35 (brs, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.08-7.21 (m, 2H), 3.78 (s, 3H, CO_2<u>Me</u>), 3.21 (m, 2H), 2.73 (m, 2H), 1.72 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 174.9, 136.3, 133.0, 126.9, 122.3, 119.6, 118.7, 111.2, 110.3, 59.2, 53.0, 41.1, 27.1, 22.3; HRMS-ESI (*m/z*) $[C_{14}H_{16}N_2O_2 + H]^+$ calcd 245.1285, found 245.1293.

1,1-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (415)



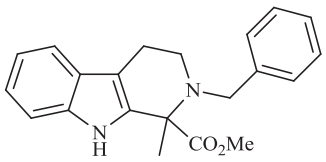
To a solution of tryptamine (500 mg, 3.12 mmol) and acetone (2 mL) in toluene (4.5 mL) at room temperature was added trifluoroacetic acid (0.5 mL). The reaction mixture was heated using microwave irradiation (minimum power) at 60 °C for 20 mins. After this time, the mixture was diluted with K_2CO_3 (5% aq. w/w, 30 mL) was added and the crude extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a pale brown amorphous solid (598 mg, 2.99 mmol, 96%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.85 (brs, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.08-7.19 (m, 1H), 3.55 (brs, 1H), 3.26 (t, *J* = 5.8 Hz, 2H), 2.77 (t, *J* = 5.7 Hz, 2H), 1.52 (s, 6H, C($\underline{CH_3}$)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 136.5, 135.6, 127.3, 121.8, 119.5, 118.3, 110.7, 107.3, 51.0, 39.7, 28.7, 22.5, 14.3; HRMS-ESI (*m/z*) $[C_{13}H_{16}N_2 + H]^+$ calcd. 201.1386, found 201.1379.

N_{10}-benzyltryptamine (178)



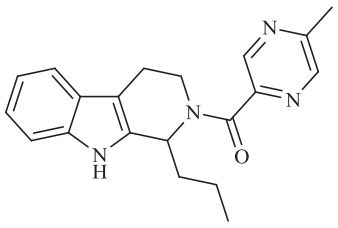
A solution containing tryptamine (300 mg, 1.87 mmol), benzaldehyde (218 mg, 2.06 mmol) and $MgSO_4$ (100 mg) in toluene (10 mL) was stirred at room temperature for 16 h. After this time, the $MgSO_4$ was filtered off and the reaction mixture concentrated *in vacuo*. The crude was taken up in methanol (10 mL) and $NaBH_4$ (71 mg, 1.87 mmol) was added and the resultant mixture stirred at ambient temperature for 90 mins. The reaction was quenched by the addition H_2O. Following removal of the volatiles, the reation mixture was diluted EtOAc and washed with $NaHCO_3$ (sat. aq., 20 mL) and brine. The organic phase was separated, dried over $MgSO_4$ and concentrated to afford the title compound as a pale orange oil (437 mg, 1.75 mmol, 93%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.49 (brs, 1H, indole-N$\underline{H}$), 7.65 (d, *J* = 7.6 Hz, 1H, Ar$\underline{H}$), 7.13-7.40 (m, 8H, Ar$\underline{H}$), 6.94 (s, 1H, Ar$\underline{H}$), 3.86 (s, 2H, C$\underline{H_2}$Ph), 3.05 (s, 4H, C$\underline{H_2}$C$\underline{H_2}$NH), 2.02 (brs, 1H, N$\underline{H}$Bn); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 140.0, 136.7, 128.7, 128.5, 127.6, 127.3, 122.6, 122.1, 119.3, 119.0, 113.4, 111.6, 53.9, 49.4, 25.8; HRMS-ESI (*m/z*) $[C_{17}H_{18}N_2 + H]^+$ calcd. 251.1543, found 251.1555.

methyl 2-benzyl-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylate (416)



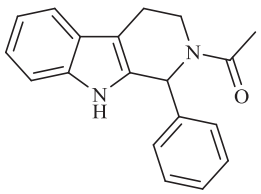
To a solution of *N*-benzyltryptamine **178** (200 mg, 0.80 mmol) and methyl pyruvate (98 mg, 0.96 mmol) in methanol (9.5 mL) at room temperature was added trifluoroacetic acid (0.5 mL). After refluxing for 4 h. the reaction mixture was concentrated. The crude was then dissolved in ethyl acetate (10 mL) and washed with $NaHCO_3$ (sat aq. 10 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:1 EtOAc:Pet. Sp.) afforded the title compound as an orange amorphous solid (90 mg, 0.27 mmol, 34%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.13 (brs, 1H), 7.52 (d, *J* = 7.8 Hz, 4H), 7.11-7.39 (m, 5H), 3.92 (q, *J* = 14.8 Hz, 2H, C$\underline{H_2}$Ph), 3.78 (s, 3H, $CO_2\underline{Me}$), 3.18 (m, 1H), 2.90 (m, 1H), 2.74 (m, 2H), 1.83 (s, 3H, C$\underline{H_3}$); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 174.7, 140.7, 136.4, 133.8, 128.4, 128.2, 127.0, 122.2, 119.6, 118.7, 111.1, 110.2, 63.8, 55.1, 52.4, 44.9, 23.2, 21.8; HRMS-ESI (*m/z*) $[C_{21}H_{22}N_2O_2 + H]^+$ calcd. 335.1754, found 335.1745.

(5-methylpyrazin-2-yl)(1-propyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)methanone (419)



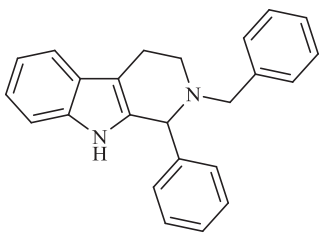
A solution containing propyl tetrahydro-*β*-carboline **405** (400 mg, 1.87 mmol), 5-methyl-2-pyrazine carboxylic acid (387 mg, 2.81 mmol), HOBt (63 mg, 0.47 mmol), EDCI (537 mg, 2.80 mmol) in CH_2Cl_2 (10 mL) was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with H_2O (20 mL) then brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography to afford the title compound as a pale yellow amorphous solid (215 mg, 0.64 mmol, 34%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.84 (s, 1H, ArH), 8.45 (s, 1H, ArH), 8.13 (brs, 1H, indole-NH), 7.45 (d, *J* = 7.3 Hz, 1H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.05-7.17 (m, 2H, ArH), 5.89 (t, *J* = 7.0 Hz, 1H, CH), 4.15 (m, 1H), 3.54 (ddd, *J* = 4.1 and 11.7 and 13.7 Hz, 1H), 2.98 (ddd, *J* = 4.9 and 13.1 and 15.9 Hz, 1H), 2.72 (dd, *J* = 3.2 and 15.0 Hz, 1H), 2.63 (s, 3H, CH_3), 1.95 (m, 2H), 1.60 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 166.5, 154.9, 147.1, 145.1, 144.2, 142.6, 136.1, 133.9, 122.1, 119.8, 118.2, 111.0, 107.9, 50.0, 41.8, 37.1, 22.5, 21.8, 19.8, 14.3; HRMS-ESI (*m/z*) $[C_{20}H_{22}N_4O + H]^+$ calcd 335.1866, found 335.1880.

1-(1-phenyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)ethanone (417)



To a solution of phenyl tetrahydro-*β*-carboline **406** (100 mg, 0.40 mmol), triethylamine (49 mg, 0.48 mmol), and DMAP (25 mg, 0.20 mmol) in DMF (5 mL) was added acetyl chloride (38 mg, 0.48 mmol). After stirring at ambient temperature for 5 h. the reaction mixture was concentrated. The crude product was purified by column chromatography (1:8 MeOH:EtOAc) to afford the title compound as a white amorphous solid (118 mg, 0.40, 100%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.94 (brs, 1H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.28 (m, 5H), 7.13 (quin, *J* = 7.0 Hz, 2H), 7.00 (s, 1H, CH), 3.85 (m, 1H), 3.43 (m, 1H), 2.91 (m, 2H), 2.18 (s, 3H, COMe); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 169.1, 140.0, 136.4, 131.8, 128.9, 128.6, 128.2, 126.8, 122.3, 119.7, 118.2, 111.2, 109.9, 51.7, 40.7, 22.2, 21.9; HRMS-ESI (*m/z*) $[C_{19}H_{18}N_2O + Na]^+$ calcd 313.1311, found 313.1313.

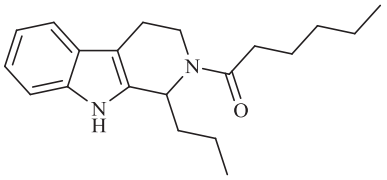
2-benzyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (418)



To a solution of phenyl tetrahydro-*β*-carboline **406** (400 mg, 1.61 mmol) in CH_2Cl_2 (10 mL) was added benzyl bromide (334 mg, 1.93 mmol). The resultant mixture was stirred at ambient temperature after which time the solvent was removed and the crude purified by column chromatography (1:3 EtOAc:Pet Sp) to afford the title compound as a pale yellow solid (376 mg, 1.11 mmol, 69%). M.p. 150.1-151.7 ^{o}C ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.52 (m, 1H), 7.46 (m, 2H), 7.25-7.40 (m, 8H), 7.16 (m, 1H), 7.10 (m, 2H), 4.65 (s, 1H, CH), 3.90 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.40 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.24 (dt, *J* = 5.0 and 11.7 Hz, 1H), 2.91 (m, 1H), 2.87 (m, 1H), 2.66 (ddd, *J* = 4.2 and 9.6 and 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 141.5, 139.6, 136.4, 135.0, 129.1,

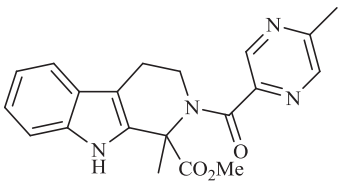
128.8, 128.7, 128.3, 128.2, 127.3, 127.0, 121.6, 119.4, 118.4, 110.9, 109.0, 64.7, 58.4, 48.5, 21.3; HRMS-ESI (*m/z*) $[C_{24}H_{22}N_2 + H]^+$ calcd 339.1856, found 339.1859.

1-(1-propyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)hexan-1-one (420)



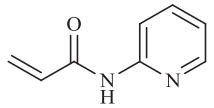
To a solution of phenyl tetrahydro-*β*-carboline **405** (300 mg, 1.40 mmol), triethylamine (170 mg, 1.68 mmol), and DMAP (86 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) was added hexanoyl chloride (226 mg, 1.68 mmol). After stirring at ambient temperature for 16 h. the reaction mixture was concentrated. The crude product was purified by column chromatography (1:3 EtOAc:Pet. Sp.) to afford the title compound as a brown oil (262 mg, 0.84 mmol, 60%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.48 (brs, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.09 (quin, *J* = 7.9 Hz, 2H), 5.81 (dd, *J* = 6.0 and 8.1 Hz, 1H, C<u>H</u>), 4.07 (d, *J* = 15.4 Hz, 2H), 3.47 (m, 1H), 2.79 (m, 2H), 2.45 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.63 (m, 4H), 1.37 (m, 6H), 0.91 (6H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 172.4, 136.1, 135.1, 126.8, 121.7, 119.5, 117.9, 111.0, 107.4, 49.0, 40.3, 36.9, 33.9, 31.8, 25.3, 22.6, 22.4, 19.7, 14.3, 14.1; HRMS-ESI (*m/z*) $[C_{20}H_{28}N_2O + H]^+$ calcd 313.2274, found 313.2268.

methyl 1-methyl-2-(5-methylpyrazine-2-carbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylate (421)



A solution containing tetrahydro-*β*-carboline methyl ester **413** (300 mg, 1.23 mmol), 5-methyl-2-pyrazine carboxylic acid (187 ng, 1.35 mmol), EDCI (283 mg, 1.48 mmol) and HOBt (50 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was stirred at ambient temperature for 16 h. After this time the reaction mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (sat. aq. 2 × 30 mL) and brine (30 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography (1:1 EtOAc:Pet. Sp.) to afford the title compound as a clear oil (197 mg, 0.54 mmol, 44%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 9.15 (brs, 1H), 8.88 (s, 1H), 8.51 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 6.3, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 4.32 (m, 1H), 3.65 (s, 3H, CO_2<u>Me</u>), 3.50 (m, 1H), 3.11 (m, 1H), 2.88 (dt, *J* = 2.9 and 15.0 Hz, 1H), 2.65 (s, 3H, ArC<u>H</u>$_3$), 2.08 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 172.2, 167.1, 155.5, 146.6, 144.6, 142.8, 136.3, 132.1, 126.4, 122.8, 120.0, 118.6, 111.5, 109.5, 62.2, 53.2, 44.6, 21.8, 21.6, 14.1; HRMS-ESI (*m/z*) $[C_{20}H_{20}N_4O_3 + H]^+$ calcd 387.1428, found 387.1435.

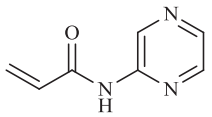
***N*-(pyridin-2-yl)acrylamide (423)**



To a cooled solution of 2-aminopyridine (1000 mg, 10.6 mmol) and triethylamine (1162 mg, 11.5 mmol) in CH_2Cl_2 (10 mL) was added acryloyl chloride (1058 mg, 11.7 mmol). After stirring at room temperature for 4 h. the reaction was quenched by the addition of H_2O. The organic layer was separate, washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound as an orange amorphous solid (1078 mg, 7.25 mmol, 68%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 9.13 (brs, 1H, N<u>H</u>), 8.32 (dt, *J* = 0.8 and 8.4 Hz, 1H, Ar<u>H</u>), 8.26 (ddd, *J* = 0.9 and 1.9 and 5.0 Hz, 1H, Ar<u>H</u>), 7.71 (ddd, *J* = 1.9 and 7.4 and 9.3 Hz, 1H, Ar<u>H</u>), 7.04 (ddd, *J* = 1.0 and 4.9 and 7.3 Hz, 1H, Ar<u>H</u>), 6.49 (dd, *J* = 1.5 and 16.9 Hz, 1H, C<u>H</u>$_2$=CH), 6.29 (dd, *J*

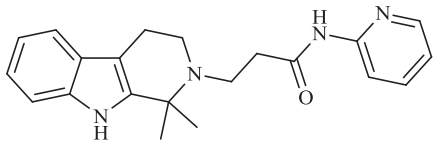
= 10.0 and 16.9 Hz, 1H, CH_2=C<u>H</u>), 5.75 (dd, *J* = 1.5 and 10.0 Hz, 1H, C<u>H_2</u>=CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 164.2, 152.0, 147.6, 138.7, 131.0, 128.6, 120.0, 115.1; HRMS-ESI (*m/z*) $[C_8H_8N_2O + H]^+$ calcd 149.0709, found 149.0702.

_N_-(pyrazin-2-yl)acrylamide (424)



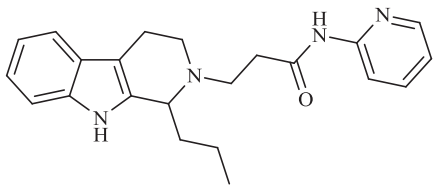
To a cooled solution of aminopyrazine (920 mg, 9.7 mmol) and triethylamine (1174 mg, 11.6 mmol) in CH_2Cl_2 (10 ml) was added acryloyl chloride (963 mg, 10.6 mmol). After stirring at room temperature for 4 h. the reaction was quenched by the addition of H_2O. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound as an orange amorphous solid (1360 mg, 9.1 mmol, 94%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 9.62 (s, 1H, N<u>H</u>), 8.36 (d, *J* = 2.6 Hz, 1H, Ar<u>H</u>), 8.24 (dd, *J* = 1.5 and 2.6 Hz, 1H, Ar<u>H</u>), 7.99 (brs, 1H, Ar<u>H</u>), 6.50 (dd, *J* = 1.1 and 11.2 Hz, 1H, C<u>H_2</u>=CH), 6.30 (dd, *J* = 10.2 and 16.9 Hz, 1H, CH_2=C<u>H</u>), 5.87 (dd, *J* = 1.1 and 10.2 Hz, 1H, C<u>H_2</u>=CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 167.7, 163.7, 142.1, 140.5, 137.3, 130.2, 129.7; HRMS-ESI (*m/z*) $[C_7H_7N_3O + H]^+$ calcd 150.0662, found 150.0669.

3-(1,1-dimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)-*N*-(pyridin-2-yl)propanamide (427)



A solution containing dimethyl tetrahydro-*β*-carboline **415** (470 mg, 2.35 mmol), and *N*-(pyridin-2-yl)acrylamide **423** (384 mg, 2.59 mmol) in methanol/THF (1:1, 10 mL) was heated to 60 ^{o}C for 16 h. After this time the reaction mixture was concentrated. Purification by column chromatography (1:1 EtOAc:Pet. Sp. to 1:9 MeOH:EtOAc) afforded the title compound as a pale orange oil (146 mg, 0.42 mmol, 18%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 10.69 (brs, 1H, amide-N<u>H</u>), 8.12 (m, 2H), 7.72 (brs, 1H, indole-N<u>H</u>), 7.61 (dt, *J* = 1.5 and 7.4 Hz, 1H), 7.47 (m, 1H), 7.34 (m, 1H), 7.07-7.19 (m, 2H), 6.88-6.93 (m, 1H), 3.03 (t, *J* = 5.7 Hz, 2H), 2.98 (t, *J* = 5.6 Hz, 2H), 2.84 (t, *J* = 5.6 Hz, 2H), 2.63 (t, *J* = 5.5 Hz, 2H), 1.50 (s, 6H, C<u>$(CH_3)_2$</u>); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.3, 151.7, 148.1, 139.7, 137.8, 136.0, 127.1, 121.5, 119.4, 119.2, 118.3, 114.0, 110.7, 107.6, 55.9, 44.3, 43.1, 34.7, 31.0, 24.1, 21.4; HRMS-ESI (*m/z*) $[C_{21}H_{24}N_4O + H]^+$ calcd. 349.2023, found 349.2035.

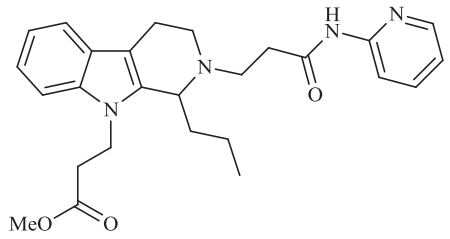
3-(1-propyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)-*N*-(pyridin-2-yl)propanamide (428)



A solution containing propyl tetrahydro-*β*-carboline **405** (200 mg, 0.93 mmol), and *N*-(pyridin-2-yl)acrylamide (153 mg, 1.0 mmol) in methanol/THF (1:1, 10 mL) was heated to 60 ^{o}C for 48 h. After this time the reaction mixture was concentrated. Purification by column chromatography (1:2 EtOAc:Pet. Sp.) afforded the title compound as a pale orange oil (148 mg, 0.41 mmol, 44%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 10.91 (brs, 1H, amide-N<u>H</u>), 8.27 (ddd, *J* = 0.9 and 1.9 and 4.9 Hz, 1H), 8.22 (m, 1H), 7.96 (brs, 1H, indole-N<u>H</u>), 7.66 (dt, *J* = 1.9 and 7.6 Hz, 1H), 7.50 (m, 1H), 7.29 (m, 1H), 7.06-7.18 (m, 2H), 6.98 (ddd, *J* = 1.0, 4.9, 7.3 Hz, 1H), 3.74 (dd, *J* = 4.7 and 7.7 Hz, 1H, C<u>H</u>), 3.41 (m, 1H), 3.13 (m, 1H), 2.88-2.99 (m, 3H), 2.50-2.60 (m, 3H), 1.94 (m, 1H), 1.74 (m, 2H), 1.53 (m, 1H), 0.93

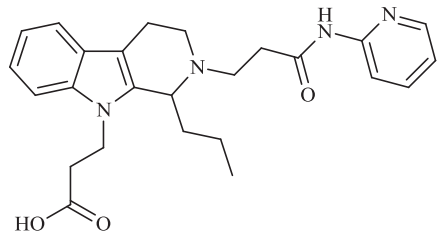
(t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.7, 152.0, 148.2, 138.1, 135.9, 134.6, 127.2, 121.7, 119.5, 119.4, 118.2, 114.4, 110.9, 107.2, 57.2, 48.7, 43.8, 37.4, 34.4, 20.3, 17.2, 14.3; HRMS-ESI (*m/z*) $[C_{22}H_{26}N_4O - H]^-$ calcd. 361.2034, found 361.2044.

methyl 3-(2-(3-oxo-3-(pyridin-2-ylamino)propyl)-1-propyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-9(2*H*)-yl)propanoate (429)



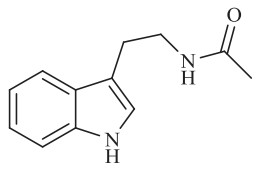
A solution containing propyl TH*β*C pyridine **428** (717 mg, 2.0 mmol), methyl acrylate (342 mg, 4.0 mmol) and K_2CO_3 (821 mg, 5.9 mmol) in DMF (5 mL) was heated to 100 °C for 16 h. After cooling to room temperature, the crude mixture was concentrated and purification by column chromatography (2:3 EtOAc:Pet Sp.) afforded the title compound as an orange oil (410 mg, 0.91 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.83 (brs, 1H, amide-NH), 8.30 (m, 1H), 8.20 (dt, *J* = 0.9 and 8.4 Hz, 1H), 7.70 (dt, *J* = 1.9 and 7.6 Hz, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.22 (dt, *J* = 1.3 and 7.0 Hz, 1H), 7.11 (dt, *J* = 1.2 and 7.7 Hz, 1H), 6.99 (ddd, *J* = 1.0, 4.9, 7.3 Hz, 1H), 4.35 (t, *J* = 7.0 Hz, 2H), 4.07 (d, *J* = 8.1 Hz, 1H, CH), 3.63 (s, 3H, CO_2Me), 3.48 (m, 1H), 3.16 (dd, *J* = 5.7 and 14.2 Hz, 1H), 2.84-3.00 (m, 3H), 2.63-2.74 (m, 3H), 2.44-2.52 (m, 1H), 1.83-1.96 (m, 2H), 1.60-1.71 (m, 4H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.1, 171.6, 152.0, 148.0, 137.9, 135.8, 135.7, 127.4, 121.4, 119.4, 119.3, 118.3, 114.2, 109.0, 106.2, 54.8, 52.0, 48.5, 42.7, 38.8, 37.2, 34.4, 33.9, 20.4, 16.7, 14.0; HRMS-ESI (*m/z*) $[C_{26}H_{32}N_4O_3 + H]^+$ calcd. 449.2547, found 449.2568.

3-(2-(3-oxo-3-(pyridin-2-ylamino)propyl)-1-propyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-9(2*H*)-yl)propanoic acid (430)



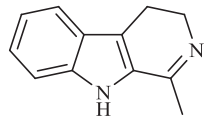
A solution containing propyl TH*β*C methyl ester **429** (300 mg, 0.45 mmol) and LiOH (1M, 9 mL) in THF (11 mL) was stirred at room temperature for 30 mins. After this time the volatiles were removed and NaOH (1M, 5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL). The aqueous phase was acidified to pH 5 using HCl (1M) then extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a beige solid (131 mg, 0.30 mmol, 68%). M.p. 147.1-149.4 °C ^{1}H NMR (300 MHz, $CDCl_3$, δ) 12.96 (brs, 1H, CO_2H), 11.23 (brs, 1H, amide-NH), 8.26 (d, *J* = 8.5 Hz, 1H), 7.92 (ddd, *J* = 0.8 and 1.8 and 5.2 Hz, 1H), 7.71 (dt, *J* = 1.8 and 7.4 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.18 (dt, *J* = 1.3 and 6.9 Hz, 1H), 7.08 (dt, *J* = 1.2 and 7.8 Hz, 1H), 6.96 (ddd, *J* = 1.0 and 5.2 and 7.3 Hz, 1H), 4.67 (dd, *J* = 2.3 and 9.9 Hz, 1H, CH), 4.50 (ddd, *J* = 2.2 and 12.3 and 14.6 Hz, 1H), 4.28 (dt, *J* = 3.2 and 14.9 Hz, 1H), 3.40 (ddd, *J* = 5.4 and 12.0 and 14.0 Hz, 1H), 3.22 (ddd, *J* = 2.8 and 12.2 and 17.7 Hz, 1H), 2.51-3.16 (m, 8H), 2.04 (s, 1H), 1.52-1.83 (m, 4H), 1.04 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 171.3, 152.0, 145.0, 140.3, 137.3, 135.3, 127.8, 121.2, 119.3, 119.2, 118.5, 115.0, 109.2, 105.5, 52.7, 50.7, 45.2, 38.7, 38.4, 37.1, 33.3, 20.4, 17.3, 14.3; HRMS-ESI (*m/z*) $[C_{25}H_{30}N_4O_3 - H]^-$ calcd. 433.2245, found 433.2239.

_N_-(2-(1_H_-indol-3-yl)ethyl)acetamide (431)



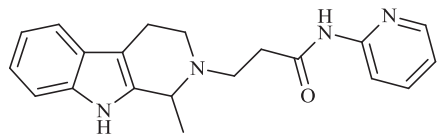
Acetic anhydride (701 mg, 6.24 mmol) was added to a solution of tryptamine (1000 mg, 6.24 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 1 h. saturated aqueous $NaHCO_3$ (20 mL) was added and stirring continued for 30 mins. The aqueous phase was then extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as an orange amorphous solid (1227 mg, 6.06 mmol, 97%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 8.37 (brs, 1H, indole-NH), 7.56-7.60 (m, 1H, ArH), 7.36 (ddd, *J* = 0.8 and 1.2 and 8.0 Hz, 1H, ArH), 7.19 (dt, *J* = 1.2 and 7.0 Hz, 1H, ArH), 7.08-7.14 (m, 1H, ArH), 7.00 (d, *J* = 2.4 Hz, 1H, ArH), 5.62 (brs, 1H, NHAc), 3.59 (q, *J* = 6.7 Hz, 2H, CH_2CH_2NH), 2.95 (dt, *J* = 0.7 and 6.7 Hz, 2H, CH_2CH_2NH), 1.90 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.3, 136.4, 127.3, 122.1, 122.0, 119.4, 118.7, 112.8, 111.4, 39.9, 25.3, 23.4; HRMS-ESI (*m/z*) $[C_{12}H_{14}N_2O + H]^+$ calcd. 203.1179, found 203.1170.

1-methyl-4,9-dihydro-3_H_-pyrido[3,4-_b_]indole (432)



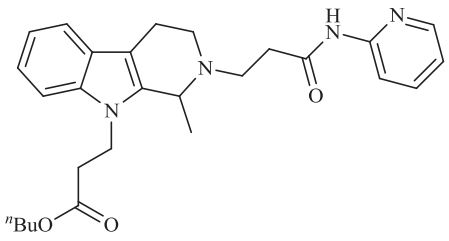
A solution of N_{10}-acetyltryptamine **431** (4894 mg, 24.2 mmol) and $POCl_3$ (4081 mg, 26.6 mmol) in acetonitrile (50 mL) was refluxed at 80 °C for 48 h. After this time, the reaction was quenched by the addition of H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a brown oil (4078 mg, 22.1 mmol, 91%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 9.86 (brs, 1H, indole-NH), 7.57 (dt, *J* = 1.0 and 7.9 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.27 (m, 1H), 7.12 (ddd, *J* = 1.0 and 7.0 and 8.0 Hz, 1H), 3.81 (dt, *J* = 1.3 and 7.6 Hz, 2H), 2.87 (t, *J* = 8.7 Hz, 2H), 2.44 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 195.0, 142.0, 129.4, 126.1, 124.2, 123.9, 121.8, 120.9, 114.1, 42.7, 19.8, 19.2; HRMS-ESI (*m/z*) $[C_{12}H_{12}N_2 + H]^+$ calcd. 185.1073, found 185.1073.

3-(1-methyl-3,4-dihydro-1_H_-pyrido[3,4-_b_]indol-2(9_H_)-yl)-_N_-(pyridin-2-yl)propanamide (434)



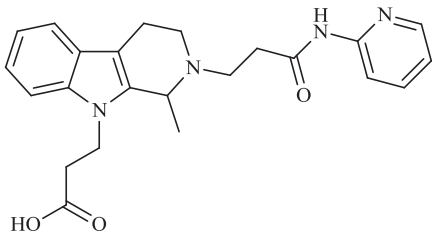
A solution containing methyl tetrahydro-*β*-carboline **433** (610 mg, 3.28 mmol), and *N*-(pyridin-2-yl)acrylamide **423** (273 mg, 6.56 mmol) in methanol/THF (1:1, 20 mL) was heated to 60 °C for 24 h. After this time the reaction mixture was concentrated. Purification by column chromatography (1:2 EtOAc:Pet. Sp.) afforded the title compound as a pale orange oil (615 mg, 1.84 mmol, 56%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 10.95 (brs, 1H, amide-NH), 8.22 (ddd, *J* = 0.9, 1.9 and 4.9 Hz, 1H), 8.17 (dt, *J* = 0.9 and 8.4 Hz, 1H), 7.91 (brs, 1H, indole-NH), 7.64 (ddd, *J* = 1.9 and 7.4 and 8.4 Hz, 1H), 7.47 (m, 1H), 7.32 (m, 1H), 7.12 (dt, *J* = 1.4 and 7.1 and 15.9 Hz, 2H), 6.95 (ddd, *J* = 1.0 and 4.9 and 7.3 Hz, 1H), 3.98 (q, *J* = 6.7 Hz, 1H, CH), 3.33 (m, 1H), 2.87-3.06 (m, 4H), 2.56-2.70 (m, 3H), 1.56 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.3, 151.9, 148.1, 137.9, 136.0, 135.2, 127.0, 121.7, 119.5, 119.3, 118.2, 114.2, 110.8, 107.5, 53.2, 48.7, 44.4, 34.0, 19.7, 18.6; HRMS-ESI (*m/z*) $[C_{20}H_{22}N_4O + H]^+$ calcd. 335.1866, found 335.1872.

butyl 3-(1-methyl-2-(3-oxo-3-(pyridin-2-ylamino)propyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-9(2*H*)-yl)propanoate (435)



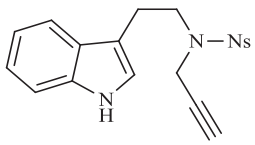
A solution containing methyl THβC pyridine **434** (1253 mg, 3.75 mmol), butyl acrylate (1441 mg, 11.24 mmol) and K_2CO_3 (1553 mg, 11.24 mmol) in DMF (10 mL) was heated to 100 ^oC for 16 h. After cooling to room temperature, the crude mixture was concentrated and purification by column chromatography (3:1 EtOAc:Pet Sp.) afforded the title compound as an pale orange oil (1137 mg, 2.46 mmol, 66%). ^1H NMR (400 MHz, $CDCl_3$, δ) 11.18 (brs, 1H, amide-NH), 8.24 (ddd, *J* = 0.6 and 1.3 and 3.3 Hz, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 7.65 (dt, *J* = 1.3 and 4.6 Hz, 1H), 7.50 (d, *J* = 5.2 Hz, 1H), 7.30 (d, *J* = 5.5 Hz, 1H), 7.19 (dt, *J* = 0.8 and 4.7 Hz, 1H), 7.11 (dt, *J* = 0.5 and 5.2 Hz, 1H), 6.98 (ddd, *J* = 0.6 and 3.3 and 4.9 Hz, 1H), 4.34 (t, *J* = 7.6 Hz, 2H), 4.27 (q, *J* = 6.5 Hz, 1H, CH), 4.01 (m, 2H), 3.41 (ddd, *J* = 5.0 and 12.1 and 13.8 Hz, 1H), 3.17 (dd, *J* = 5.6 and 13.8 Hz, 1H), 3.02 (m, 1H), 2.87-2.94 (m, 3H), 2.62 (m, 3H), 2.55 (m, 1H), 1.62 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.51 (m, 2H), 1.26 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 171.7, 171.4, 152.2, 148.2, 138.0, 136.6, 136.0, 127.5, 121.6, 119.5, 119.3, 118.5, 114.4, 109.2, 106.4, 64.9, 51.2, 48.8, 41.8, 38.9, 34.3, 34.0, 30.6, 20.3, 19.1, 17.5, 13.8; HRMS-ESI (*m/z*) $[C_{27}H_{34}N_4O_3 + H]^+$ calcd. 463.2704, found 463.2705.

3-(1-methyl-2-(3-oxo-3-(pyridin-2-ylamino)propyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-9(2H)-yl)propanoic acid (436)



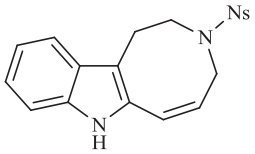
A solution containing butyl ester tetrahydro-β-carboline **435** (200 mg, 0.43 mmol) and LiOH (1M, 1.08 mL) in THF/H_2O (1:1, 10 mL) was stirred at room temperature for 2 h. After this time the volatiles were removed and the reaction mixture diluted with H_2O (10 mL). Following extraction with CH_2Cl_2 (3 × 5 mL) the aqueous phase was acidified to pH 5 using HCl (1M). The reaction mixture was then extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow solid (125 mg, 0.31 mmol, 71%). M.p. 202.1-203.9 ^oC ^1H NMR (270 MHz, $CDCl_3$, δ) 11.21 (s, 1H, amide-NH), 8.25 (d, *J* = 8.5 Hz, 1H), 7.95 (dd, *J* = 1.8 and 5.2 Hz, 1H), 7.73 (dt, *J* = 1.9 and 7.4 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.18 (dt, *J* = 1.0 and 7.1 Hz, 1H), 7.08 (dt, *J* = 0.7 and 7.8 Hz, 1H), 6.99 (ddd, *J* = 0.7 and 5.1 and 7.0 Hz, 1H), 4.96 (brs, 1H, CO_2H), 4.48 (ddd, *J* = 2.0 and 12.5 and 14.8 Hz, 1H), 4.30 (dt, *J* = 3.1 and 14.9 Hz, 1H, CH), 3.43 (m, 1H), 3.23 (m, 1H), 3.08 (m, 1H), 2.63-2.91 (m, 8H), 1.50 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 177.5, 171.0, 151.8, 145.0, 140.3, 135.4, 127.7, 121.3, 119.4, 118.5, 115.1, 109.2, 105.1, 50.6, 48.4, 45.0, 38.6, 38.0, 33.4, 31.0, 29.8, 20.5, 17.6; HRMS-ESI (*m/z*) $[C_{23}H_{26}N_4O_3 + H]^+$ calcd 407.2078, found 407.2071.

_N_-(2-(1_H_-indol-3-yl)ethyl)-2-nitro-_N_-(prop-2-yn-1-yl)benzenesulfonamide (437)



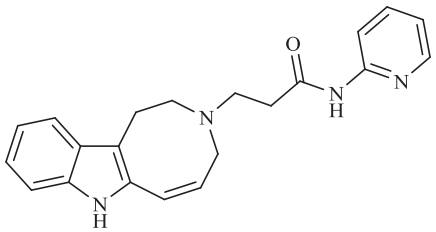
A solution containing N_{10}-nosyltryptamine **140** (700 mg, 2.03 mmol), propargyl bromide (241 mg, 2.23 mmol) and K_2CO_3 (842 mg, 6.09 mmol) in DMF was heated to 60 ^oC for 6 h. After this time the reaction mixture was diluted with HCl (1M, 100 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:3 EtOAc:Pet Sp.) afforded the title compound as a yellow oil (778 mg, 2.03 mmol, 100%). ^1H NMR (300 MHz, $CDCl_3$, δ) 7.96 (brs, 1H, indole-NH), 7.94 (d, *J* = 8.1 Hz, 1H, ArH), 7.50-7.60 (m, 4H, ArH), 7.31 (d, *J* = 8.0 Hz, 1H, ArH), 7.18 (t, *J* = 7.0 Hz, 1H, ArH), 7.11 (t, *J* = 7.7 Hz, 1H, ArH), 7.05 (s, 1H, ArH), 4.28 (d, *J* = 2.2 Hz, 2H, $CH_2C{\equiv}CH$), 3.74 (t, *J* = 7.2 Hz, 2H, CH_2CH_2NH), 3.12 (t, *J* = 7.3 Hz, 2H, CH_2CH_2NH), 2.24 (t, *J* = 2.4 Hz, 1H, $CH_2C{\equiv}CH$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 195.1, 148.0, 136.1, 133.4, 132.8, 131.5, 130.6, 127.1, 124.1, 122.3, 122.1, 119.5, 118.5, 111.8, 111.2, 73.9, 47.2, 36.7, 24.0; HRMS-ESI (*m/z*) $[C_{19}H_{17}N_3O_4S + H]^+$ calcd. 384.1013, found 384.0997.

(_Z_)-3-((2-nitrophenyl)sulfonyl)-2,3,4,7-tetrahydro-1_H_-azocino[5,4-_b_]indole (438)



A solution containing nosyltryptamine **437** (800 mg, 2.09 mmol) and $AuCl_3$ (32 mg, 5 mol%) in CH_2Cl_2 was heated to 40 ^oC for 3 h. After cooling to room temperature the reaction mixture was filtered through a plug of Celite and concentrated. Purification by column chromatography (1:4 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (410 mg, 1.07 mmol, 51%). ^1H NMR (270 MHz, $CDCl_3$, δ) 7.81 (d, *J* = 1.8 Hz, 1H, ArH), 7.78 (d, *J* = 1.1 Hz, 1H, ArH), 7.74 (brs, 1H, indole-NH), 7.44-7.55 (m, 4H, ArH), 7.06-7.22 (m, 2H, ArH), 6.59 (d, *J* = 11.3 Hz, 1H, $CH{=}CHCH_2$), 5.93 (dt, *J* = 6.6 and 11.2 Hz, 1H, $CH{=}CHCH_2$), 4.05 (dd, *J* = 0.8 and 6.6 Hz, 2H, $CH{=}CHCH_2$), 3.65 (m, 2H, CH_2CH_2NH), 3.06 (m, 2H, CH_2CH_2NH); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 147.9, 136.1, 133.2, 131.6, 131.5, 130.6, 128.1, 127.5, 124.2, 123.9, 123.5, 122.8, 119.8, 118.4, 112.3, 111.3, 110.8, 46.3, 24.8; HRMS-ESI (*m/z*) $[C_{19}H_{17}N_3O_4S + Na]^+$ calcd 406.0832, found 406.0846.

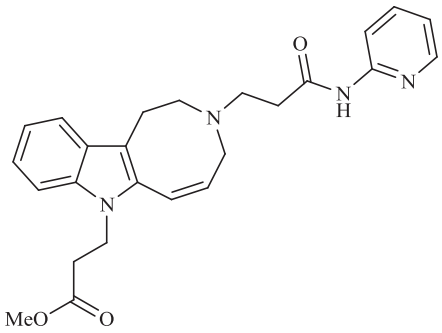
(_Z_)-3-(1_H_-azocino[5,4-_b_]indol-3(2_H_,4_H_,7_H_)-yl)-_N_-(pyridin-2-yl)propanamide (439)



A solution containing indoloazocine **438** (214 mg, 0.56 mmol), thiophenol (136 mg, 1.23 mmol) and potassium carbonate (232 mg, 1.68 mmol) in DMF (10 mL) was heated to 40 ^oC for 4 h. After this time the reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The deprotected product was then taken up in MeOH/THF (1:1, 10 mL) and following the addition of *N*-(pyridin-2-yl)acrylamide **423** (163 mg, 1.1 mmol) was heated to 60 ^oC for 48 h. The reaction mixture was concentrated and purification by column chromatography (1:2 EtOAc:Pet. Sp. to 2:3 EtOH:EtOAc) afforded the title compound as a yellow amorphous solid (130 mg, 0.38 mmol, 67% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$, δ) 11.03 (s, 1H, amide-NH), 8.27 (d, *J* = 3.9 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.91 (brs, 1H, indole-NH), 7.65 (t, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.4 Hz,

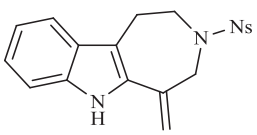
1H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.99 (m, 1H), 6.71 (d, *J* = 10.9 Hz, 1H, C<u>H</u>=CHCH$_2$), 5.93 (m, 1H, CH=C<u>H</u>CH$_2$), 3.61 (d, *J* = 7.7 Hz, 2H, CH=CHC<u>H$_2$</u>), 3.19 (m, 4H), 2.94 (t, *J* = 4.7 Hz, 2H), 2.57 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.4, 152.0, 148.0, 137.9, 130.4, 128.8, 125.9, 125.8, 122.6, 119.5, 119.3, 118.6, 114.4, 112.3, 110.5, 51.0, 49.4, 49.3, 33.9, 29.7, 22.7; HRMS-ESI (*m/z*) $[C_{21}H_{22}ON_4 + H]^+$ calcd 347.1866, found 347.1859.

(*Z*)-methyl 3-(3-(3-oxo-3-(pyridin-2-ylamino)propyl)-3,4-dihydro-1*H*-azocino[5,4-*b*]indol-7(2*H*)-yl)propanoate (440)



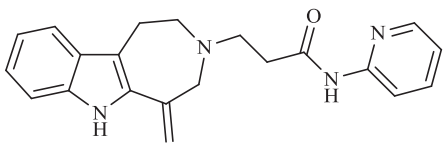
A solution containing indoloazocine pyridine **439** (113 mg, 0.33 mmol), methyl acrylate (56 mg, 0.65 mmol) and K_2CO_3 (135 mg, 0.98 mmol) in DMF (5 mL) was heated at 100 ^{o}C for 16 h. The reaction mixture was then diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as an orange oil (124 mg, 0.29 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 10.97 (s, 1H, amide-N<u>H</u>), 8.21 (m, 1H), 8.15 (m, 1H), 7.63 (m, 1H), 7.54 (m, 1H), 7.19-7.30 (m, 2H), 7.11 (m, 1H), 6.96 (ddd, *J* = 1.0 and 4.9 and 7.3 Hz, 1H), 6.83 (d, *J* = 11.0 Hz, 1H, C<u>H</u>=CHCH$_2$), 6.06 (m, 1H, CH=C<u>H</u>CH$_2$), 4.38 (t, *J* = 7.3 Hz, 2H, CH=CHC<u>H$_2$</u>), 3.64 (s, 3H, CO$_2$<u>Me</u>), 3.49 (d, *J* = 7.7 Hz, 2H), 3.08 (m, 4H), 2.95 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.6, 171.5, 152.0, 148.1, 138.0, 136.4, 132.0, 128.5, 128.1, 123.5, 122.5, 119.5, 119.4, 118.8, 114.4, 109.0, 52.0, 50.8, 50.0, 49.9, 39.3, 34.6, 33.9, 29.8, 22.7; HRMS-ESI (*m/z*) $[C_{25}H_{28}O_3N_4 + Na]^+$ calcd 455.2054, found 455.2053.

5-methylene-3-((2-nitrophenyl)sulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (442)



A solution containing nosyl tryptamine **437** (3000 mg, 7.84 mmol) and (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (303 mg, 5 mol%) in CH_2Cl_2 (40 mL) was stirred at room temperature for 16 h. After this time, the reaction mixture was filtered through a plug of Celite and concentrated. Purification by column chromatography (1:4 EtOAc:Pet Sp.) afforded the title compound as a pale yellow oil (2047 mg, 5.34 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.19 (s, 1H, indole-NH), 7.91 (dd, *J* = 1.1 and 5.4 Hz, 1H, Ar<u>H</u>), 7.42-7.57 (m, 5H, Ar<u>H</u>), 7.18 (dt, *J* = 0.9 and 7.0 Hz, 1H, Ar<u>H</u>), 7.09 (t, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 5.27 (s, 1H, C<u>H$_2$</u>=C), 5.20 (s, 1H, C<u>H$_2$</u>=C), 4.34 (s, 2H, CC<u>H$_2$</u>N), 3.75 (t, *J* = 5.7 Hz, 2H, CH$_2$C<u>H$_2$</u>NH), 3.12 (t, *J* = 5.9 Hz, 2H, C<u>H$_2$</u>CH$_2$NH); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 148.0, 137.4, 135.9, 133.6, 133.0, 132.8, 131.7, 130.4, 128.4, 124.0, 123.2, 119.7, 118.6, 112.8, 112.2, 110.9, 52.9, 49.1, 24.6; HRMS-ESI (*m/z*) $[C_{19}H_{17}N_3O_4S + Na]^+$ calcd 406.0832, found 406.0824.

3-(5-methylene-1,2,4,5-tetrahydroazepino[4,5-*b*]indol-3(6*H*)-yl)-*N*-(pyridin-2-yl)propanamide (443)



A solution containing azepinoindole **442** (2047 mg, 5.34 mmol), thiophenol (1369 mg, 12.43 mmol) and potassium carbonate (2214 mg, 16.02 mmol) in DMF (10 mL) was heated to 40 ^{o}C for 4 h. After this time the reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The deprotected product was then taken up in MeOH/THF (1:1, 20 mL) and following the addition of *N*-(pyridin-2-yl)acrylamide **423** (1582 mg, 10.68 mmol) heated to 60 ^{o}C for 48 h. The reaction mixture was concentrated and purification by column chromatography (3:1 EtOAc:Pet. Sp.) afforded the title compound as a yellow oil (573 mg, 1.65 mmol, 31% over 2 steps). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 10.80 (brs, 1H, amide-NH), 8.27 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.00 (brs, 1H, indole-NH), 7.66 (ddd, *J* = 2.0 and 7.6 and 8.7 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.19 (dt, *J* = 1.0 and 6.9 Hz, 1H), 7.09 (dt, *J* = 1.0 and 7.9 Hz, 1H), 6.99 (ddd, *J* = 0.8 and 5.0 and 7.3 Hz, 1H), 5.35 (s, 1H, CH_2=C), 5.17 (s, 1H, CH_2=C), 4.09 (s, 2H, CCH_2N), 3.42 (t, *J* = 5.4 Hz, 2H), 3.05 (m, 4H), 2.58 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 171.6, 152.1, 148.1, 139.0, 138.2, 135.9, 134.0, 129.0, 123.3, 119.8, 119.5, 118.9, 114.5, 114.4, 112.9, 110.7, 59.1, 53.5, 45.9, 33.1, 22.4; HRMS-ESI (*m/z*) $[C_{21}H_{22}N_4O + H]^+$ calcd. 347.1866, found 347.1869.

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Appendix One
Publications

JOC Note
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Domino Heck−Aza-Michael Reactions: Efficient Access to 1-Substituted Tetrahydro-β-carbolines

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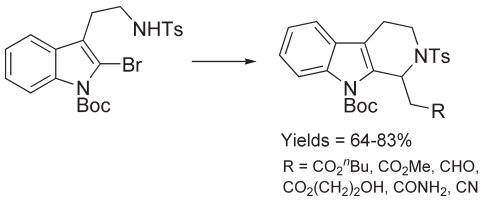

A simple and efficient palladium-catalyzed domino reaction for the synthesis of a series of C1-substituted tetrahydro-β-carbolines is described. This domino process involves a Heck reaction at the indole 2-position of a halogenated tryptamine precursor, followed by intramolecular aza-Michael addition.

Tetrahydro-β-carbolines (THβCs or tryptolines) substituted at the 1-position are central to a number of pharmaceutical targets with potential for the treatment of medical conditions including breast cancer, type-2 diabetes, and bacterial infections.[1] This ring system is prevalent in several more structurally complex natural products, including the secologanin-type terpenoid indole alkaloid ajmalicine (**1**) (Figure 1) and the antihypertensive agent reserpine (**2**).[1a,2] Biosynthetically, attaching a 3-(l-Δ′-pyrroliniumyl)propanal to this carboline ring system accesses the alkaloid elaeocarpidine (**3**) containing an additional indolizidine ring fragment.[3]

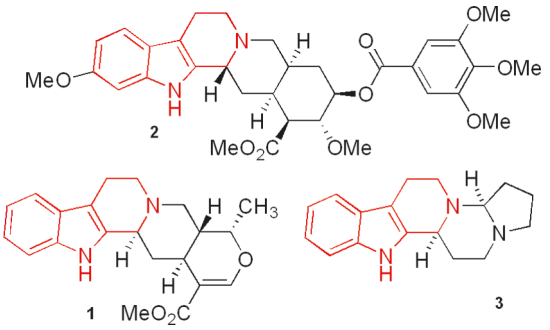

FIGURE 1. Natural products (**1**−**3**) containing the tetrahydro-β-carboline heterocyclic core.

Domino reactions are an attractive proposition for the modern synthetic chemist, generating a high level of molecular complexity in one efficient step.[4] A domino reaction is defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation."[4,5]

These reactions are appealing to industry and research laboratories because of their potential to minimize the use of solvents, reagents, time, and energy.[4] The more conceivable domino reactions are those where all transformations occur under similar reaction conditions, for example, where each of the steps are palladium-catalyzed.[5,6] The range of single-step reactions involving palladium catalysis has grown to the extent where palladium-mediated reactions are commonplace in most synthetic laboratories. Consequently, the number of palladium-mediated domino reactions has also increased over the past decade.[7] In spite of this increase, domino Heck−Michael methodology remains relatively underutilized, with limited examples in the literature.[8] Of those reported, only one details a domino Heck−aza-Michael process, used in the synthesis of benzo-fused sultams.[8c]

Due to their biological relevance, it is important that molecularly diverse THβCs are prepared containing multiple sites for further functionalization. Traditionally, C1-substituted THβCs are accessed through the acid-catalyzed Pictet−Spengler reaction between tryptamine and an appropriate aldehyde.[9] Alternatively, a four-step process involving a

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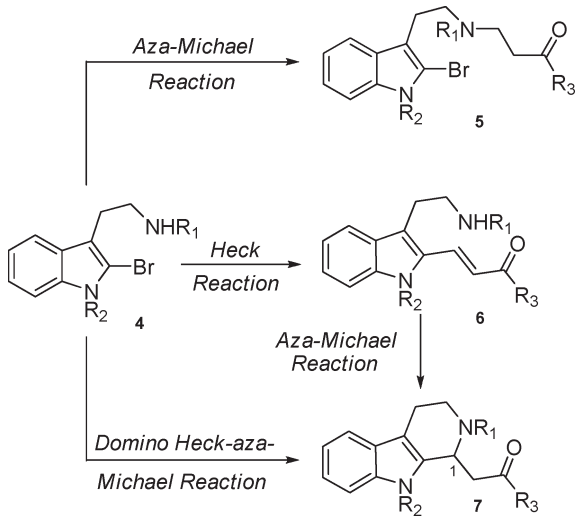
SCHEME 1. Single Step versus a Domino Process To Access THβCs



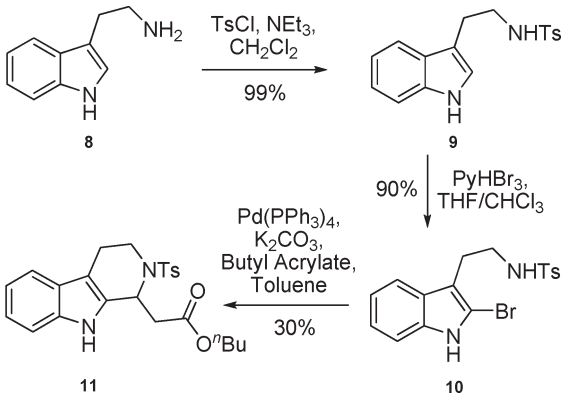
Bischler−Napieralski reaction to afford the dihydro-β-carboline and subsequent reduction is effective in producing specific THβCs.[10]

More recently, due to difficulties in the preparation and handling of the requisite aldehydes (for example, β-formyl esters[11]), modified Pictet−Spengler reactions have been developed using alternatives such as alkynoates[2a] and perhydro-1,3-heterocycles.[2c] To complement these existing methodologies, a domino Heck−aza-Michael reaction of a tryptamine derivative (such as compound 4, Scheme 1) was foreseen as an efficient method for introducing molecular diversity at C1 of the THβC scaffold. Using cheap and readily available acrylates under mild conditions, an orthogonally protected THβC scaffold containing multiple sites for further functionalization would be readily accessible.

The indole C2-position of tryptamine was considered ideal for further functionalization using a domino Heck−aza-Michael reaction (Scheme 1). Palladium-catalyzed cross-coupling of C2-halogenated indole compounds, namely, the Heck, Sonogashira, and Suzuki reactions, has been reported by our group and others.[12] As the Heck reaction regenerates the olefin functionality following *syn*-elimination and is reliably efficient with electron-deficient terminal alkenes, the potential exists for a second nucleophilic addition reaction. In this case, a 1,4-Michael addition should be suitable, depending on the nature of the tethered amine and if it reacts before or after the Heck reaction (an intra- vs intermolecular aza-Michael reaction; see Scheme 1).

As such, a domino Heck−aza-Michael transformation with an appropriately functionalized tryptamine was considered highly likely as both aza-Michael addition[13] and the Heck reaction[14] take place under mildly basic conditions. In this domino process, a new C−C and C−N bond would be created in sequence, at the same carbon atom.

SCHEME 2. Initial Attempts of the Domino Heck−Aza-Michael Reaction in the Synthesis of the Tetrahydro-β-carboline 11



Initially, several protecting groups (at R_1, Scheme 1) including *tert*-butoxycarbonyl, trifluoroacetate, tosyl, benzenesulfonyl, and 2-nitrobenzenesulfonyl were trialed to influence the acidity of the proton on the protected amine, tuning nucleophilicity at the tryptamine N10 nitrogen. During these preliminary investigations, the tosyl group was quickly identified as most suited to our domino system.[6b]

The tosyl protection of the primary amine within tryptamine (**8**) proceeded in quantitative yields to afford sulfonamide **9**. Similarly, bromination of the C2 position proceeded readily to give 2-bromoindole **10** in excellent yields (90%). Following preliminary treatment of the precursor **10** with $Pd(PPh_3)_4$, K_2CO_3 and butyl acrylate, the target tetrahydro-β-carboline **11** was isolated in a promising yield of 30% (Scheme 2).

The synthesis of carboline **11** from tryptamine (**8**) was achieved in three steps in a moderate overall yield of 27%. More importantly, this encouraging result confirmed that the domino Heck−aza-Michael reaction was applicable to this particular ring system. To improve the yield, three features of the domino Heck−aza-Michael reaction were identified for further optimization, namely, the Heck reaction, the nucleophilicity of the sulfonamide, and the degree of electron deficiency of the Michael acceptor. The Heck reaction, the initial step of this domino process, was optimized first, with the roles of the palladium catalyst, base, and the solvent investigated (Table 1).

The results from this investigation were consistent with previous reports of the Heck reaction at the indole 2-position,[12c,15] with $Pd(PPh_3)_4$ (10 mol %) providing the highest yields. Interestingly, the use of Na_2CO_3 (Table 1, entry 5) produced only the Heck adduct **12** in excellent yields, whereas K_2CO_3 facilitated the formation of the desired tetrahydro-β-carboline **11** (Scheme 2). Unfortunately, the highly reactive catalytic system pioneered by Fu[16] afforded only a moderate yield for the Heck product (Table 1, entry 3).

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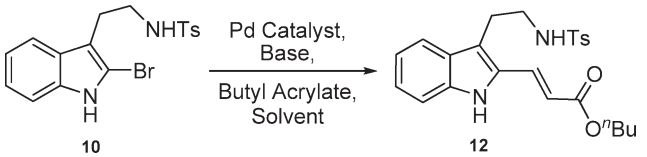
TABLE 1. Optimization of the Heck Transformation of Arylbromide 10



entry	catalyst (10 mol %)	base	solvent	yield (%)
1	$Pd(OAc)_2/PPh_3$[a]	NEt_3	toluene	22
2	$Pd_2(dba)_3/P(tBu)_3$[a]	NEt_3	toluene	43
3	$Pd_2(dba)_3/P(tBu)_3$[a]	Cy_2NMe	toluene	65
4	$Pd(PPh_3)_4$	NEt_3	toluene	39
5	$Pd(PPh_3)_4$	Na_2CO_3	toluene	99
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	trace[b]
7	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[b]
8	$Pd(PPh_3)_4$	K_2CO_3	dioxane	32
9	$Pd(PPh_3)_4$	CH_3CO_2Na	toluene	75

[a]Catalyst and ligand used in a 1:1 ratio. [b]Trace is $<10\%$ as determined by ^{1}H NMR.

With the Heck reaction proceeding in excellent yields, the second step in the domino sequence, the aza-Michael addition, was explored (Table 2).[17] A range of organic amines (i.e., NEt_3, DBU) and inorganic bases (i.e., Na_2CO_3, K_2CO_3, Cs_2CO_3) did not improve the domino transformation.

A range of solvents were also trialed to improve the $Pd(PPh_3)_4$, K_2CO_3 catalytic system; however, solvents more polar than toluene (MeCN, DMF, and dioxane, Table 2, entries 6–8) failed to increase the yield of the domino process with many of these increasing the propensity for the sulfonamide to undergo an initial 1,4-addition (to compound **5**, Scheme 1). In such cases, the relatively slow rate of the Heck reaction is secondary to the more reactive intermolecular aza-Michael addition.

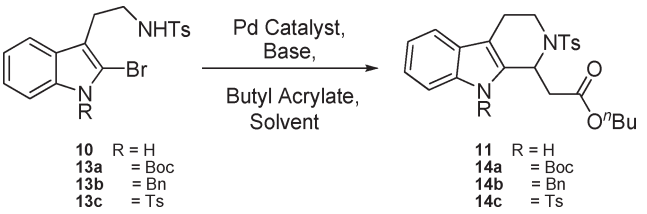
The addition of the phase transfer agent TBAC to improve the rate of key steps in the catalytic cycle (Table 2, entries 10 and 11) also failed to increase the yield of the domino process beyond 30%.[14,18] Alternatively, a change in the reactivity of the α,β-unsaturated moiety in the initial Heck adduct was envisaged through protection of the indole nitrogen. To our delight, this approach proved successful and the domino reaction using *N*-Boc indole **13a** produced the desired carboline **14a** in an excellent yield of 83% (Table 2, entry 14).

To further investigate the role of indole *N*-substitution on the domino process, two additional protecting groups were trialed (Table 2, entries 18 and 19). These substrates were reacted according to the previously identified conditions for the domino process, and a marked improvement in the yield of the desired tetrahydro-β-carbolines was observed.

The highest yields (up to 83%) for the domino process were obtained following the addition of $Pd(PPh_3)_4$ (10 mol %), alkene (1.1 equiv), and K_2CO_3 (3.0 equiv) to a sealed tube containing 2-bromoindole (1.0 equiv) in toluene (5 mL) that was subsequently stirred at 120 °C for 16 h. A simple purification protocol, including column chromatography, furnished the desired tetrahydro-β-carbolines. Reproducible yields for this domino process were obtained on various scales (ranging from 0.1 to 1.1 mmol).

To illustrate the versatility of this methodology, the domino Heck–aza-Michael reaction was repeated using a

TABLE 2. Optimization of the Domino Heck–Aza-Michael Reaction of Arylbromides



10 R = H
13a = Boc
13b = Bn
13c = Ts

11 R = H
14a = Boc
14b = Bn
14c = Ts

entry	substrate, product	catalyst (10 mol %)	base	solvent	yield (%)
1	**10**, **11**	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	0
2	**10**, **11**	$Pd(PPh_3)_4$	NEt_3	toluene	trace[a]
3	**10**, **11**	$Pd(PPh_3)_4$	DBU	toluene	trace[a]
4	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	30
5	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	30[b]
6	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[a]
7	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	DMF	trace[a]
8	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	dioxane	0
9	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	14[c]
10	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	trace[a,d]
11	**10**, **11**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	17[d]
12	**10**, **11**	$Pd_2(dba)_3/P(tBu)_3$[f]	NEt_3	toluene	trace[a]
13	**10**, **11**	$Pd_2(dba)_3/P(tBu)_3$[f]	Cy_2NMe	toluene	0
14	**13a**, **14a**	$Pd(PPh_3)_4$	K_2CO_3	toluene	83
15	**13a**, **14a**	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[a]
16	**13a**, **14a**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	27
17	**13a**, **14a**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	86[e]
18	**13b**, **14b**	$Pd(PPh_3)_4$	K_2CO_3	toluene	54
19	**13c**, **14c**	$Pd(PPh_3)_4$	K_2CO_3	toluene	54

[a]Trace is $<10\%$ as determined by ^{1}H NMR. [b]Using 2 equiv of butyl acrylate. [c]Using 3 equiv of butyl acrylate also resulted in a large formation of only the aza-Michael product **5**. [d]Tetra-*n*-butylammonium chloride added to initial reaction mixture. [e]A one-pot process where tetra-*n*-butylammonium chloride was added to reaction mixture after 12 h at 120 °C, with stirring at 120 °C continued for 4 h. [f]Catalyst and ligand used in a 1:1 ratio.

number of terminal alkenes, each possessing a suitably conjugated Michael-type acceptor (Table 3). This domino process allowed access to a series of tetrahydro-β-carboline scaffolds, containing a variety of sites available for further functionalization.

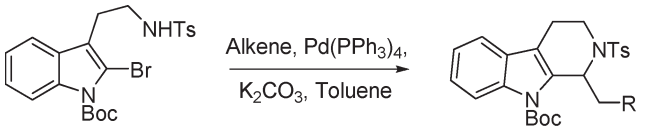
The two-step domino process performed well for all alkenes employed (except in the case of acrylic acid) with isolated yields ranging from 64 to 83% (Table 3).

In conclusion, a novel domino Heck–aza-Michael reaction has been developed. This methodology has been applied to the synthesis of a series of C1-substituted tetrahydro-β-carbolines. Using mild conditions, this domino process affords indole-based heterocyclic scaffolds, highly amenable to larger total syntheses. Furthermore, the domino Heck–aza-Michael conditions reported by Hanson et al. failed for those systems in which the sulfonyl moiety was not contained *within* the heterocyclic ring formed.[8c] The domino Heck–aza-Michael process reported herein proved successful in the synthesis of tetrahydro-β-carbolines with the sulfonyl group *external* to the newly constructed heterocycle. To the best of our knowledge, this is the first example of a domino Heck–aza-Michael reaction for the synthesis of a carbon–nitrogen heterocycle. Complementing existing methodology, this domino process

(17) Our attention turned to the optimal conditions to bring about a simple 1,4-addition. In this case, the tosylamine tether was reactive enough for aza-Michael addition to occur under mild basic conditions.

(18) The phase transfer agent used in an attempt to improve the solubility of K_2CO_3 failed to significantly increase the yield.

TABLE 3. Preparation of Diverse 1-Substituted THβCs



13a 14a, 15-20

entry	alkene	R	product	yield (%)
1	butyl acrylate	$CO_2(CH_2)_3CH_3$	**14a**	83
2	methyl acrylate	CO_2CH_3	**15**	79
3	2-hydroxyethyl acrylate	$CO_2(CH)_2OH$	**16**	64
4	acrolein	CHO	**17**	64
5	acrylamide	$CONH_2$	**18**	80[a]
6	acrylonitrile	CN	**19**	67
7	acrylic acid	CO_2H	**20**	0

[a]Conversion calculated for desired product; however, partial Boc deprotection during synthesis resulted in an inseparable mixture of indole *N*-Boc and indole *N*-H tetrahydro-β-carbolines. See Supporting Information.

allows synthetic flexibility when access to a specific C1-substituted tetrahydro-β-carboline is required.

Current work within this group is focused on variations of this domino process, including the use of more highly substituted alkenes and the introduction of chirality through the use of tryptophan-derived starting materials.

Experimental Section

Typical Procedure for the Preparation of 1-Substituted THβCs 14a, 15−19 (Butyl Acetate THβC 14a as Example). A sealed tube containing a 2-bromoindole **13a** (100 mg, 0.20 mmol), $Pd(PPh_3)_4$ (23 mg, 10 mol %), K_2CO_3 (84 mg, 0.61 mmol), and butyl acrylate (29 mg, 0.22 mmol) in toluene (4 mL) was heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude product purified by column chromatography (1:4 EtOAc/Pet Sp) to afford the tetrahydro-β-carboline **14a** (91 mg, 0.17 mmol, 83%) as a pale yellow oil: FT-IR (ν, cm^{-1}, KBr) 1730vs, 1457, 1374, 1324, 1159, 747; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.10 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.14−7.28 (m, 3H), 7.03 (d, J = 8.6 Hz, 1H), 6.12 (dd, J = 3.6 and 10.6 Hz, 1H), 4.05 (m, 3H), 3.50 (m, 1H), 3.00 (dd, J = 3.7 and 14.3 Hz, 1H), 2.70 (dd, J = 10.6 and 14.3 Hz, 1H), 2.39−2.60 (m, 2H), 2.18 (s, 3H), 1.75 (s, 9H), 1.60 (m, J = 7.8 Hz, 2H), 1.34 (m, J = 7.6 Hz, 1H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 169.8, 149.9, 143.4, 137.5, 135.9, 133.0, 129.2, 128.6, 127.1, 124.8, 122.9, 118.0, 115.7, 114.9, 85.0, 64.9, 51.1, 40.3, 37.9, 30.6, 28.4, 21.4, 19.7, 19.2, 13.8; HRMS-ESI (m/z) $[C_{29}H_{36}N_2O_6S - H]^-$ calcd 539.22213, found 539.22187.

Supporting Information Available: Experimental procedures, characterization, copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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PAPER

A general approach to *N*-heterocyclic scaffolds using domino Heck–aza-Michael reactions†

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Palladium-catalyzed domino Heck–aza-Michael reactions for the synthesis of a series of C1-substituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines are described. The domino process involves the initial intermolecular Heck reaction of an aryl bromide with an electron deficient alkene, followed by an intramolecular aza-Michael reaction to form the new *N*-heterocycle in high yield.

Introduction

In the ongoing pursuit of environmentally friendly reaction processes, domino reactions have emerged as a powerful tool for synthetic chemists.[1,2] These domino processes generate a high level of molecular complexity in one efficient step, minimising solvent use, reagents, time and energy.[1] A domino reaction is defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation".[1,2] The more feasible domino reactions are those where all transformations occur under similar reaction conditions, for example, where each of the reaction steps is palladium-catalysed.[2–5] Likewise, because of the reliance of base in many Pd cross-coupling reactions, domino reactions involving both a Pd-catalysed and a base-initiated synthetic step are also plausible.

In spite of this possibility, the domino Heck–Michael methodology for the formation of heterocycles has not been widely reported.[6–8] Domino Heck–aza-Michael reactions have been applied to a series of unique benzo-fused sultams,[7] and isoindolinones using terminal alkene esters.[8] However, attempts to expand the scope of these methods to related substrates have proved problematic. Recently, our group has reported a domino Heck–aza-Michael reaction for the synthesis of a series of C1-substituted tetrahydro-β-carbolines.[9] Herein, we report that the scope of this novel domino process has been successfully expanded to include other *N*-heterocycles, namely tetrahydroisoquinolines and isoindolines.

The tetrahydro-β-carboline, tetrahydroisoquinoline and isoindoline scaffolds are all present in important biologically-active compounds. Tetrahydro-β-carbolines (THβCs or tryptolines) form the core of the antihypertensive agent reserpine (**1**) (Fig. 1), along with a range of other biologically-active natural products.[10–17] Likewise, the tetrahydroisoquinoline ring system forms the central part of a number of naturally-occurring alkaloids,[18–22] including the antitumor natural product quinocarcinol **2**.[23,24] In comparison, isoindoline-based natural products are not as prevalent. Nevertheless, this scaffold is found in a range of potential pharmaceutical agents,[25–28] such as compound **3** (Fig. 1), synthesized as a ligand for the melanocortin subtype-4 receptor (MC4R).[29]

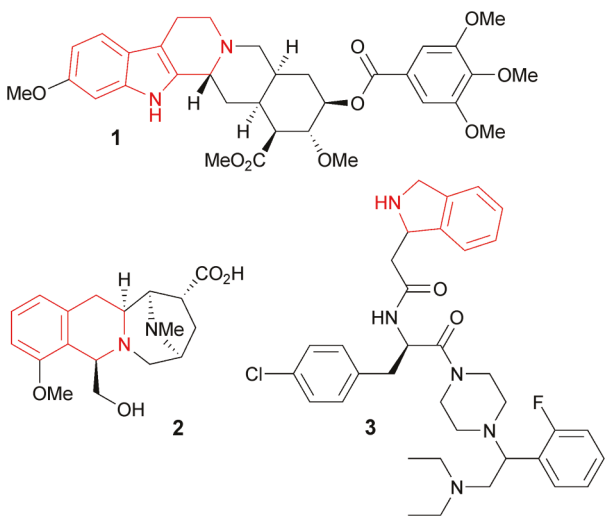

Fig. 1 Biologically-active compounds containing the tetrahydro-β-carboline (**1**), tetrahydroisoquinoline (**2**) and isoindoline (**3**) *N*-heterocyclic core.

As the importance of these classes of compounds grows in a medicinal chemistry setting, so does the focus on a general method for their synthetic preparation. Tetrahydro-β-carbolines and tetrahydroisoquinolines have traditionally been prepared by

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† Electronic supplementary information (ESI) available. ^{1}H and ^{13}C NMR spectra for compounds listed in the experimental section. See DOI: 10.1039/c0ob00835d

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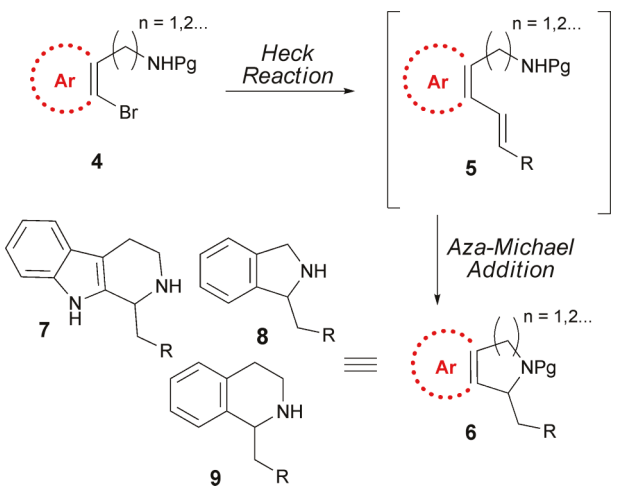
reacting tryptamine or phenethylamine with a suitable aldehyde; namely the Pictet–Spengler reaction.[30–34] Similarly, the Bischler–Napieralski reaction affords these ring systems through the cyclodehydration of an appropriately substituted amide.[32,35–39] Alternatives to the Pictet–Spengler or the Bischler–Napieralski reactions are limited. One of the most recent, the Ferracioli synthesis of tetrahydroisoquinolines, involves palladium-catalyzed *ortho*-alkylation/vinylation followed by an aza-Michael reaction.[40] Isoindolines substituted at the C1-position have also been accessed using an aryl radical cyclization of *N*-benzylenaminone esters.[41] More recently, 1,3-disubstituted isoindolines have been synthesized using a Brønsted acid-catalyzed 1,2-addition followed by an aza-Michael addition.[42]

A general approach to *N*-heterocycles using a domino Heck–aza-Michael strategy would complement existing methods and in some instances provide a more attractive option, for example, when suitable aldehydes for the Pictet–Spengler reaction are not readily available.[14,17,43] In order to be applied to a range of substrates, the domino process needs to occur under mild conditions using a readily available catalyst, base and with inexpensive electron deficient alkenes. As a wide range of suitable acrylates (such as acrolein, acrylonitrile, acrylic acid, *etc.*) are commercially available, the C1 functionality of the new heterocycle can be customised by appropriate alkene selection. To this end, we herein describe our recent efforts to expand our domino Heck–aza-Michael methodology from THβCs to include tetrahydroisoquinolines and isoindolines.

Results and discussion

In planning the Heck–aza-Michael domino process, a suitable halogenated aryl ring system for a rapid Heck reaction with an electron-withdrawn terminal alkene was sought. Aryl bromides **4** were selected due to the higher commercial cost of aryl iodides. Initial C–H activation was also envisaged but deemed to be too slow and less regioselective in the initial step of the domino sequence.[44]

The ring size of the newly formed *N*-heterocycle (compounds **7**–**9**, Scheme 1) is governed by the length of the alkyl chain connecting the amine to the aryl portion of starting material **4**. Similarly, the selection of a suitable protecting group for the tethered amine is important when considering the Michael addition step. An ideal protecting group would control the amine reactivity, avoiding the likelihood of an intermolecular 1,4-addition, prior to the Heck reaction.



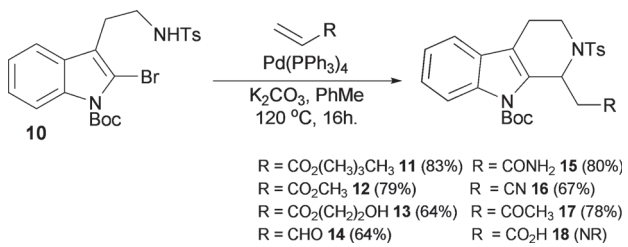
Scheme 1 Generic plan for the domino Heck–aza Michael reaction.

As the Heck reaction at the C2 position of substituted tryptamines is known from previous investigations within the group,[5] it was trialled first. Readily available *ortho*-halogenated benzylamines and phenethylamines were also identified as ideal substrates for this investigation, as the *ortho*-tethered amine is well positioned for the aza-Michael addition to form a new *N*-heterocycle, following the initial Heck reaction.

Tetrahydro-β-carbolines

The detailed optimisation of a domino Heck–aza-Michael reaction for the synthesis of tetrahydro-β-carbolines has previously been described by our group.[9] As the Heck reaction of 2-bromoindoles has been reported,[5,45,46] the limiting factor was the aza-Michael reaction. A key finding of our THβC investigation was that the tosyl protecting group of the tethered amine (superior to Boc, Ac and trifluoroacetyl) allowed the aza-Michael reaction to take place subsequent to the initial cross-coupling reaction. Following optimisation, the highest yields for the domino process between halogenated indole-*N*-Boc substrate **10** and butyl acrylate were obtained by using the $Pd(PPh_3)_4$, K_2CO_3 and toluene catalytic system.

The versatility of this domino Heck–aza-Michael reaction was then investigated using a number of suitably conjugated terminal alkenes (Scheme 2). The two-step domino process, forming a new 6-membered *N*-heterocycle, performed well for the alkenes employed, except in the case of acrylic acid, with isolated yields ranging from 64–83% (compounds **11–16**).‡ In addition to these previously reported scaffolds,[9] this domino process has now been expanded to include 3-buten-2-one, which afforded ketone-functionalised THβC **17** (78% yield). These tetrahydro-β-carboline scaffolds contain a series of C1 functionalities that allow for further synthetic manipulation and possible application as part of total syntheses.[9]



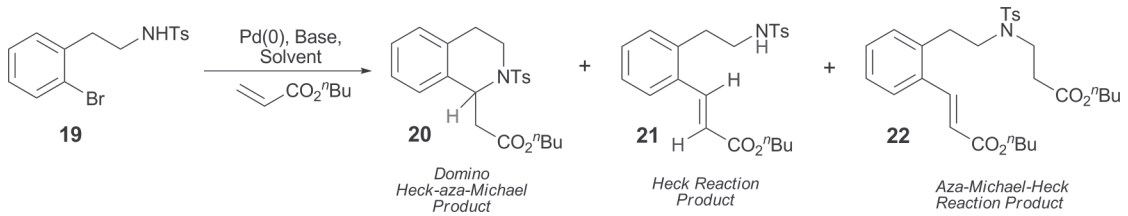
Scheme 2 The synthesis of tetrahydro-β-carbolines using a domino Heck–aza-Michael process.

Tetrahydroisoquinolines

Given the success of this initial series of domino reactions to generate tetrahydro-β-carbolines **7**, the synthesis of

‡ The unreactive nature of acrylic acid may be explained by the poor solubility of the corresponding carboxylate ion.

Table 1 Investigations into the domino reaction of aryl bromide **26**



Entry	Palladium catalyst[a] (10 mol%)	Base	Solvent	Major product[b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	**22**
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	**21**
3	$Pd_2(dba)_3/P(^tBu)_3$	Cy_2NMe	PhMe	**21**
4	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	**21**
5	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	PhMe	NR[d]
6	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	**21**
7	$Pd_2(dba)_3$/DavePhos	K_2CO_3	PhMe	**20** (79)[e]
8	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	**20** (80)[e]
9	Herrmann–Beller palladacycle[f]	Cy_2NMe	DMF–MeCN–H_2O[c]	**20** (67)[e]

[a] Palladium catalyst and ligand used in a 1 : 1 molar ratio. [b] As determined by ^{1}H NMR analysis of the crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra δ: 5.46 (red), 4.60 (green), 7.84 (blue) and 6.28 (purple). [c] DMF–MeCN–H_2O (5 : 5 : 1). [d] NR = No reaction. [e] Yield (%). [f] The Herrmann–Beller catalyst is [*trans*-di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]dipalladium(II)].

tetrahydroisoquinolines **9** using a domino Heck–aza-Michael reaction was investigated. As in the case of the THβCs, the tosyl (Ts) protecting group was employed to control amine nucleophilicity,[9] and the desired domino substrate (sulfonamide **19**) was prepared in 86% yield. Using this substrate, a series of trial reactions were carried out to determine if a domino Heck–aza-Michael process was feasible. These reactions were initially performed by treating aryl bromide **19** with butyl acrylate, a palladium catalyst, base and solvent in a pressure vessel, and heating to 120 °C for 16 h. The identification of the products (**20–22**) was performed by means of ^{1}H NMR spectroscopy of the crude reaction mixture (Table 1).

The ideal catalytic system for this domino process would *rapidly* produce Heck product **21**, with the base and solvent promoting the aza-Michael addition to form desired tetrahydroisoquinoline **20**, but not to an extent where intermolecular 1,4-nucleophilic addition of the acrylate occurs prior to the Heck reaction.

In the first attempt, the optimum conditions identified for the synthesis of THβCs ($Pd(PPh_3)_4$, K_2CO_3, PhMe; Table 1, entry 1) produced adduct **22** exclusively, *i.e.* the aza-Michael reaction is favoured but the Heck reaction is slow.

A number of alternative Pd catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3/P(^tBu)_3$ and $Pd(OAc)_2/PPh_3$) combined with a range of bases (Table 1, entries 2–4) were subsequently trialled; however, only Heck adduct **21** was produced. It is apparent that whilst the Heck reaction was proceeding, the base used (Na_2CO_3, Cy_2NMe and NEt_3; Table 1, entries 2, 3 and 4, respectively) in each of these trials was not strong enough to induce either intra- or intermolecular aza-Michael addition, as only traces of these products were observed. From the previous work on THβCs, it is known that the aza-Michael process is sensitive to subtle variations in the base used. Again, for the synthesis of tetrahydroisoquinolines, slightly changing the base (*e.g.* from K_2CO_3 to Na_2CO_3; Table 1, entries 1 and 2) either facilitates or reduces the likelihood of the aza-Michael reaction. Of the bases trialled to this point (Table 1, entries 1–6), only K_2CO_3 was successful in enabling the aza-Michael reaction to occur (albeit intermolecularly).

To ensure rapid formation of the Heck adduct, the highly reactive and electron-rich $Pd_2(dba)_3$/DavePhos catalyst system, developed by Buchwald and Hartwig, was used in combination with K_2CO_3.[47]§ To our delight, this catalytic system furnished desired tetrahydroisoquinoline **20** in high yield (Table 1, entry 7).

Following further trials, other catalytic systems (Table 1, entries 8 and 9) also resulted in clean conversion of domino precursor **19** to tetrahydroisoquinoline **20**. These additional successes indicate that a judicious choice of base and solvent is crucial for promoting the desired aza-Michael cyclisation (compare Table 1, entries 4 and 8). In assessing each of these procedures, the $Pd(OAc)_2/PPh_3$ and K_2CO_3 in toluene catalytic system was deemed the most attractive due to its relatively low cost and commercial availability.

A range of acrylates were subject to this domino process to afford a series of C1-substituted tetrahydroisoquinolines **9** (Table 2). The resulting products from this series of reactions contain a range of functionalities, including ester, ketone and nitrile (Table 2, entries 1–5). In each of these cases, there seems to be no clear differentiation in the yield, suggesting that small differences in the electronics of each of these acrylates does not dramatically affect the domino process. Unfortunately, reactions attempted with both acrolein and acrylic acid did not furnish the desired tetrahydroisoquinolines, even though the reaction with acrolein had been successfully employed in a THβC domino Heck–aza-Michael reaction (Scheme 2).[9]

Isoindolines

With the successful development of domino Heck–aza-Michael reactions for the formation of two 6-membered *N*-heterocyclic

§ The possibility of a C–N cross-coupling was disregarded due to the strained ring system that would be generated as part of this process.

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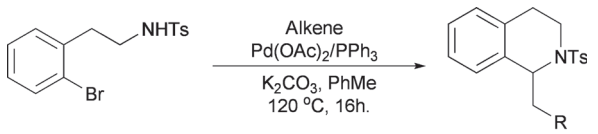
Table 2 Synthesis of a series of C1-substituted tetrahydroisoquinolines



19 20, 23-26

Entry	Alkene	R	Product	Yield (%)
1	Butyl acrylate	$CO_2{}^nBu$	**20**	80
2	Methyl acrylate	CO_2Me	**23**	83
3	2-Hydroxyethyl acrylate	$CO_2(CH_2)_2OH$	**24**	76
4	Acrylonitrile	CN	**25**	82
5	3-Buten-2-one	$COCH_3$	**26**	79
6	Acrylamide	$CONH_2$	**27**	Trace[a]
7	Acrolein	CHO	**28**	NR[b]
8	Acrylic acid	CO_2H	**29**	NR[b]

[a] Trace = less than 10%, as determined by ^{1}H NMR. [b] NR = No reaction.

systems, our attention turned to a third scaffold. To expand the scope of this methodology to include 5-membered *N*-heterocycles, an appropriately substituted benzylamine **30**, was prepared in 99% yield as a precursor to C1-substituted isoindolines **8**.

As with both the THβCs and tetrahydroisoquinolines, a range of conditions were evaluated for the preparation of the desired isoindoline **31** (Table 3). Bromosulfonamide **30**, butyl acrylate, a palladium catalyst, base and solvent were combined in a pressure vessel, and heated to 120 °C for 16 h. Following a simple work up, the major product was identified by ^{1}H NMR spectroscopy.

The first trial with tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) afforded mixtures of the three predicted products, **31**, **32** and **33** (Table 3, entry 1). Repeating the reaction with $Pd(PPh_3)_4$ but changing the base and solvent (Table 3, entries 2–4) also proved unsuccessful. The highly active catalytic system of $Pd_2(dba)_3/P(^tBu)_3$ minimised the formation of aza-Michael–Heck product **33**; however, complete conversion of the Heck adduct to the desired isoindoline was not realised (Table 3, entry 5).[48]

A high yield of desired isoindoline **31** was observed when $Pd(OAc)_2/PPh_3$ and triethylamine were used in either toluene or DMF (Table 3, entries 8 and 9). The use of other highly active Pd catalysts also proved successful when teamed with an amine base in DMF. Again, it was apparent that a suitable base (in this case, an organic base rather than an inorganic base) was crucial to effect the desired cyclisation following the Heck reaction.

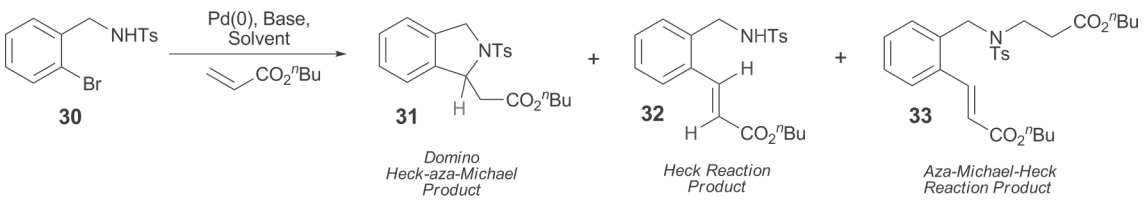
Even though the Pd_2dba_3/DavePhos catalytic system (Table 3, entry 10) provided isoindoline **31** in the highest yield, it was not significantly greater than that obtained when the $Pd(OAc)_2/PPh_3$ system was used (Table 3, entry 9). This latter system was subsequently used for the remainder of this investigation due to its low cost and commercial availability.

This optimized domino system was then used with a range of acrylates to afford a series of C1-substituted isoindolines (Table 4). The products synthesised contain a range of functionalities, including carboxylic acid, ester, ketone, amide and nitrile. This time, the use of acrylic acid resulted in the formation of isoindoline acetic acid **38**, presumably due to the increased solubility of the carboxylate ion in the triethylamine/DMF solvent system. Unfortunately, the use of acrolein[49] once again did not yield the desired isoindoline.

Conclusions

Following the successful development of a domino Heck–aza-Michael reaction for the synthesis of the tetrahydro-β-carbolines,[9]

Table 3 Preliminary investigations into the formation of isoindolines



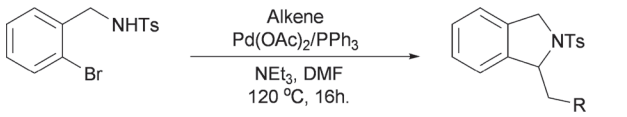
30 31 32 33

Domino Heck-aza-Michael Product *Heck Reaction Product* *Aza-Michael-Heck Reaction Product*

Entry	Palladium catalyst[a] (10 mol%)	Base	Solvent	Major product[b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	Mixture (**31**/**32**/**33**)
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	Mixture (**31**/**32**/**33**)
3	$Pd(PPh_3)_4$	Cs_2CO_3	PhMe	NR[d]
4	$Pd(PPh_3)_4$	K_2CO_3	DMF	NR[d]
5	$Pd_2(dba)_3/P(^tBu)_3$	Cy_2NMe	PhMe	**31**/**32**
6	$Pd_2(dba)_3{\cdot}CHCl_3$	NEt_3	DMF	NR[d]
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	NR[d]
8	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	**31** (74)[e]
9	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	**31** (77)[e]
10	$Pd_2(dba)_3$/DavePhos	Cy_2NMe	DMF	**31** (79)[e]
11	$Pd_2(dba)_3$/XPhos	Cy_2NMe	DMF	**31** (62)[e]
12	$Pd_2(dba)_3$/SPhos	Cy_2NMe	DMF	**31** (48)[e]
13	Herrmann–Beller palladacycle[f]	Cy_2NMe	DMF–MeCN–H_2O[c]	**31** (54)[e]

[a] Palladium and ligand used in a 1 : 1 molar ratio. [b] As determined by ^{1}H NMR analysis of the crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra δ: 5.28 (red), 5.10 (green), 7.62 (blue) and 6.38 (purple). [c] DMF–MeCN–H_2O (5 : 5 : 1). [d] NR = No reaction. [e] Yield (%). [f] The Herrmann–Beller catalyst is [*trans*-di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]-dipalladium(II)].

Table 4 Synthesis of a series of C1-substituted isoindolines



30 31, 35-39

Entry	Alkene	R	Product	Yield (%)
1	Butyl acrylate	$CO_2{}^nBu$	**31**	77
2	Methyl acrylate	CO_2Me	**34**	Unknown[a]
3	2-Hydroxyethyl acrylate	$CO_2(CH_2)_2OH$	**35**	84
4	Acrylamide	$CONH_2$	**36**	71
5	Acrylonitrile	CN	**37**	68
6	Acrylic acid	CO_2H	**38**	85
7	3-Buten-2-one	$COCH_3$	**39**	86
8	Acrolein	CHO	**40**	NR[b]

[a] This domino process also performed well using methyl acrylate; however, the isoindoline product could not be separated from the remaining starting material by column chromatography. [b] NR = No reaction.

the scope of this new methodology has been expanded to include the tetrahydroisoquinoline and isoindoline *N*-heterocyclic scaffolds. The key considerations of the domino Heck–aza-Michael methodology were identified as (i) the relatively quick formation of the Heck adduct (controlled through appropriate selection of Pd catalyst) and (ii) the nucleophilicity of the tethered amine (mediated through careful selection of the protecting group, base and solvent).

In determining the appropriate conditions for the Heck reaction, a palladium catalyst was required that facilitated a fast, high-yielding reaction between the aryl halide and the alkene in the presence of a mild base and a relatively non-polar solvent. It is important that the acrylate is consumed rapidly by the Heck process so that the intermolecular aza-Michael reaction cannot take place. For the Heck reaction at the indole 2-position, $Pd(PPh_3)_4$ afforded the highest yields. In the case of the benzyl- and phenethylamine aryl halides, the use of $Pd(OAc)_2/PPh_3$ proved optimal.

More importantly, an appropriate base is required; one that is able to sufficiently promote aza-Michael reaction, but not to the extent that it occurs before a high concentration of the Heck adduct is realised. Indeed, the outcome of reactions that were repeated, varying only the base used, ranged from a rapid intermolecular Michael reaction prior to the Heck reaction through to the desired domino Heck–aza-Michael process. For the synthesis of both THβCs and tetrahydroisoquinolines, K_2CO_3 was required to effect the cyclisation; however, in the case of the isoindolines, the new *N*-heterocycle formed in the presence of a milder amine base (either NEt_3 or Cy_2NMe).

Other parameters that could limit reaction progress included (i) the size of the *N*-heterocycle being formed, and (ii) the sterics associated with the Heck reaction and subsequent Michael addition. If the steric bulk of the proximal sulfonamide (benzylamine *vs.* phenethylamine) was a critical factor, the initial Heck reaction would be faster for the formation of compounds **11** and **20** over isoindoline **31**. Furthermore, for 5-membered isoindoline series **8**, a strained transition state in the Michael addition step may also hinder the progress of the domino reaction. Nevertheless, as little difference in the overall yields were observed for each of the domino processes studied herein, the role of ring size and sterics appears to be minor.

In conclusion, high yielding domino Heck–aza-Michael reactions to access C1-substituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines have been successfully developed as a general approach to *N*-heterocycles. These reactions employ mild conditions, and readily available palladium catalysts and acrylates. The mild conditions described suggest this domino process may be applied to more complex substrates and key transformations in total syntheses. As indicated, the use of other highly active palladium catalysts may benefit the scope of this process and its functional group tolerance.

Experimental

General experimental

All proton (^{1}H NMR) and carbon (^{13}C NMR) spectra were recorded on a 270 MHz FT-NMR, 400 MHz FT-NMR or 300 MHz FT-NMR spectrometer as indicated. Samples were dissolved in deuterated chloroform ($CDCl_3$). Proton peaks are reported as follows: chemical shift δ (ppm) (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integral, coupling constant J (Hz), assignment). Carbon peaks are reported as chemical shift δ (ppm). High resolution mass spectra (HRMS) were recorded on a TOF mass spectrometer with the following conditions: drying gas, nitrogen (7 mL min^{-1}, 350 °C); nebulizer gas, nitrogen (16 psi); capillary voltage, 4.0 kV; vaporizer temperature 350 °C; and cone voltage, 60 V. HPLC grade methanol was used as the mobile phase. Samples were dissolved in acetonitrile (less than 1 mg per mL). IR spectra were acquired on an FT-IR instrument using KBr discs and are reported in wave numbers (cm^{-1}). Column chromatography was performed using silica gel, 60 (70-230 mesh). Petroleum spirits (pet. sp) refers to the fraction boiling at 40–60 °C. All solvents used were AR grade. $Pd(PPh_3)_4$ was prepared according to a literature procedure.[50]

Full experimental details for the preparation of compounds **10**–**16** are described in an earlier communication.[9]

Specific experimental

(*R*,*S*)-2-(9-*tert*-Butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)propan-2-one (17). A sealed tube containing 2-bromoindole **10** (300 mg, 0.61 mmol), $Pd(PPh_3)_4$ (70 mg, 10 mol%), K_2CO_3 (252 mg, 1.82 mmol) and 3-buten-2-one (51 mg, 0.73 mmol) in toluene (3 mL) was flushed with argon, then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, and the solvent removed *in vacuo*. Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded tetrahydro-β-carboline **17** as a pale yellow oil (228 mg, 0.47 mmol, 78%). FT-IR (ν, cm^{-1}, KBr) 1716vs, 1465, 1386, 1327, 1159, 698; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.96 (dt, J = 0.9, 8.3 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.12–7.27 (m, 3H), 7.00 (dd, J = 0.6, 8.6 Hz, 2H), 6.23 (dd, J = 3.3, 10.6 Hz, 1H), 4.05 (dd, J = 6.5, 15.3 Hz, 1H), 3.38–3.50 (m, 1H), 3.08 (dd, J = 3.5, 14.2 Hz, 1H), 2.70 (dd, J = 10.6, 14.2 Hz, 1H), 2.41–2.58 (m, 2H), 2.35 (s, 3H), 2.14 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.0, 150.1, 143.5, 136.8, 135.2, 133.5, 129.1, 128.5, 127.0, 124.5, 122.8, 117.9, 115.6, 114.5, 84.8, 50.5, 48.8, 37.7, 29.2, 28.3, 21.2, 19.2;

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HRMS-ESI (m/z) $[C_{26}H_{30}N_2O_5S + Na]^+$ calc. 505.1768, found 505.1790.

***N*-(2-Bromophenethyl)-*p*-toluenesulfonamide (19).** To a cooled solution (0 °C) of 2-bromophenethylamine (400 mg, 2.0 mmol) and triethylamine (242 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (420 mg, 2.2 mmol) in one portion. The reaction mixture was stirred for 2 h. at ambient temperature. The reaction mixture was then washed with HCl (1 M, 2 × 10 mL), NaOH (Aq. 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford phenethylamine **19** as a colorless oil (624 mg, 1.76 mmol, 88%). FT-IR (ν, cm^{-1}, KBr) 3152, 1598, 1233, 1059, 754, 647; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 1.2, 7.9 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H) 7.03–7.20 (m, 3H), 4.57 (brt, J = 6.2 Hz, 1H), 3.21 (q, J = 6.9 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 143.4, 137.1, 133.0, 131.1, 129.7, 129.0, 128.2, 127.7, 127.1, 124.4, 42.5, 36.3, 21.5; HRMS-ESI (m/z) $[C_{15}H_{16}BrNO_2S + Na]^+$ calc. 375.9977, found 375.9979.

General procedure A for tetrahydroisoquinoline formation

A sealed tube containing a 2-bromophenethylamine **19** (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), K_2CO_3 (3.0 equiv.) and alkene (1.2 equiv.) in toluene (3 mL) was flushed with argon and then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-Butyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (20). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), butyl acrylate (44 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **20** as a pale yellow oil (90 mg, 0.22 mmol, 80%). FT-IR (ν, cm^{-1}, KBr) 2959, 1732, 1338, 1161, 1091, 756, 660, 548; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.08–7.10 (m, 3H), 6.95 (m, 1H), 5.46 (t, J = 6.9 Hz, 1H), 4.04 (dt, J = 3.5, 6.7 Hz, 2H), 3.71–3.80 (m, 1H), 3.47–3.58 (m, 1H), 2.88 (dd, J = 7.2, 14.6 Hz, 1H), 2.63–2.74 (m, 3H), 2.32 (s, 3H), 1.58 (m, 2H), 1.32 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ); 170.4, 143.3, 137.2, 135.5, 133.1, 129.5, 129.0, 127.3, 127.2, 126.7, 126.5, 64.8, 53.4, 43.6, 39.7, 30.6, 27.0, 21.5, 19.1, 13.8; HRMS-ESI (m/z) $[C_{22}H_{27}NO_4S + H]^+$ calc. 402.1734, found 402.1734.

(*R*,*S*)-Methyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-acetate (23). General procedure A was followed using 2-bromophenethylamine **19** (200 mg, 0.56 mmol), methyl acrylate (58 mg, 0.67 mmol), $Pd(OAc)_2$ (12 mg, 10 mol%), PPh_3 (14 mg, 10 mol%), potassium carbonate (232 mg, 1.68 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **23** as a pale yellow oil (168 mg, 0.47 mmol, 83%). FT-IR (ν, cm^{-1}, KBr) 3464, 2924, 1744, 1333, 1158, 932, 750, 665, 546; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.64 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.08–7.10 (m, 3H), 6.95 (m, 1H), 5.47 (t, J = 7.2 Hz, 1H), 3.77 (m, 1H), 3.65 (s, 3H), 3.53 (m, 1H), 2.90 (dd, J = 7.6, 14.6 Hz, 1H), 2.62–2.75 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ); 170.7, 143.3, 137.2, 135.3, 133.1, 129.5, 129.1, 127.3, 127.2, 126.6, 126.5, 53.5, 52.0, 43.4, 39.7, 26.9, 21.5; HRMS-ESI (m/z) $[C_{19}H_{21}NO_4S + Na]^+$ calc. 382.1084, found 382.1080.

(*R*,*S*)-2-Hydroxyethyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (24). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), 2-hydroxyethyl acrylate (39 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (2 : 3 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **24** as a pale yellow oil (83 mg, 0.21 mmol, 76%). FT-IR (ν, cm^{-1}, KBr) 2924, 1737, 1597, 1336, 1158, 1091, 756, 659, 547; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.61 (d, J = 8.4 Hz, 2H), 7.06–7.15 (m, 5H), 6.91 (m, 1H), 5.47 (t, J = 5.9 Hz, 1H), 4.21–4.31 (m, 2H), 3.71–3.78 (m, 2H), 3.50–3.59 (m, 2H), 2.91 (ddd, J = 1.5, 8.2, 14.8 Hz, 1H), 2.78 (dd, J = 5.7, 14.8 Hz, 1H), 2.60–2.65 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 170.0, 143.2, 137.1, 135.2, 133.0, 129.5, 129.0, 127.2, 127.1, 126.7, 126.6, 126.4, 62.5, 53.4, 43.3, 39.6, 26.7, 21.4; HRMS-ESI (m/z) $[C_{20}H_{23}NO_5S + Na]^+$ calc. 412.1189, found 412.1178.

(*R*,*S*)-2-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (25). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), acrylonitrile (18 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **25** as a pale yellow oil (75 mg, 0.23 mmol, 82%). FT-IR (ν, cm^{-1}, KBr) 2249, 1652, 1401, 1162, 1006, 862, 702, 548; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, J = 8.4 Hz, 2H), 7.13–7.22 (m, 5H), 7.07 (m, 1H), 5.17 (t, J = 5.7 Hz, 1H), 3.64–3.74 (m, 1H), 3.48–3.57 (m, 1H), 2.98 (dd, J = 4.0, 5.9 Hz, 2H), 2.64–2.92 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 144.1, 135.8, 134.1, 132.7, 130.0, 129.2, 128.2, 127.4, 127.1, 126.9, 117.3, 52.8, 41.1, 28.0, 27.7, 21.6; HRMS-ESI (m/z) $[C_{18}H_{18}N_2O_2S - H]^-$ calc. 325.1016, found 325.1009.

(*R*,*S*)-1-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (26). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), 3-buten-2-one (24 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **26** as a pale yellow oil (76 mg, 0.22 mmol, 79%). FT-IR (ν, cm^{-1}, KBr) 3412, 2924, 1713, 1597, 1335, 1159, 1091, 758, 663, 550; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.63 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.07–7.09 (m, 3H), 6.94 (m, 1H), 5.50 (t, J = 6.2 Hz, 1H), 3.67–3.74 (m, 1H), 3.46–3.56 (m, 1H), 3.05 (dd, J = 5.9, 16 Hz, 1H), 2.82 (dd, J = 6.4, 16 Hz, 1H), 2.64–2.69 (m, 2H), 2.32 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 205.4, 143.4, 136.7, 136.2, 132.8, 129.5, 128.8, 127.2, 127.0, 126.7, 126.6, 52.7, 52.1, 40.1, 30.4, 27.2, 21.5; HRMS-ESI (m/z) $[C_{19}H_{21}NO_3S + Na]^+$ calc. 366.1134, found 366.1135.

***N*-(2-Bromobenzyl)-*p*-toluenesulfonamide (30).** To a cooled solution (0 °C) of 2-bromobenzylamine hydrochloride (400 mg, 1.80 mmol) and triethylamine (401 mg, 3.96 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (378 mg, 1.98 mmol)

in one portion. The reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was then washed with HCl (1 M, 2 × 10 mL), NaOH (aq. 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford benzylamine **30** as a colorless oil (610 mg, 1.79 mmol, 99%). FT-IR (ν, cm^{-1}, KBr) 3087, 1622, 1159, 785, 667; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 1.2, 7.9 Hz, 1H), 7.19–7.30 (m, 4H), 7.07 (dt, J = 1.7, 7.7 Hz, 1H), 5.11 (brt, J = 5.9 Hz, 1H), 4.21 (d, J = 6.2 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 143.5, 136.9, 135.5, 132.8, 130.5, 129.6, 129.5, 127.7, 127.1, 123.5, 47.5, 21.5; HRMS-ESI (m/z) $[C_{14}H_{14}BrNO_2S - H]^-$ calc. 337.9856, found 337.9862.

General procedure B for isoindoline formation

A sealed tube containing a 2-bromobenzylamine **30** (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), triethylamine (3.0 equiv.) and alkene (1.2 equiv.) in DMF was flushed with argon and then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-Butyl 2-(2-tosylisoindolin-1-yl)acetate (31). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), butyl acrylate (45 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded isoindoline **31** as a pale yellow oil (86 mg, 0.22 mmol, 77%). FT-IR (ν, cm^{-1}, KBr) 3444, 2960, 1731, 1348, 1164, 1095, 666, 553; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.18–7.27 (m, 5H), 7.10–7.13 (m, 1H), 5.27 (m, J = 3.0, 3.7 Hz, 1H), 4.73(dd, J = 2.5, 13.8 Hz, 1H), 4.53 (d, J = 13.8 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.30 (dd, J = 3.9, 16.5 Hz, 1H), 2.86 (dd, J = 7.9, 16.5 Hz, 1H), 2.36 (s, 3H), 1.53–1.63 (m, 2H), 1.23–1.40 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.0, 143.7, 139.6, 135.5, 134.0, 129.8, 128.1, 127.9, 127.6, 122.7, 122.4, 64.6, 62.1, 53.9, 42.8, 30.6, 21.5, 19.1, 13.7; HRMS-ESI (m/z) $[C_{21}H_{25}NO_4S + Na]^+$ calc. 410.1397, found 410.1380.

(*R*,*S*)-2-Hydroxyethyl 2-(2-tosylisoindolin-1-yl)acetate (35). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), 2-hydroxyethyl acrylate (40 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (2 : 3 EtOAc : pet. sp.) afforded isoindoline **35** as a pale yellow oil (91 mg, 0.24 mmol, 84%). FT-IR (ν, cm^{-1}, KBr) 3523, 2924, 1732, 1343, 1162, 1094, 754, 666, 555; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, J = 8.2 Hz, 2H), 7.19–7.28 (m, 5H), 7.09–7.16 (m, 1H), 5.31 (m, 1H), 4.73 (dd, J = 2.5, 14.1 Hz, 1H), 4.50 (d, J = 13.8 Hz, 1H), 4.32 (m, 1H), 4.19 (m, 1H), 3.81 (m, 2H), 3.17 (dd, J = 4.9, 15.8 Hz, 1H), 2.99 (dd, J = 5.9, 16.0 Hz, 1H), 2.36 (s, 3H), 2.33 (brt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.1, 144.0, 139.3, 135.5, 133.8, 129.9, 128.3, 128.0, 127.6, 122.6, 122.5, 66.6, 62.3, 61.0, 53.9, 43.0, 21.5; HRMS-ESI (m/z) $[C_{19}H_{21}NO_5S + Na]^+$ calc. 398.1033, found 398.1024.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetamide (36). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), acrylamide (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 1 EtOAc : pet. sp.) afforded isoindoline **36** as a pale yellow oil (68 mg, 0.21 mmol, 71%). FT-IR (ν, cm^{-1}, KBr) 3419, 2924, 1682, 1330, 1162, 1093, 667; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.18–7.29 (m, 5H), 7.10–7.14 (m, 1H), 5.86 (brs, 1H), 5.40 (brs, 1H), 5.18 (m, J = 3.2, 3.9 Hz, 1H), 4.73 (dd, J = 2.0, 13.8 Hz, 1H), 4.53 (d, J = 13.8 Hz, 1H), 3.15 (dd, J = 3.7, 15.0 Hz, 1H), 2.90 (dd, J = 7.1, 15.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 172.0, 144.2, 139.2, 135.0, 133.2, 130.1, 128.3, 128.2, 127.8, 123.3, 122.4, 62.6, 54.2, 43.7, 21.6; HRMS-ESI (m/z) $[C_{17}H_{18}N_2O_3S + H]^+$ calc. 331.1111, found 331.1126.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetonitrile (37). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), acrylonitrile (18 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 6 EtOAc : pet. sp.) afforded isoindoline **37** as a pale yellow oil (62 mg, 0.20 mmol, 68%). FT-IR (ν, cm^{-1}, KBr) 3429, 2361, 2254, 1352, 1350, 1160, 756, 664, 559; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.76 (d, J = 8.2 Hz, 2H), 7.18–7.33 (m, 6H), 5.11 (m, 1H), 4.80 (dd, J = 2.7, 13.8 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 3.16 (s, 1H), 3.14 (d, J = 1.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 144.4, 136.7, 135.8, 133.8, 130.1, 129.1, 128.4, 127.5, 122.9, 122.6, 116.7, 61.5, 53.9, 26.9, 21.5; HRMS-ESI (m/z) $[C_{17}H_{16}N_2O_2S + H]^+$ calc. 313.1005, found 313.1013.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetic acid (38). General procedure B was followed using 2-bromobenzylamine **30** (100 mg. 0.29 mmol), acrylic acid (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (3 : 1 EtOAc : pet. sp.) afforded isoindoline **38** as a pale yellow oil (82 mg, 0.25 mmol, 85%). FT-IR (ν, cm^{-1}, KBr) 3435 (vs), 2923, 1697, 1574, 1397, 1339, 1162, 1094, 666, 555; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.18–7.22 (m, 3H), 7.10–7.13 (m, 1H), 5.28 (m, 1H), 4.73 (dd, J = 2.2, 13.9 Hz, 1H), 4.53 (d, J = 13.9 Hz, 1H), 3.39 (dd, J = 3.9, 16.5 Hz, 1H), 2.91 (dd, J = 7.9, 16.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 176.5, 143.9, 139.2, 135.4, 133.8, 129.9, 128.3, 128.1, 127.6, 122.7, 122.5, 61.8, 53.9, 42.7, 21.5; HRMS-ESI (m/z) $[C_{17}H_{17}NO_4S + Na]^+$ calc. 354.0771, found 354.0759.

(*R*,*S*)-1-(2-Tosylisoindolin-1-yl)propan-2-one (39). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), 3-buten-2-one (24 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded isoindoline **39** as a pale yellow oil (82 mg, 0.25 mmol, 86%). FT-IR (ν, cm^{-1}, KBr) 3448, 2923, 1714, 1342, 1161, 667, 559; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.16–7.20 (m, 3H), 7.07–7.12 (m, 1H), 5.30 (m, 1H), 4.75 (dd, J = 2.4, 13.9 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 3.50 (dd, J = 3.4, 17.8 Hz, 1H), 2.99 (dd, J = 7.7, 18.0 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.5, 143.8, 140.2, 135.1, 133.5, 129.9, 128.7, 128.0, 127.7, 122.9, 122.3, 61.1, 53.9, 52.2, 30.8, 21.5; HRMS-ESI (m/z) $[C_{18}H_{19}NO_3S + Na]^+$ calc. 352.0978, found 352.0993.

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A One-Pot, Three-Component Approach to Functionalised Tetrahydroisoquinolines Using Domino Heck–aza-Michael Reactions

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Keywords: Tetrahydroisoquinoline / Multicomponent reactions / Domino reactions / Heck reaction / Aza-Michael addition / Palladium

A one-pot, three-component method incorporating a domino Heck–aza-Michael reaction has been developed for the rapid synthesis of functionalised tetrahydroisoquinolines. Following the in situ generation of an acrylamide, a domino process involving intermolecular Heck reaction and subsequent intramolecular aza-Michael addition affords tetrahydroisoquinolines bearing C1-acetamide functionality.

Introduction

In recent years, palladium-catalysed domino Heck–aza-Michael reactions have been developed for the synthesis of a range of functionalised N-heterocycles including benzofused sultams,[1] tetrahydro-β-carbolines,[2] tetrahydroisoquinolines,[2b,3] isoindolines[2b] and isoindolinones.[4] These N-heterocyclic scaffolds have been prepared by treating aryl halides with relatively cheap palladium catalysts and are somewhat limited to the range of commercially available acrylate-based starting materials. The ideal domino Heck–aza-Michael process would allow for the use of functionalised electron-deficient terminal alkenes. As such, the scope of these reactions could be dramatically improved if, in one pot, the alkene could be readily generated and then undergo the domino Heck–aza-Michael reaction.

One-pot, multicomponent processes, like domino reactions, are an efficient means of completing multiple synthetic steps without the need for purification of intermediates. Three-component domino Heck–aza-Michael reactions to date have involved variations in the domino precursor, that is, the first step of the multicomponent reaction was the preparation of the aryl halide.[1,3] However, the electron-deficient terminal alkenes employed for these three-component domino reactions have been limited to commercially available ester, carboxylic acid and ketone derivatives. Attempted domino Heck–aza-Michael processes, where the alkene employed has been generated in situ, have not been successful.[1a]

The tetrahydroisoquinoline scaffold is central to a number of naturally occurring alkaloids, some of which exhibit interesting biological activity as antitumor and antibiotic agents.[5] The C1-acetamide tetrahydroisoquinoline core (Figure 1) has also been employed in medicinal chemistry studies,[6] for example compound **1**, which was developed as a ligand for the melanocortin subtype-4 receptor.[7] Further examples include those generated as reversible inhibitors of cysteine proteases,[8] as well as bradykinin 1 antagonists for treating pain and inflammation (compound **2**, Figure 1).[9]

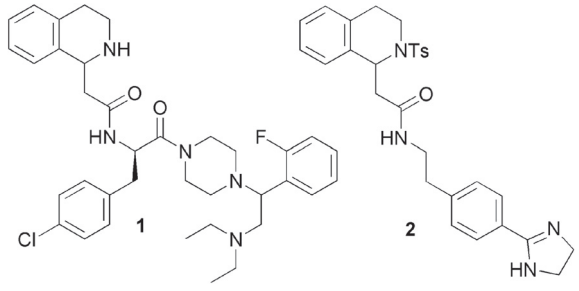

Figure 1. C1-amide substituted tetrahydroisoquinoline medical chemistry agents.

A range of synthetic strategies have been reported to access C1-substituted tetrahydroisoquinoline scaffolds.[3,10] Our group has recently discovered a palladium-catalysed domino Heck–aza-Michael reaction for the synthesis of a series of C1-substituted tetrahydroisoquinolines (Scheme 1).[2b] The domino Heck–aza-Michael process requires a catalytic system that facilitates fast Heck reaction between the domino precursor and an electron-deficient terminal alkene. Following this process aza-Michael cyclisation takes place to form the new N-heteroycle (Scheme 1).

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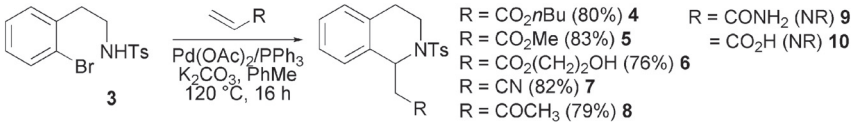
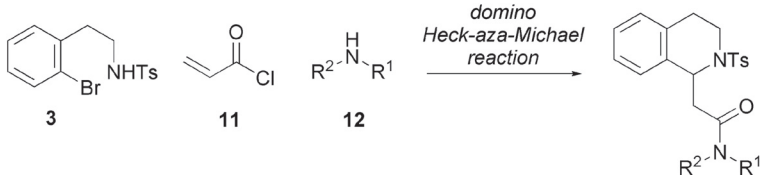


Scheme 1. Domino Heck–aza-Michael reaction to access C1-substituted tetrahydroisoquinolines.



Scheme 2. Proposed three-component domino Heck–aza-Michael reaction to access tetrahydroisoquinolines.

Using this method tetrahydroisoquinolines **4**–**8** were formed by reaction of 2-bromophenethylamine (**3**) with commercial acrylates using either the $Pd(OAc)_2/PPh_3$ or the $Pd(OAc)_2$/DavePhos in K_2CO_3 and toluene catalytic system.

This methodology allowed for the incorporation of various functionalities at R including ester, nitrile and ketone; however, neither the reaction with acrylic acid nor acrylamide was amenable (most likely due to deprotonation under the reaction conditions). As the generation of tetrahydroisoquinolines bearing C1-acetamide functionality was desirable, a modification of the original domino process was sought. To this end, a three-component domino Heck–aza-Michael process that would provide rapid and efficient access to C1-functionalised tetrahydroisoquinolines was devised (Scheme 2). Nucleophilic addition of primary or secondary amines **12** to acryloyl chloride (**11**), prior to the aforementioned domino reaction would afford a vast array of acrylamides. If acrylamide formation occurred under the same mildly basic conditions required for both the Heck and aza-Michael steps in this domino process, a sequential one-pot three-component acylation and domino Heck–aza-Michael reaction for the synthesis of tetrahydroisoquinolines was plausible.

Herein we report the first three-component domino Heck–aza-Michael reaction, for the synthesis of functionalised tetrahydroisoquinolines, where in one pot, the electron-deficient alkene is generated, then subsequently undergoes domino Heck–aza-Michael reaction.

Results and Discussion

To investigate this one-pot process, benzylamine was initially chosen as the amine nucleophile. This first reaction involved the addition of acryloyl chloride (**11**) to a solution of benzylamine, and potassium carbonate in toluene. After stirring at room temperature for 1 h, $Pd(OAc)_2$, PPh_3 and the 2-bromophenethylsulfonamide substrate **3** were added sequentially and the resultant mixture heated to 120 °C for 16 h. To our delight, a simple workup followed by flash chromatography afforded the desired *N*-benzylacetamidotetrahydroisoquinoline **13** in excellent yield (97%). (As expected, no domino product or Heck adduct was observed when the reaction was repeated by using only acryloyl chloride; attempts to also generate the tetrahydroisoquinolines in a multicomponent manner where all reagents were present from the outset, also failed.) Following this initial success, a range of amines, varying in nucleophilic character were subsequently used in this one-pot process. The amines, including alkyl primary amines (Table 1, Entries 1–7), arylamines (Table 1, Entries 8–10), acyclic secondary amines (Table 1, Entries 11), cyclic secondary amines (Table 1, Entries 12–13), and amino acids (Table 1, entries 14–16), were tested to explore the scope of this reaction sequence.

The first attempt with tryptamine only resulted in trace amounts of the desired tetrahydroisoquinoline. This lack of reactivity appeared to be due to the insolubility of either the initial amine or corresponding acrylamide in toluene. To overcome this, a few drops of DMF were added to the reaction mixture following addition of the amine nucleophile. This approach quickly proved successful with the second attempt using tryptamine to afford tetrahydroisoquinoline **14** in 92% yield (Entry 2, Table 1). During the synthesis of a series of C1-acetamide substituted tetrahydroisoquinolines, a number of other amines also required the addition of DMF to improve solubility.

The one-pot, three-component domino Heck–aza-Michael process proved to be quite general, with high yields (up to 97%) of the C1-acetamide tetrahydroisoquinolines observed when alkylamines, arylamines, secondary amines and amino acids were used. Several of the tetrahydroisoquinolines accessed by using this methodology (**14**, **26**, **27**) resemble a number of the aforementioned medicinal chemistry agents (Figure 1). The only limiting factor in this process appeared to be solubility of the amine and corresponding acrylamide.

For the domino process employing 2-nitrobenzylamine hydrochloride (Table 1, Entry 7), the in situ deprotection of the 2-nitrobenzyl group occurred to afford tetrahydroisoquinoline **19**. The 2-nitrobenzyl group is readily cleaved under photolytic conditions in polar solvents (254–365 nm),[11] As this reaction was carried out in toluene in a dark fumehood, deprotection of the 2-nitrobenzyl group under our reaction conditions was unexpected. However, the basic

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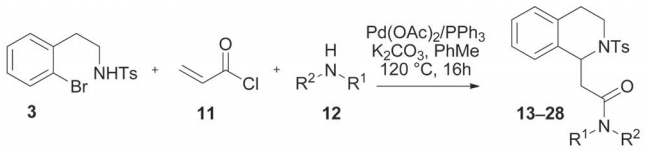
Table 1. Formation of functionalised tetrahydroisoquinolines by using a three-component domino Heck–aza-Michael reaction.



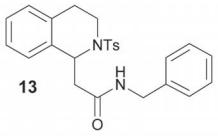
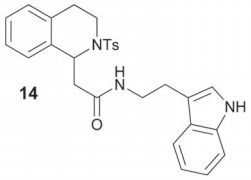
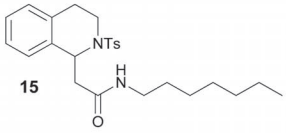
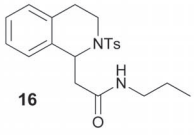
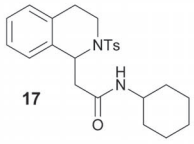
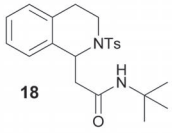
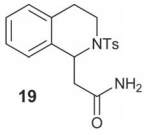
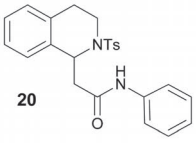
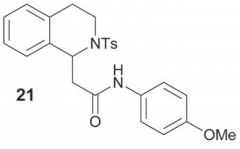
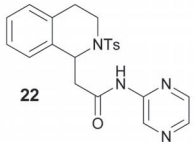
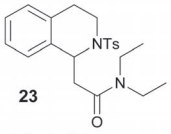
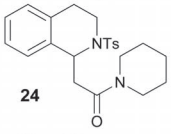
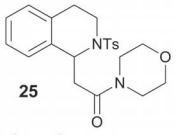
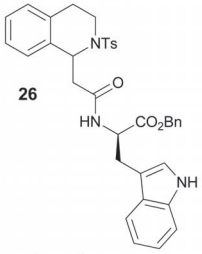
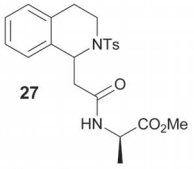
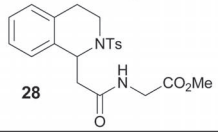
Entry	Amine	Product	Isolated yield [%]
1	benzylamine	 13	97
2	tryptamine[a]	 14	92
3	*n*-heptylamine	 15	89
4	propylamine	 16	42
5	cyclohexylamine	 17	77
6	*tert*-butylamine	 18	93
7	2-nitrobenzylamine hydrochloride[a]	 19	32[b]
8	aniline	 20	83
9	*p*-anisidine	 21	79
10	2-aminopyrazine[a]	 22	28

Table 1. *(Continued)*.

Entry	Amine	Product	Isolated yield [%]
11	diethylamine	 23	57
12	piperidine	 24	88
13	morpholine	 25	78
14	L-tryptophan benzyl ester hydrochloride[a]	 26	96[c]
15	L-alanine methyl ester hydrochloride[a]	 27	54[c]
16	glycine methyl ester hydrochloride[a]	 28	72

[a] A few drops of DMF were added to aid in amine solubility. [b] In situ deprotection of the 2-nitrobenzyl group occurred during reaction, and the product isolated was the tetrahydroisoquinoline acetamide in 32% yield. [c] When chiral amino acids were subject to this domino process (Entries 14–15, Table 1) the resultant tetrahydroisoquinoline was isolated as a mixture of diastereomers in a ratio of 1:1.

conditions and high temperatures employed in this reaction sequence proved sufficient to cleave the 2-nitrobenzyl group.

Multicomponent reactions using a chiral amino acid precursor (Table 1, Entries 14, 15) were carried out to identify whether a stereoselective variant of this one-pot process was achievable. The introduction of a stereogenic centre at the C1-position of the newly formed tetrahydroisoquinoline was monitored by NMR spectroscopy. Unfortunately, in these particular cases where a chiral amino acid was used, the products were determined to be present as a 1:1 mixture of diastereomers, inseparable by standard column chromatography. As such, the presence of a stereocentre in the acrylamide R moiety had no significant induction effects on the stereochemistry at the C1-position of the tetrahydroisoquinoline heterocycle formed during the domino process.

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Conclusions

A domino Heck–aza-Michael process has been developed where in one pot, the electron-deficient alkene generated by reaction between acryloyl chloride and an amine, undergoes domino Heck–aza-Michael reaction to afford a series of C1-acetamide tetrahydroisoquinolines. This is the first example of a domino Heck–aza-Michael reaction that allows the electron-deficient terminal alkene to be readily varied in a one-pot process. This multicomponent domino reaction proved to be quite general, by using a range of primary and secondary amines to afford functionalised tetrahydroisoquinolines, in moderate to excellent yields (28–97%). This one-pot process, when employed in a medicinal chemistry setting would facilitate the rapid generation of compound libraries.

Supporting Information (see footnote on the first page of this article): Detailed description of all experimental procedures and analytical data for all compounds.

[1] a) A. Rolfe, K. Young, P. R. Hanson, *Eur. J. Org. Chem.* **2008**, 5254; b) A. Rolfe, K. Young, K. Volp, F. Schoenen, B. Neuenswander, G. H. Lushington, P. R. Hanson, *J. Comb. Chem.* **2009**, *11*, 732.

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