Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

Calver A. Main MSci (Hons)

A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy.

UNIVERSITY *of* GLASGOW

Department of Chemistry
University of Glasgow
Glasgow G12 8QQ

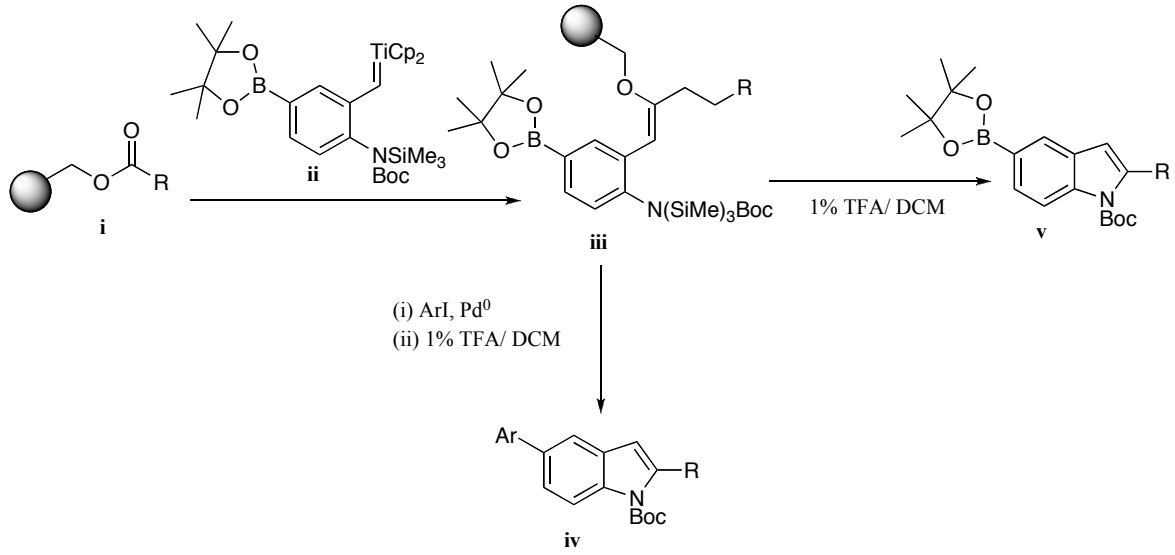
April 2008

For my gorgeous Pamela

(…you don't have to read it)

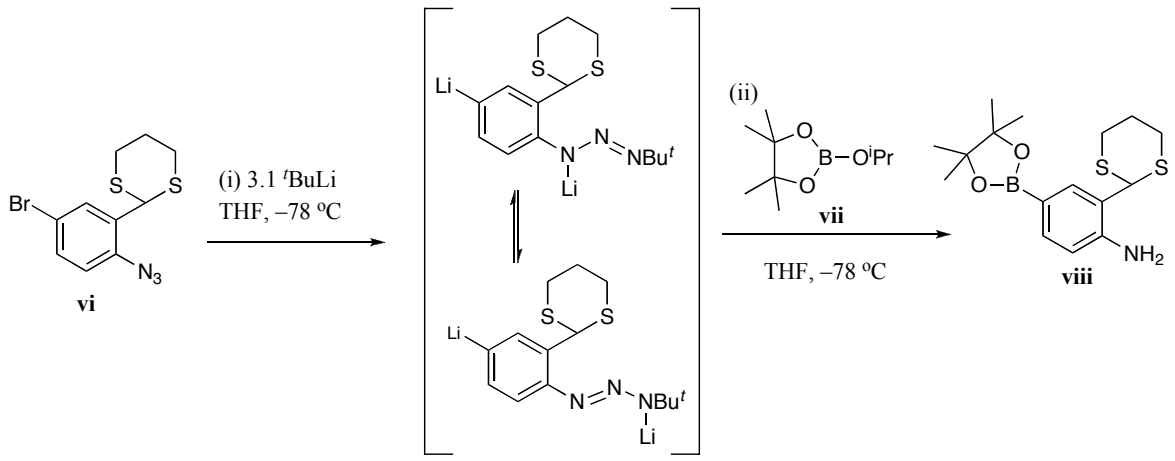
Abstract

A new synthetic strategy for the preparation of a 96-member library of 2,5-disubstituted indoles involving traceless cleavage from resin is presented.

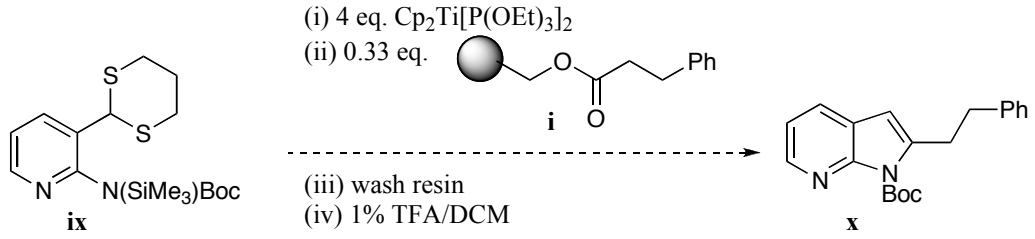


A boronate-bearing titanium alkylidene **ii** was prepared and used to convert 8 resin-bound esters **i** into immobilised enol ethers **iii**. Cleavage from resin in mild acid with concomitant cyclisation yielded boronate-bearing indoles **v**. Capitalising on the immobilised boronate functionality in enol ethers **iii**, Suzuki cross-coupling reactions were performed with 12 aryl iodides to give a 96-member library after cleavage from resin with mild acid. 79 members of the library were confirmed to be 2,5-disubstituted indoles **iv**.

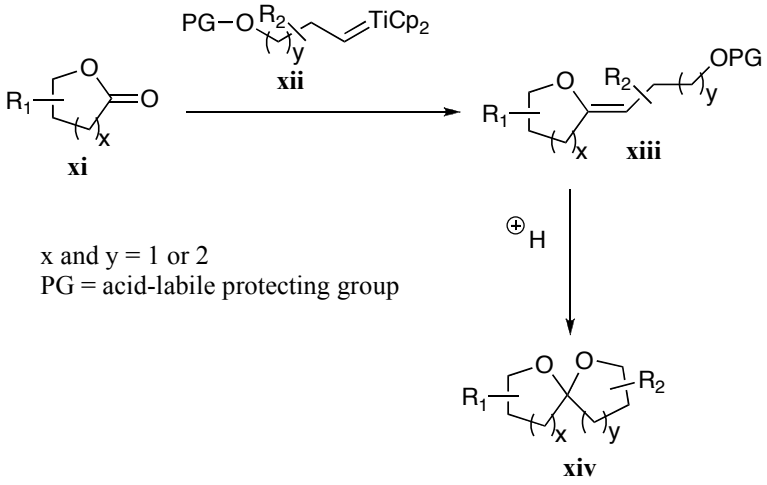
Also reported is the use of tertiary butyllithium and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **vii** to convert an aryl bromide **vi** into an arylboronate **viii** in the presence of a dithiane, with simultaneous reduction of an aryl azide to an amine.



In a similar route, we synthesised dithiane **ix** for the attempted conversion of resin-bound esters **i** into functionalised 7-azaindoles **x** after cleavage from resin. Further investigation with a different *ortho*-nitrogen protecting group may yet prove successful.



Alkylidenation of lactones **xi** with functionalized titanium carbenoid reagents **xii** followed by acid-induced cyclisation of the resulting enol ethers **xiii** constitutes a new method for the preparation of [4.4], [4.5], and [5.5] spiroacetals (1,6-dioxaspiro[4.4]nonanes, 1,6-dioxaspiro[4.5]decanes and 1,7-dioxaspiro[5.5]undecanes) **xiv**. The titanium carbenoids **xii** are easily generated from readily available thioacetals.



Acknowledgements

I am grateful to the Loudon bequest (University of Glasgow) and GlaxoSmithKline for financial support of this work.

I would like to take this opportunity to express my gratitude and thanks to Dr Richard Hartley a constant source of inspiration, boundless enthusiasm and most importantly for believing in my capabilities. I would also like to thank Dr Shahzad Rahman, for looking after me during my time with GlaxoSmithKline – Harlow, and my second supervisor Dr Andrei Malkov for reading my reports and providing positive feedback.

Technical support was very much appreciated and my thanks go to Dr David Adams (NMR), Mr Jim Tweedie and Ms Isabel Freer (Mass spec) and Ian Davidson (Mass spec – GSK). Thanks also to Dr Louis Farrugia for his crystallography expertise.

I would like also to express my gratitude to all members of the Hartley team past and present, my colleague Dr Louis Adriaenssens, my long suffering fumehood partner Ms Caroline Quin and the Takeda crew: Drs Guthrie, McLeod, McKiernan, Roberts, Petersson, Gibson and Austin.

My thanks go to the Sutherland group the "other side" of the Loudon lab, especially Drs Andy S and J, and also Nicola Jobson, the badger mug is a constant source of inspiration.

My thanks also go to everyone who welcomed me to GSK – Harlow; Mel Crawshaw, "The Frenchies", Shazhad, Graham, Neville and Andy and not forgetting my former colleagues at KemFine-UK; James Garrity and James Hitchin.

Finally a "Calver" size hug to all my friends (especially Guilherme), and family who whilst not knowing exactly what I have been doing for the last three or four years have always provided encouragement albeit mostly in forms of "liquid refreshment".

Declaration

This thesis represents the original work of Calver Amos Main unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow in the Loudon and Henderson laboratories during the period October 2004 to September 2007, under the supervision of Dr Richard Hartley. Additional PhD traineeship and research was also carried out at GlaxoSmithKline laboratories, Harlow, during the period April 2006 to June 2006, under the supervision Dr Shahzad Rahman and Dr Richard Hartley. No part of this thesis has been previously submitted for a degree at the University of Glasgow or any other University. Portions of the work described herein have been published elsewhere as listed below.

Richard C. Hartley, Jianfeng Li, Calver A. Main and Gordon J. McKieran. *Tetrahedron* **2007**, *63*, 4825–4864.

Louis J. Farrugia, Richard C. Hartley, Calver A. Main and Shahzad S. Rahman. *Acta Cryst.* **2007**, *E63*, 2540-2541.

Calver A. Main, Hanna M. Petersson, Richard C. Hartley, and Shahzad S. Rahman. *Tetrahedron* **2008**, *64*, 901–914.

Calver A. Main, Richard C. Hartley, and Shahzad S. Rahman. *Tetrahedron Letters* **2008**, *49*, 4771-4774.

Abbreviations

Å	Angstrom
aa	amino acid
Ac	acetyl
AcOH	acetic acid
a.m.u.	atomic mass unit
aq.	aqueous
Ar	aryl
atm	atmosphere (pressure)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbanoyl
Bu	butyl
t-Bu/ *tert*-Bu	tertiary butyl
b.p.	boiling point
bs	broad singlet (NMR spectroscopy)
°C	degrees centigrade
cat.	catalytic
CI	chemical ionisation
cm	centimetre
conc.	concentrated
Cp	cyclopentadienyl anion
Cp'	pentamethylcyclopentadienyl anion
Cy	cyclohexyl
d	doublet (NMR spectroscopy)
dba	dibenzylideneacetone
DBU	1,8-diazaundec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DIEA	*N*,*N*-diisopropylethylamine
DIPEA	*N*,*N*-diisopropylethylenediamine
DMAP	4-*N*,*N*-(dimethylamino)pyridine
DMF	dimethylformamide
2,2-DMP	2,2-diazabicyclo[5,4,0]undec-7-ene
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EI	electron impact
eq.	equivalent(s)
FAB	fast atom bombardment
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infrared
LDA	lithium diisopropylamide
Ln	ligand
LVT	low valent titanium
M	molarity
m	multiplet (NMR spectroscopy)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
meq	milliequivalents
MHz	megahertz
MOM	methoxymethyl
mL	millilitre
min(s)	minute(s)
mol	mole(s)
m.p.	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
Py	pyridine
PPTS	pyridinium *para*-toluenesulfonate
quant.	quantitative
q	quartet (NMR spectroscopy)
quin	quintet (NMR spectroscopy)
Rac	racemic

Rt	retention time
RT	room temperature
s	singlet (NMR spectroscopy)
SAR	structure-activity relationship
SET	single electron transfer
SM	starting material
SPS	solid-phase synthesis
t	triplet (NMR spectroscopy)
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (*para*-toluenesulfonyl)
TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
Vis	visible light

Table of Contents

CHAPTER 1 – Drug Discovery

Created as an alliance between chemistry and pharmacology, drug research is not older than a century; driven by chemistry and increasingly guided by pharmacology, drug research has contributed more to the progress of medicine than any other scientific factor.[1]

As chemistry grew, with pioneering discoveries, the formulated structure of aromaticity by August Kekulé brought with it decisive research into coal-tar derivatives, particularly dyes. In doing so, the evolution of dye chemistry formed the foundation of medicinal chemistry.[2] The selective affinities of dyes for biological tissues discovered by Paul Ehrlich, led him to postulate the existence of "chemoreceptors". He later argued that certain chemoreceptors on microorganisms, parasites and cancer cells would differ from analogous structures in the host tissue, and these differences could be exploited therapeutically. The idea of receptors acting as selective binding sites for chemotherapeutic agents was born. A more functional concept was introduced from pharmacology by J. Langley; of receptors serving as a "switch" that receives and generates specific signals, which could be turned off by antagonists or turned on by agonists.[3] However, the institutions that had supported these seminal efforts, pharmacies, university laboratories or the dye companies, did not represent suitable platforms for emerging drug research. New institutes, supporting interdisciplinary drug research and development grew out of pharmacies or were founded as pharmaceutical divisions in chemical dye companies. A new way of finding, characterising and developing medicines led to the formation of a new industry.[1]

The advent of genomic sciences, rapid DNA sequencing, combinatorial chemistry, cell-based assays and high throughput screening (HTS) has led to a "new" concept of drug discovery. Large numbers of theoretical targets are incorporated into *in vitro* or cell-based assays and exposed to even larger numbers of compounds, representing numerous variations on a chemical theme or conversely fewer variations on a greater number of themes in high throughput configurations. The total number of all possible low molecular weight organic compounds has been calculated to be 10^{30} – 10^{200},[4] the consideration of which, brought the concept of chemical space, a description of all possible "drug-like" structures in relation to each other. The hope was that through experimental design the discovery of "hit" compounds, *i.e.* compounds that elicit a positive response in a particular assay, would be made easier. These hits would then give rise to leads, *i.e.* compounds that continue to show the initial response in more complex models (*in vivo* in rats) in a dose-dependant manner. Although some pharmaceutical companies have acknowledged that

HTS has resulted in a large number of hits, some industry leaders have been left disappointed that very few hits turn into leads.[5] Recent designs of combinatorial libraries have centred on generating a high degree of structural diversity. However, the design and sampling of compounds is not only being guided by including structural diversity but by the inclusion of descriptors of biological activity. The discovery of these biological descriptors can come from information gained in previous high-throughput screening programmes.[6] Including structural motifs that have been shown to have an increased percentage of hits in various assays compared to other structural motifs, focuses the synthesis in the direction of structures most likely to interact with biological targets.

1.1 Diversity Orientated Synthesis (DOS)

The production of many libraries of small molecules is needed to explore chemical space. Diversity Orientated Synthesis (DOS) explores chemical space by producing libraries of structurally diverse compounds in a highly automated process, more often than not, *via* solid phase synthesis (SPS).[7] Drug discovery programmes investigate the ability of these small molecules to bind to protein targets in the hope of discovering new medicines. An additional directive for DOS is the synthesis of a collection of small molecules capable of perturbing any disease-related biological pathway, leading eventually to the identification of therapeutic protein targets capable of being modulated by small molecules.[8]

The application of SPS allows not only the DOS of collections of structurally diverse compounds but also single target compounds or collections of related compounds.[9] If the structure of a protein target is known and/ or a structure-activity relationship (SAR) for compounds binding to it have been determined, Target Orientated Synthesis (TOS) utilises structure-based rational design to create “focused libraries”. This is where collections of compounds with common structural features that facilitate binding to pre-selected targets are synthesised.[10] In many cases, there is no pre-existing SAR and the structure or identity of a specific receptor or enzyme is not known or the information is not detailed enough to allow a directed synthesis. In these scenarios DOS is used in efforts to identify simultaneously therapeutic protein targets and their small molecule regulators.[7]

One of the goals of DOS is to produce small molecules with diverse structures to populate defined coordinates in chemical space. It is by no means certain to what extent molecular diversity, corresponds to diversity as “recognised” by a biological target such as receptor

or enzyme. Increasingly, the direction of DOS is being guided by the incorporation of descriptors of biological activity.[1]

Medicinal chemists have noticed that common pharmacophores exist throughout diverse drug classes, the recognition of the presence of these reoccurring structural units in many receptor ligands led to the term "privileged structures".[11] Defined by Evans *et al*. as "a single molecular framework to produce ligands for diverse receptors" or in essence descriptors of biological activity.[12] Whilst many groups took their initial lead from pharmacophores or structural units found in successful drugs, other groups sourced from nature's collection of secondary metabolites that because of their origin must interact with biological machinery.

The incorporation of privileged structures, with their inherent affinity for diverse biological receptors, may allow a library based upon one core scaffold, screened against a variety of receptors to yield several active compounds.[11]

1.2 Privileged structure directed DOS

Privileged structures and substructures represent an ideal source of potential lead compounds. Several groups have used DOS based on privileged structures to produce libraries of small biologically potent molecules.[13] After developing a synthetic route for the synthesis of a number of 1,4-benzodiazepin-2-ones **1**, Bunin *et al.* synthesised a small diversity orientated library of 192 molecules based on the 1,4-benodiazepin-2-one core. Screening these compounds against the cholecystokinin-A, receptor identified a number of active compounds. Subsequently, a larger library with more diversity based around the 1,4-benzodiazepin-2-one privileged structure core was synthesised and screened against a number of target receptors and enzymes. Inhibitors of pp60 tyrosine kinase and ligands capable of blocking an autoimmune DNA antibody interaction, implicated in systemic lupus erythematosus, were identified [14] (Figure 1).

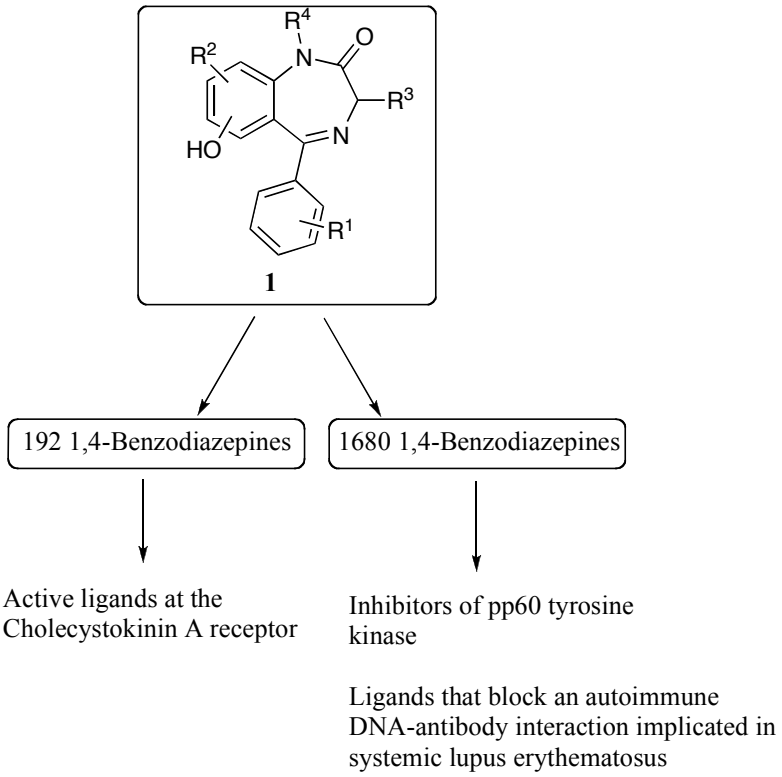
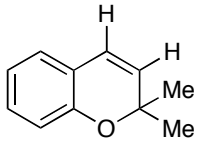


Figure 1

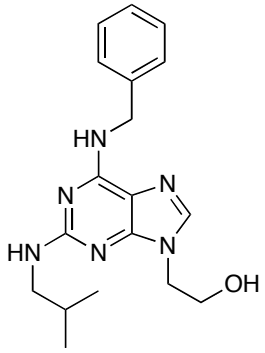
Nicolaou and colleagues used a benzopyran scaffold **2** in a solid-phase and solution-phase DOS to a 10,000 membered library of biologically relevant, natural product-like, small organic molecules based upon privileged structures.[15] This work was achieved in order to contribute to screening programmes against a number of biological targets (Figure 2).



Benzopyran scaffold **2**

Figure 2

Schultz and co-workers, made use of the purine privileged structure scaffold in a DOS, from which 348 purine derivatives were prepared. Evaluation of the library carried out using a microtiter-based solution-phase assay for protein kinase activity identified a number of Cyclin Dependent Kinase (CDK) inhibitors.[16] CDK enzymes and their regulatory proteins play a significant role in the development of human tumours. The most potent CDK inhibitor **3** from the library had an IC_{50} (600 nM), more than an order of magnitude lower than that measured for oloumucine (7 μM), which had been observed as the most effective inhibitor up until that point (Figure 3).



Purine derivative **3**

Figure 3

There has therefore been a significant interest in the identification of new privileged structures, with many groups utilizing computational procedures and models to identify them. A recent example is RECAP a computational technique that has been developed to identify privileged structures from biologically active molecules for use in library development.[17]

The DOS of libraries based on privileged structures should continue to allow the rapid discovery of biologically active compounds across a broad range of therapeutic areas.

CHAPTER 2 – Solid-Phase Synthesis (SPS)

Solid-phase organic synthesis, adapted from the original solid-phase peptide synthesis, serves as the linchpin in DOS allowing the preparation of large numbers of diverse small molecules for screening.[7]

2.1 Background

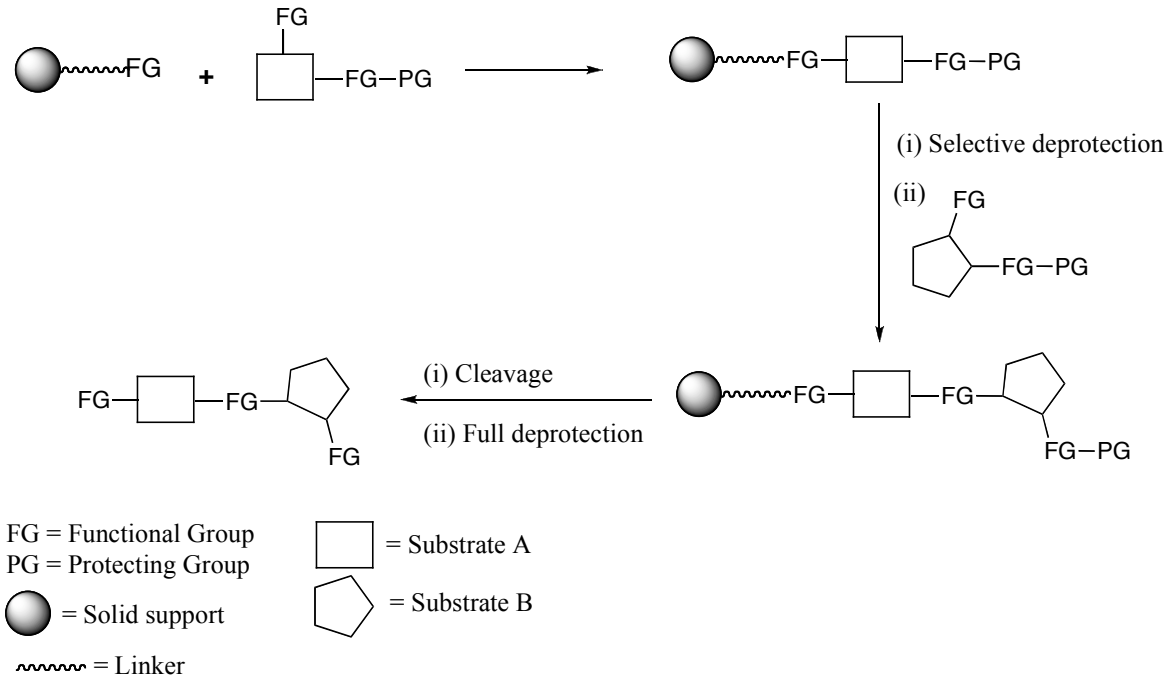
In 1963, Merrifield described the use of a solid support as a means of overcoming the technical challenge of performing multiple amide bond couplings to yield long chain polypeptides.[18] Solid-phase synthesis (SPS) was soon adapted to include the preparation of non-peptidic small molecules; in doing so it evolved into solid-phase parallel synthesis, also known as combinatorial synthesis. Combinatorial synthesis, employed by universities and pharmaceutical companies, provides a staggering increase in the ability of organic synthesis to produce collections/ libraries of small molecules.[19]

The successful use of solid supports for organic synthesis relies on three interconnected requirements, although in many cases the last requirement is not always a necessity (Scheme 1).

(i) The solid support (resin): a cross-linked insoluble polymeric material that is inert to the conditions of synthesis.

(ii) Linker: a means of linking the substrate to the solid support, capable of tolerating a variety of reaction conditions and permitting selective cleavage of some or all of the product from the solid support, during synthesis for analysis of the extent of the reaction(s) and ultimately to give the final product of interest.

(iii) Protecting group: a chemical protection strategy to allow selective protection and deprotection of reactive groups. If no protecting group chemistry is required, the exposed reacting groups form the target compound.



Scheme 1

The substrate is immobilised by attachment to the solid support (resin) *via* the linker, allowing coupling reagents to be added in high molar excess, driving the reaction to completion. By-products and unreacted reagents are removed by simply washing the resin-bound product, removing the need for costly column chromatography.

The immobilised resin-bound substrates can be contained within porous polypropylene reactors (Kans) that subsequently each receive a unique set of coupling reagents. The Kans are then pooled, separated by radiotag-directed sorting and further derivatised by coupling to different reagents, this results in large collections of resin-bound compounds with a unique predetermined compound within each Kan.[20] This "one Kan, one compound" strategy produces libraries consisting of thousands of separate individual compounds for screening.[21]

The features of SPS must not only allow for the automated production of large numbers of compounds but must also allow these compounds to be obtained in a purity of greater than 90 % to ensure that, when screening in a bioassay, any biological activity can be directly attributed to the library member and is not due to an impurity. The greater the purity of the compound that is released from resin, the greater the ease of purification before testing.

2.2 Linkers

Amongst other considerations, success of a SPS hinges upon the robustness of the linker. The group that joins the substrate to resin must fulfil a number of criteria based on the type of chemical conditions required in the synthesis. The linker must not be affected by the chemistry used to modify or extend the attached substrate, it must remain dormant until the point of cleavage. The cleavage step should proceed under conditions that do not damage or compromise the integrity of the target molecule released from resin. Cleavage should be in near quantitative yield. Ideally, the linker should upon cleavage leave no memory or trace of its presence in the released library member or should incorporate itself as desired functionality within the final compounds (Chapter 2.2.2).

Therefore, careful choice of linker is required when planning a SPS, as successful SPS is often based on the correct selection of linker. With numerous linkers reported in the literature, there are many to choose from.[22] The selection of linkers discussed in the following section relate most closely to my own work (Chapters 6 and 7).

2.2.1 Acid-Labile Linkers

The first linking group employed in SPS came from the work by Merrifield. Merrifield resin **4** is a cross-linked copolymer of styrene, functionalised with a chloromethyl group (Figure 4).[18]

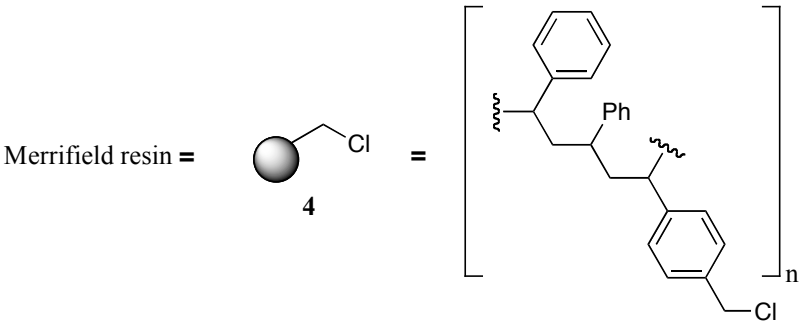
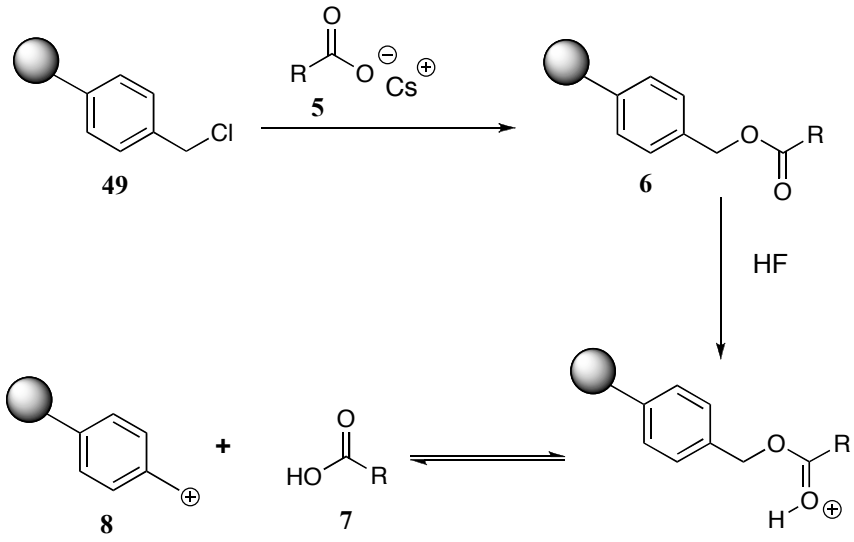


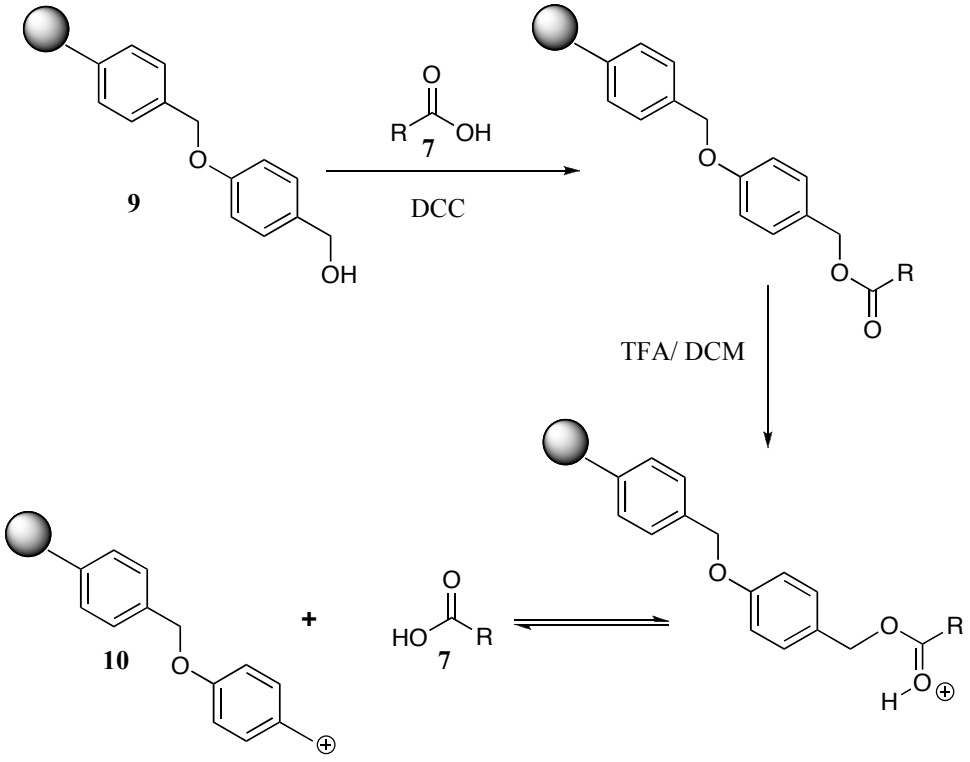
Figure 4

Carboxylic acids are attached to Merrifield resin **4**, *via* their corresponding caesium carboxylate salts **5** in DMF, by nucleophilic displacement of the chloride. Cleavage, to regenerate the carboxylic acid **7** is usually achieved with hydrofluoric acid (HF). The lability of the linker depends directly upon the relative stability of the cation formed on cleavage. The cation **8** formed in the case of Merrifield linker **6** is relatively unstable and thus requires strong acid such as HF. The problem of using HF, apart from the obvious handling dangers, is that few compounds will tolerate these conditions (Scheme 2).



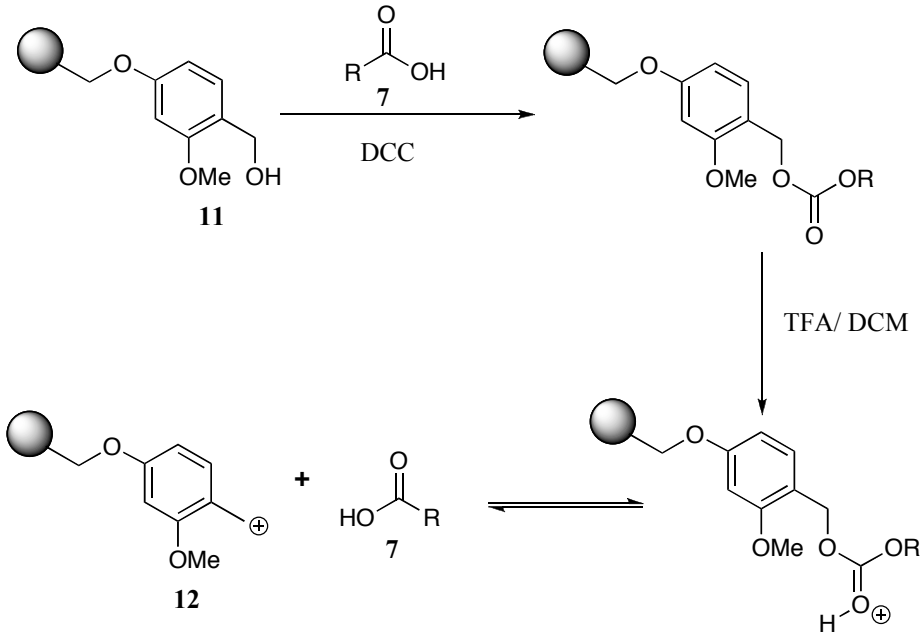
Scheme 2

In order to achieve cleavage under milder conditions, the cation produced upon cleavage must be more stabilised. A second major class of linker also used for carboxylic acid came from the Wang group[23] (Scheme 3). The Wang linker is generally attached to cross-linked polystyrene, TentaGel or polyacrylamide to form the corresponding Wang resin **9**. Designed purposefully to be more acid-labile than Merrifield resin, the resulting benzylic cation **10** formed upon cleavage is resonance stabilized allowing for milder cleavage conditions (50 % trifluoroacetic acid in DCM).[24]



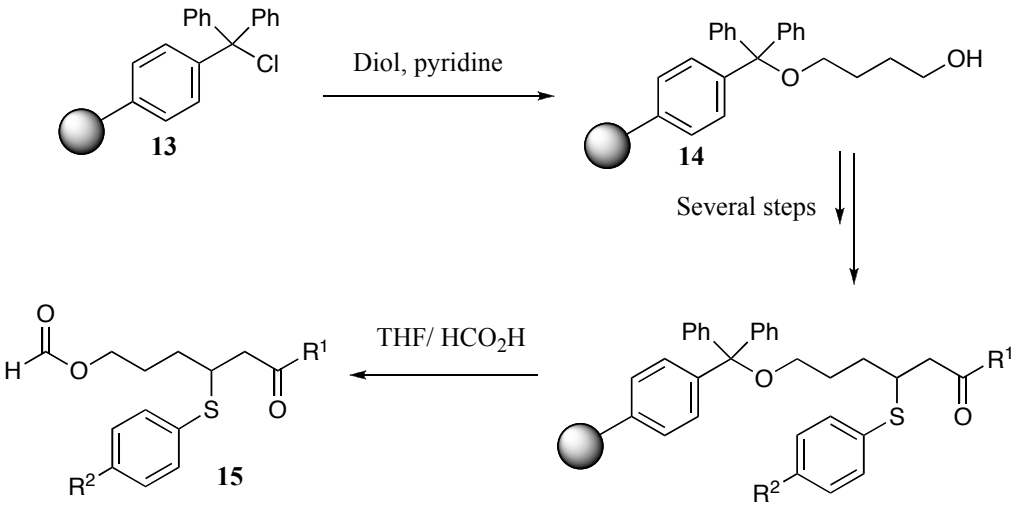
Scheme 3

Increased sensitivity to acid is found in the SASRIN (Super Acid Sensitive Resin) resin **11**. SASRIN, based on Wang resin **9**, has the addition of a *ortho* methoxy unit which contributes to greater cation stabilisation **12** and thus higher lability, allowing for even milder cleavage conditions, only 0.5 % to 1 % TFA (trifluoroacetic acid) in DCM (Scheme 4).[25]



Scheme 4

Another good acid-liable linker is the trityl group. The trityl group is a very good protecting group for heteroatoms, and as such can be incorporated as linker **13** between resin and corresponding heteroatom **14**, as the group is acid liable, cleavage can be affected in mild acid. The trityl group has been used in this manner to anchor alcohols in the synthesis of a library of β-mercaptoketones **15** (Scheme 5).[26]



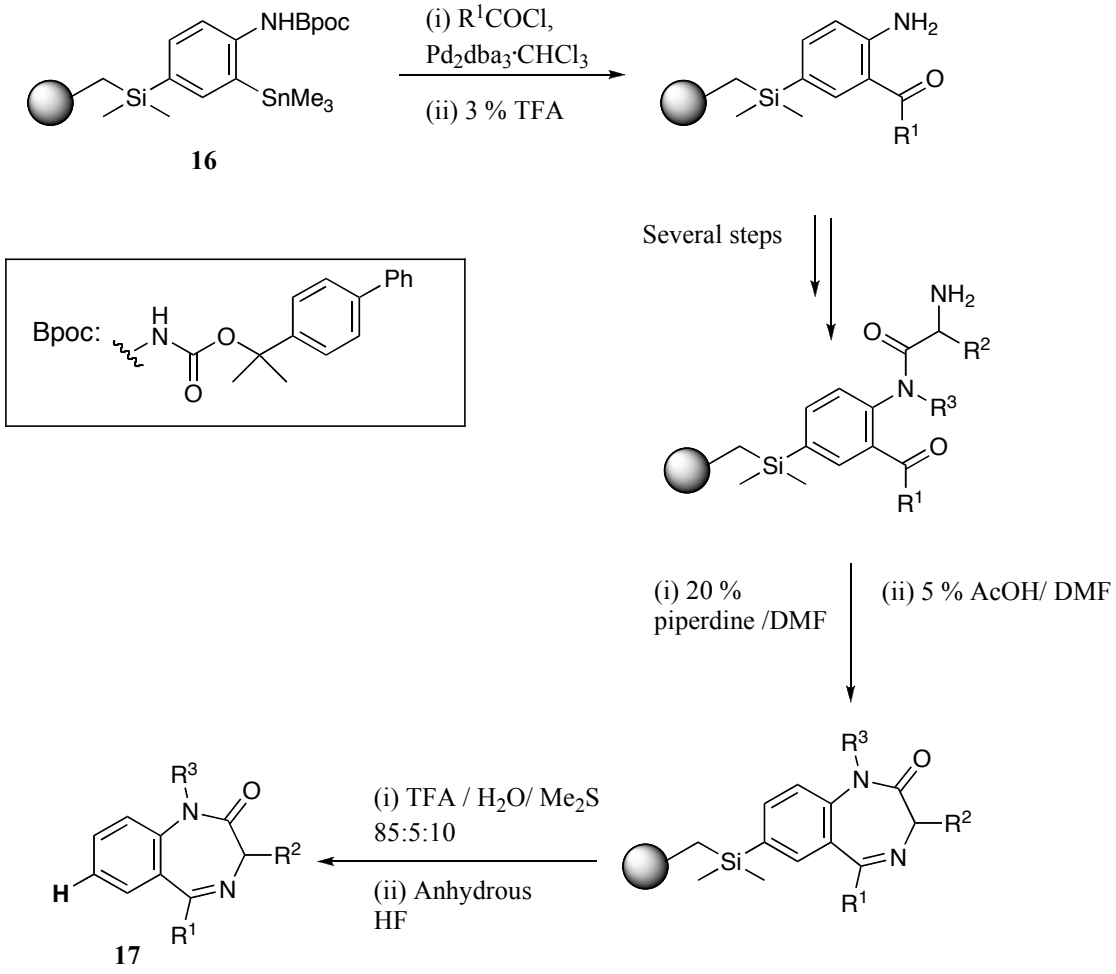
Scheme 5

2.2.2 Traceless Linkers

The cleavage of the final product from a conventional linker generally leaves behind trace of the former site of attachment in the form of a functional group: a carboxylic acid, amide or alcohol. In the work on solid-phase peptide synthesis, amide or carboxylic acid functionality left over from cleavage was perfectly acceptable, as the target compound required this functionality. However, in the combinatorial synthesis of libraries of low molecular weight compounds, left over functionality is undesired principally as it could affect the SAR when these small drug-like compounds are screened.[27] There is a need for linkers that display non-specific functionality, *i.e.* no trace, of their presence after cleavage. Such linkers are called "traceless linkers".[28]

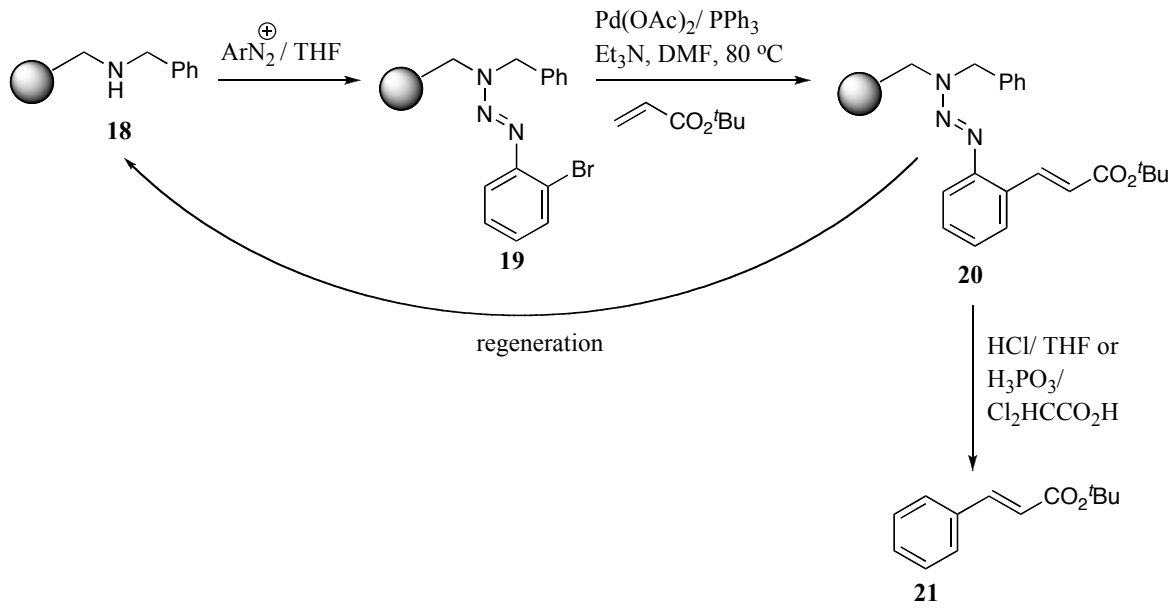
The first example and most widely explored of these traceless linkers came from the development of aryl silicon linkers by Ellman[29] (Scheme 6). The original linker **16** employed in the synthesis of 1,4–benzodiazepine derivatives **17** proved to be robust to number of reaction conditions including transition metal–mediated cross-coupling and very basic conditions. Cleavage was initiated by the addition of HF to affect protodesilylation of the silicon-aryl bond, forming a carbon-hydrogen bond at the former site of attachment.

The method was extremely successful, however cleavage with harsh conditions (HF) presented problems with certain functional groups, such as debenzylation of one of the target 1,4-benzodiazepine derivatives.[30]



Scheme 6

Many groups went onto modify Ellman's original linker and develop their own linkers by utilising germanium[31], sulfur[32], boron[33], phosphorous[34] and chromium[35]. Nitrogen linkers have also been developed. Although numerous examples of traceless cleavage of nitrogen linkers have been reported, a very elegant example comes from the work of Bräse and Enders. In their work, diazonium chemistry is utilized to synthesise triazene linker **19**, known as a T1-triazene traceless linker (Scheme 7).[36]

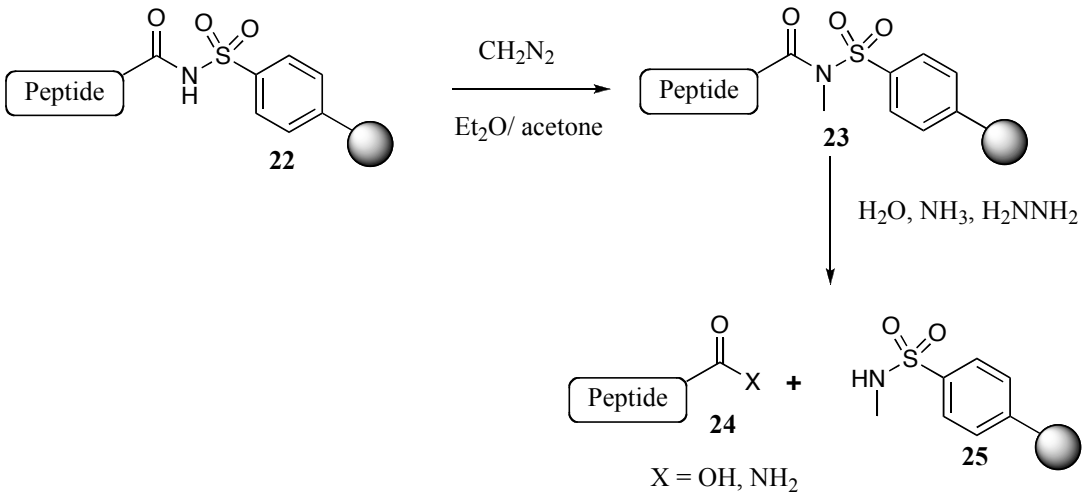


Scheme 7

The benzylamine resin **18** was synthesised in one step from Merrifield resin and converted to triazene **19**. In one example, Heck reaction yielded resin-bound α,β-unsaturated ester **20** and reductive deamination using H_3PO_2 in dichloroacetic acid gave ester **21** (81 % yield from resin). Other coupling partners (styrene acrylate, dihydrofuran, cyclohexene) were used in the Heck reaction and other reactions were performed after the Heck coupling including Sharpless dihydroxylation and Diels-Alder reactions giving library members in 29 % to 78 % yields from resin. The amino precursor **18** was regenerated in the cleavage step and could be reused with only slight loss of reactivity.

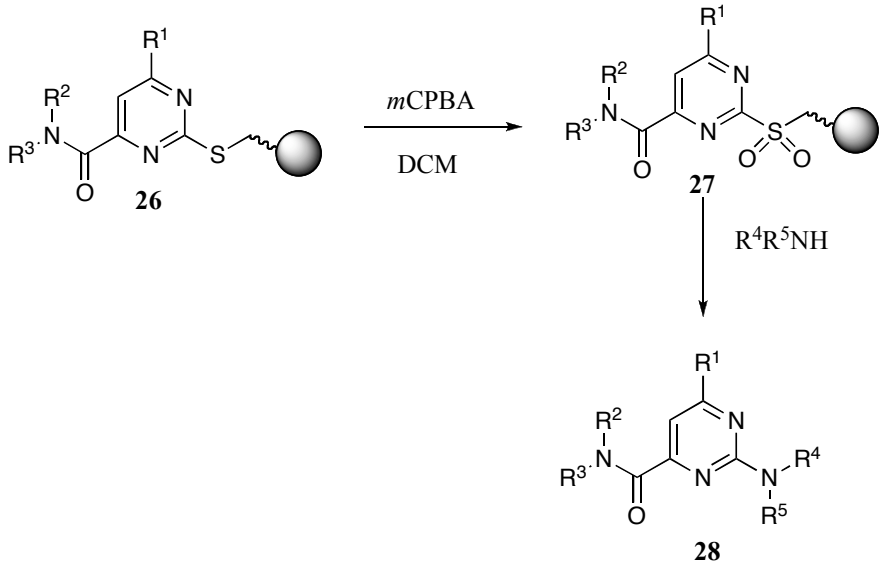
2.2.3 Safety Catch Linkers

The safety-catch principle is based upon chemoselective conversion of a linker that is very stable during SPS into a linker that is labile and therefore cleavable under relatively mild conditions.[37] The power of this strategy is particularly evident when strong reaction conditions are required during SPS. Among the first examples used to demonstrate the safety-catch principle was the acyl sulfonamide linker **22** developed by Kenner and co-workers.[38] Acyl sulfonamides are stable to strong anhydrous acids such as HBr as well as strongly nucleophilic reagents. Safety-catch activation by *N*-methylation with diazomethane in diethyl ether /acetone gives the labile species **23**, which can then be cleaved by alkali, aminolysis or by hydrazinolysis to give the free peptide **24** and the resin-bound sulfonamide **25** (Scheme 8).[38]



Scheme 8

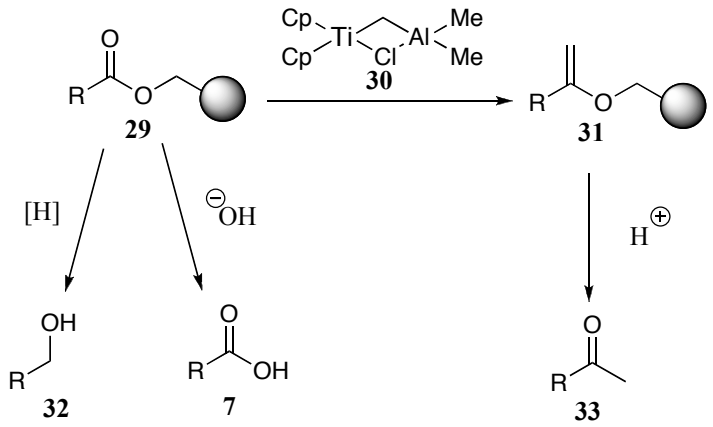
A safety-catch linker **26** described by a Hoffman–La Roche research group introduces desired functionality as part of the cleavage step after activation of the safety catch, effectively creating a productive cleavage step (Scheme 9). This traceless safety-catch linker strategy involves the use of a 2-thiopyrimidine skeleton that is activated upon oxidation. To demonstrate the robustness of the linker in its inert form, the resin-bound pyrimidine derivatives were subjected to a variety of reaction conditions including saponification, acid chloride formation and Mitsunobu alkylation. After activation of the linker with *m*CPBA in DCM to give the corresponding sulfone **27,** S_{NAr} substitution of the sulfone group with a range of nucleophiles, gave products **28** in high yields and purities (Scheme 9).[39]



Scheme 9

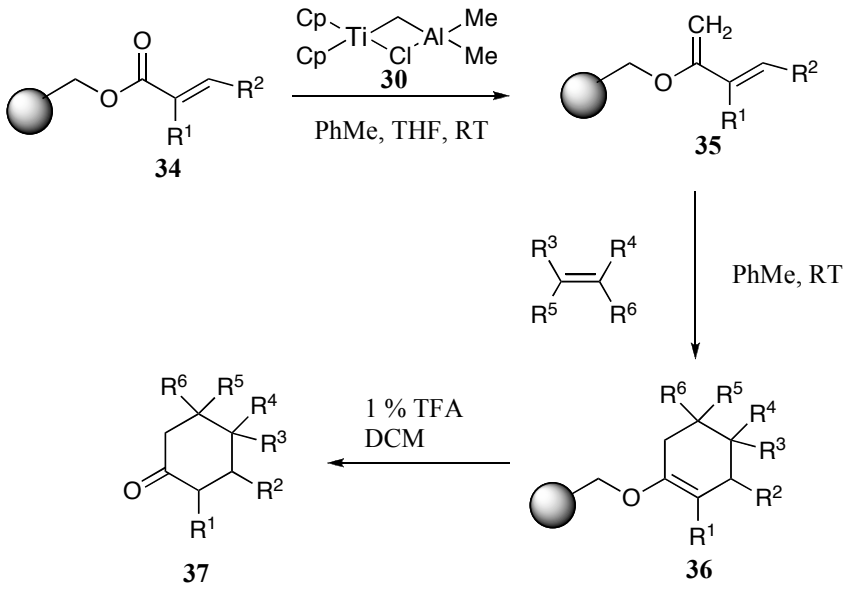
2.2.4 Chameleon-Catch Linkers

Chameleon-catch linkers stand apart from safety-catch linkers in offering more diverse products. The chameleon-catch linkers, first introduced by Barrett and co-workers,[40] can be cleaved under one set of conditions to give a range of products, but can also be chemoselectively converted into a new linker that is cleaved under orthogonal conditions to give a different range of products. The purity of the products of this second linker is ensured by the fact that any of the original linker that may be present is unaffected by the conditions used to cleave the new linker. Thus, resin-bound esters **29** can be cleaved to give alcohols **32** and carboxylic acids **7**, but can also be converted into enol ether linked compounds **31** by treatment with the Tebbe reagent **30** (Scheme 10). Treating enol ethers **31** with acid gives ketones **33** leaving unreacted ester **29** unchanged.



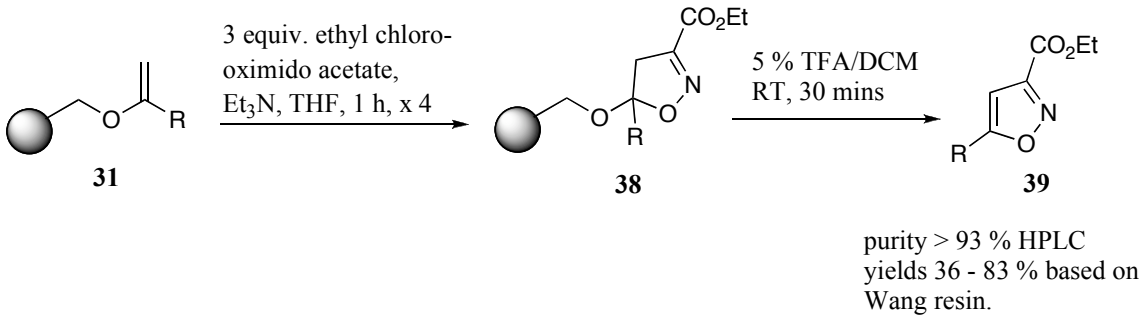
Scheme 10

Barrett and co-workers also demonstrated that reactions could be carried out on the new linker before cleavage. Thus α, β-unsaturated esters **34** were converted into dienes **35** and then underwent Diels Alder reaction to give the resin-bound cyclic enol ethers **36**. Treatment with acid then gave a range of cyclohexanones **37** (Scheme 11).[40]



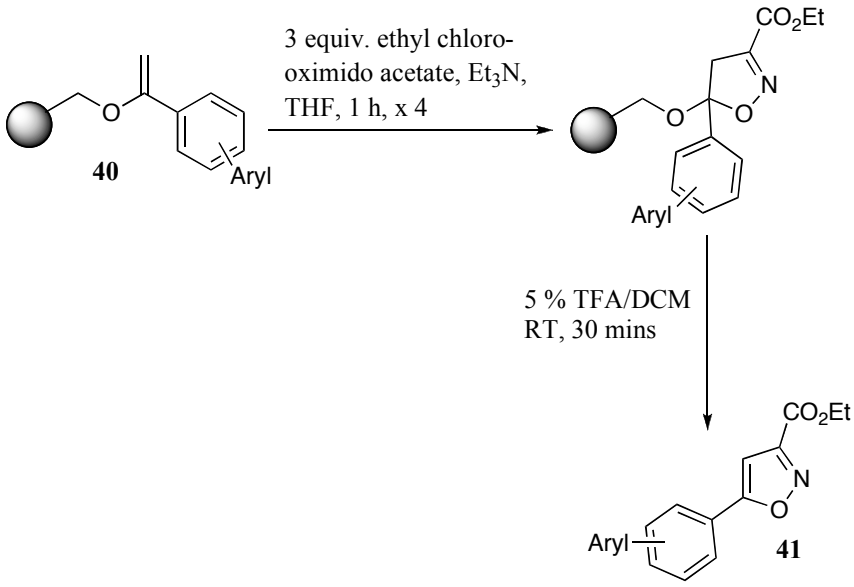
Scheme 11

Barrett's most recent contribution to chameleon catch strategy has been from the SPS of isoxazole moieties.[41] Methylenation of the resin-bound esters with Tebbe reagent gave the corresponding vinyl ethers **31**. Reaction of nitrile oxides to vinyl ethers for the synthesis of supported isoxazolines **38** occurred in a regioselective [3 + 2] cycloaddition, subsequent transformation to isoxazoles **39** was brought by elimination and release from the support upon addition of mild acid (Scheme 12).



Scheme 12

As the Tebbe reagent is not compatible with a range of functional groups, Suzuki coupling reactions in the formation of **40** were examined to increase the diversity of the isoxazoles formed. Several ethyl 5-biphenyl-3-yl-isoxazole-3-carboxylates **41** were synthesized, following this strategy in good purities (90 %) and reasonable yields (38-80 %) (Scheme 13).

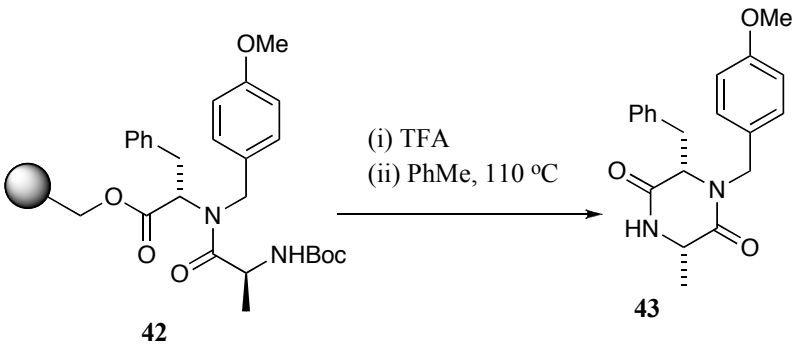


Scheme 13

Chameleon-catch strategy has been used extensively by the Hartley group and is discussed in further detail in a later chapter (Chapter 4).

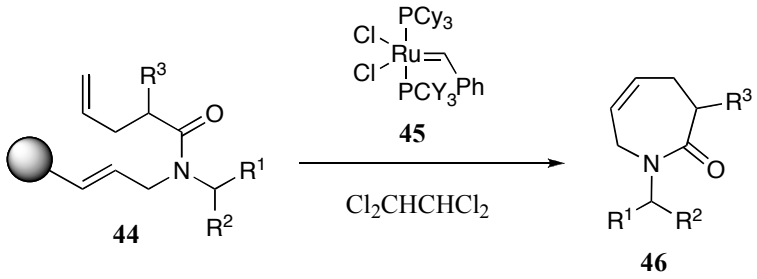
2.2.5 Cyclative Cleavage

Cyclative cleavage occurs when intramolecular cyclisation induces cleavage in the final step of a SPS, to release a cyclic compound from resin. This process has the key advantage that only cyclised compound is released, ensuring the high purity of the product. Cyclative cleavage generally involves an internal nucleophile attacking resin-bound linker functionality,[27] *e.g.* carbamate **42** is deprotected in the final step of SPS to generate an amine that attacks the resin-bound ester functionality. This results in intramolecular cyclisation and cleavage from resin to give the cyclic dipeptide **43** (Scheme 14).[42]



Scheme 14

Cyclative cleavage can also be achieved *via* ruthenium-catalysed ring closing methasis (RCM). This has been demonstrated with the SPS of 7-membered lactam **46** from dienes **44** using Grubbs' first generation catalyst **45** (Scheme 15).[43]

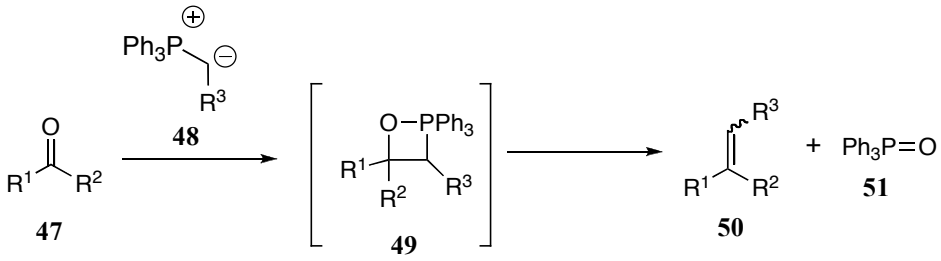


Scheme 15

CHAPTER 3 – Carbonyl Alkenation

3.1 Alkenation: The Wittig and Related Reactions

One of the most fundamental reactions in organic chemistry is the alkenation of carbonyl compounds. A variety of reactions have been developed to accomplish the conversion of carbonyl compounds into alkenes, and the Wittig reaction stands out as one of the most effective and general methods. It has become the standard by which all subsequent methodology is judged.[44] The reaction involves the addition of an aldehyde or ketone **47** to a phosphonium ylide **48** to give an oxaphosphacyclobutane **49**; the formation of the phosphine oxide **51** by-product then drives the reaction to produce the corresponding alkene **50** (Scheme 16).



Scheme 16

The Wittig reaction proceeds with defined positional selectivity, often with chemoselectivity, and with control of the geometry of the resulting alkene. The stereoselectivity depends on the nature of the substituents on the carbon atom of the ylide. In general a stabilised ylide, those with conjugating or anion-stabilising substituents (carbonyl groups) adjacent to the negative charge, will produce an *E*-alkene and an unstabilised ylide will produce a *Z*-alkene (Figure 5).

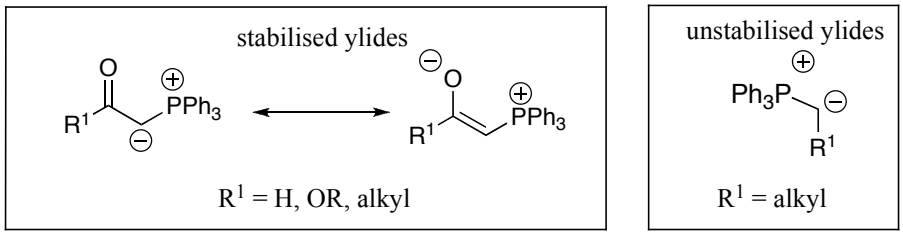
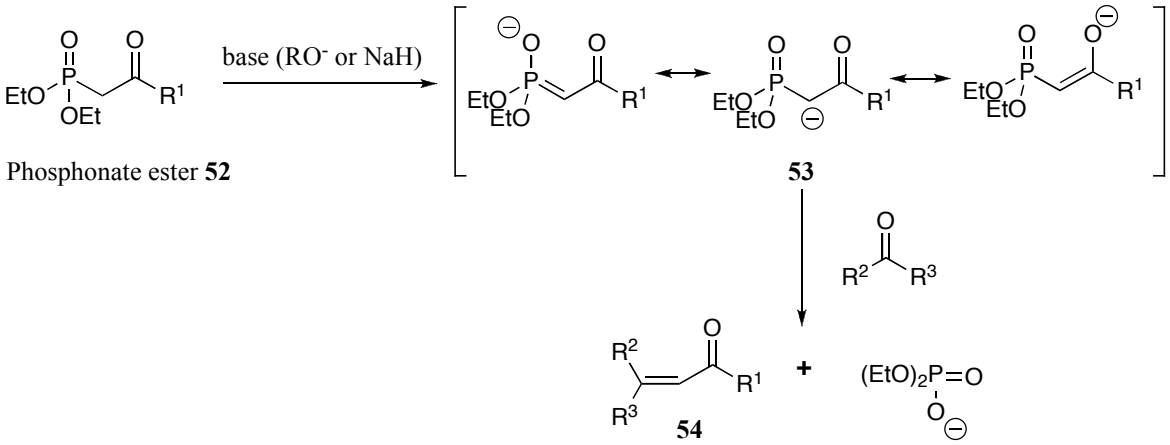


Figure 5

3.1.1 Horner-Wadsworth-Emmons (HWE) Reactions

Stabilised ylides can be fairly unreactive, many indeed are so inert that they can often be recrystallised from water.[45] A more reactive alternative to a stabilised ylide is the anion **53** prepared from the corresponding phosphonate ester **52**. The enolate anions **53** react well with aldehydes and ketones to give the desired alkenes **54** [*via* the Horner-Wadswoth-Emmons (HWE) reaction][46,47] (Scheme 17).



Scheme 17

3.1.2 Julia and Peterson Reactions

Other procedures have been developed to overcome some of the problems associated with phosphorus-based alkenations, improving on the selectivity and/ or reactivity of the phosphorus ylides. Such methods include the Peterson and the Julia alkenations using reagents **55** and **56**, respectively (Figure 6).[48,49]

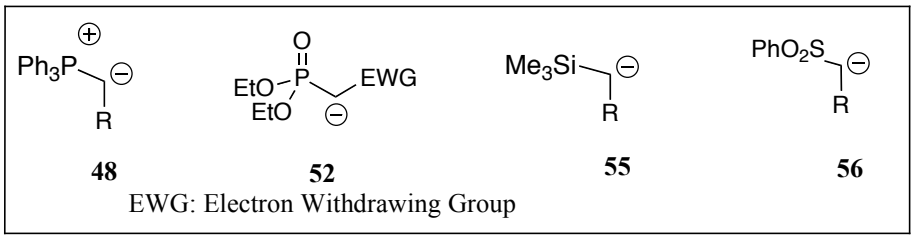


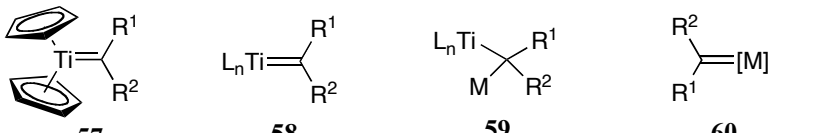
Figure 6

The above methodologies all suffer from one serious limitation: they can generally only be applied to the alkenation of ketones and aldehydes. Other disadvantages include unfavourable steric interactions between substrate and reagent, also the bascity of anions can lead to undesired side reactions when applied to base-sensitive substrates.[50]

These problems have been overcome through the use of transition metal carbenoid chemistry, in particular titanium-based reagents. The application of titanium-based reagents offers many advantages over other alkylidenation methods (*e.g.* the Wittig reaction), above all the ability to alkylidenate carboxylic acid derivatives.[51] Furthermore, titanium carbenoids are more effective at alkylidenating sterically hindered carbonyl groups. They are also non-basic, and thus will not deprotonate easily enolisable carbonyl groups.

3.2 Titanium Alkylidenes and 1,1-Bimetallics

Titanium-based carbenoids, used in the conversion of carbonyl groups, such as esters, thioesters, amides, carbonates and ureas into alkenes, fall into two main categories: those in which the reactive agent is a titanium alkylidene complex **57** or **58**, or those considered to be 1,1-bimetallics **59** (Figure 7). Titanium alkylidene complexes **57** and **58** are typical examples of Schrock carbenes **60**. Interaction between a nucleophilic carbene, carbon atom, and an electrophilic transition metal (*e.g.* titanium), in a high formal oxidation state, gives rise to the Schrock carbene **60**. The metal is a good σ acceptor and a good π donor. Electron transfer from the metal to the carbon atom is very effective due to the efficiency of the overlap between the filled metal d-orbital and the empty carbon p-orbital.[52] This gives rise to the high energy HOMO that causes the high affinity of Schrock carbenes toward the relatively low LUMO of carbonyl groups.



57 **58** **59** **60**

M = [Ti], ZnX, MgX

L = ligand

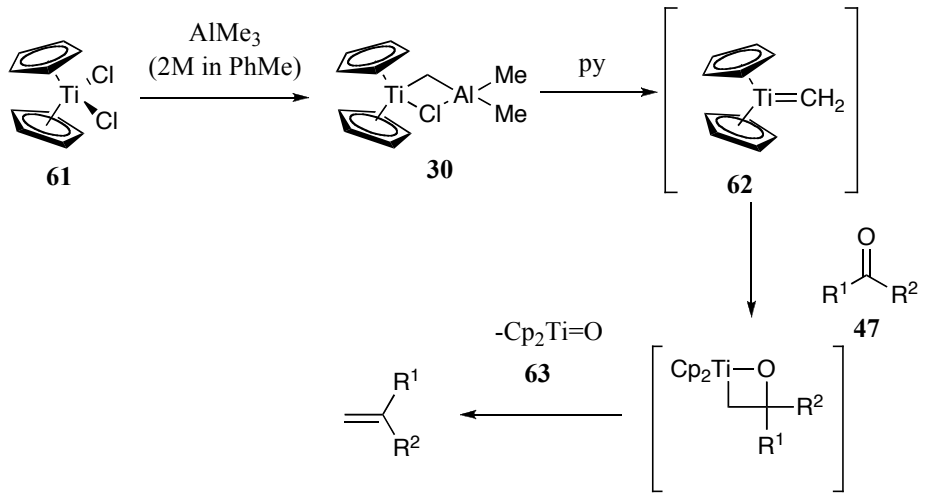
Schrock carbene

Figure 7

A comprehensive review of alkylidenation reactions covering not only carboxylic acid and carbonic acid derivatives, but also alkylidenation of ketones and aldehydes was published by the Hartley team in 2007.[53]

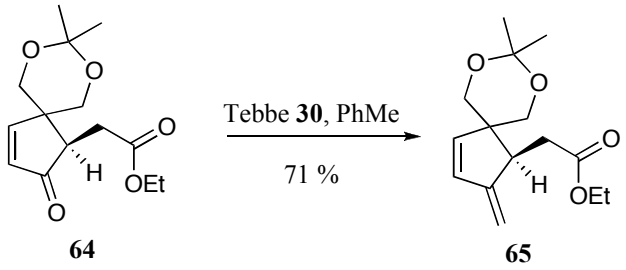
3.2.1 Tebbe Reagent

The Tebbe reagent **30**, first reported in 1978, can be prepared from titanocene dichloride **61** and 2 equivalents of trimethylaluminium in toluene by following Pine and co-workers' procedure or it can be purchased commercially as a solution in toluene.[54] The reactive species, a highly reactive titanocene alkylidene **62,** is formed upon addition of a Lewis base, such as pyridine or THF, to the titanium-aluminium metallacycle **30**. The component responsible for alkenation, titanocene methylidene **62**, is an example of a typical Schrock carbene **60**. It is nucleophilic at carbon and electrophilic at titanium, and its reactivity and thus nucleophilicity towards carbonyl groups **47** is dominated by its high energy HOMO.[55] The driving force in the methylenation of a carbonyl group is the irreversible formation of the strong Ti-O double bond in oxide **63** (Scheme 18).



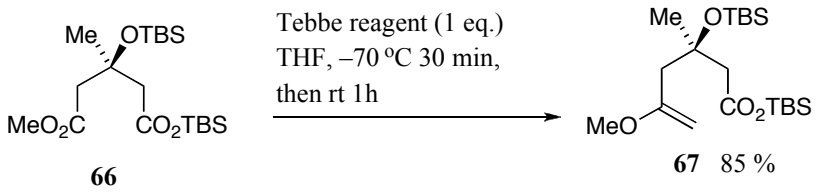
Scheme 18

The Tebbe reagent is capable of methylenating a broad range of carbonyl groups including aldehydes, ketones, esters, thioesters, amides and carbonates.[56] Selective methylenation can also be achieved in the presence of carbonyl groups of differing electrophilicity. Aldehydes and ketones are methylenated preferentially, in the presence of esters or amides, as they are more electrophilic. Thus, ketone **64** reacted with 1 equivalent of the Tebbe reagent in a straightforward synthesis of diene **65** (Scheme 19).[57]



Scheme 19

Regioselectivity can also be achieved in the Tebbe methylenation of esters and, with methylenation occurring at the less sterically hindered of the two carbonyl groups (Scheme 20). Using one equivalent of Tebbe reagent and low temperature, the diester **66** was selectively methylenated to provide the enol ether **67** in very good yield.[58]



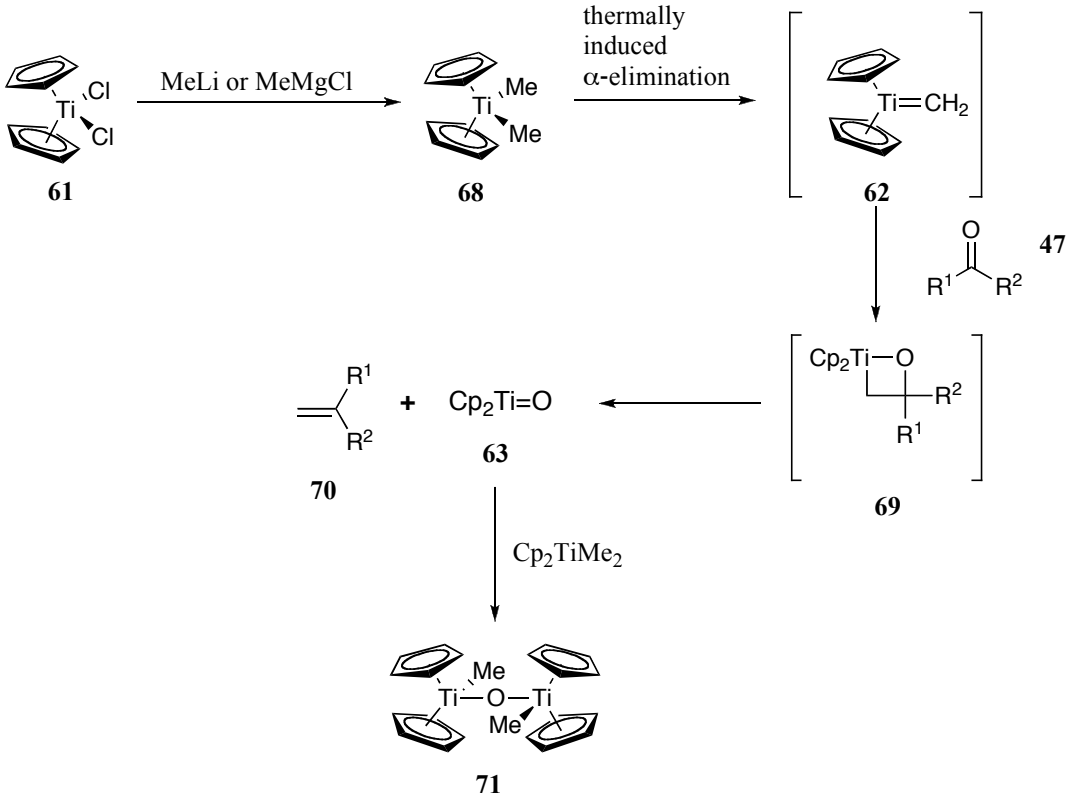
Scheme 20

Methylenation of tertiary amides and carbonates to give enamines and ketene acetals have also been reported. However, methylenation with the Tebbe reagent does not proceed with some substrates. Carbonyls with good leaving groups, such as acid chlorides, undergo formation of titanium enolates; anhydrides and imides also react in a similar fashion to acid chlorides.[59] Additionally, methylenation of thioesters to give vinyl sulfides is rare.

Although, the Tebbe reagent is known to tolerate a wide degree of functionality in its ester substrates, variants containing functionality or having hydrogen atoms beta to the metal cannot be prepared, thus it is limited entirely to methylenation.[53] Furthermore, the highly reactive bimetallic species **30** and the by-products formed by its decomposition are Lewis acidic. The Tebbe reagent is also air and moisture sensitive.

3.2.2 Petasis Reagents

Dimethyltitanocene (DMT) **68** developed by Petasis and Bzowej as an alternative to the Tebbe reagent is easily prepared by reacting methyllithium or methylmagnesium chloride with titanocene dichloride **61** (Scheme 21).[60] Definitive procedures for the preparation of DMT have been published by Hughes and also by Payack's team at Merck Research Laboratories. [61] Unlike the Tebbe reagent, DMT can be stored refrigerated in a solution of THF or toluene (10 wt %), is relatively stable to air and moisture and is non-pyrophoric. The reactive titanocene methylidene species **62** is formed from DMT by heating to 60–70 °C in THF or toluene and reacts rapidly in the presence of the carbonyl compound **47** *via* oxatitanacyclobutane **69** to give the alkene **70** and titanocene oxide **63**, which forms titanocene dimer **71** by further reaction with DMT (Scheme 21).

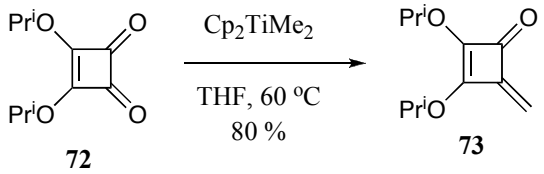


Scheme 21

Confirmation that the titanocene methylidene **62** is the active species in the mechanism of methylenation comes from the work of Hughes *et al.*[62] They have shown that titanocene methylidene formation proceeds *via* heat-induced α-elimination, and that this is the overall rate-determining step of the alkylidenation reaction. Additionally, the recent work of Meurer *et al.*[63] has confirmed the second and third steps of the mechanism. Utilizing

atmospheric pressure chemical ionisation mass spectrometry (APCI-MS) and tandem mass spectrometry (APCI-MS/MS) the oxatitanacylcobutane intermediate **69** has been spectroscopically characterised in observing its dissociation into $Cp_2Ti{=}OH^+$ and $R_1R_2CCH_2H^+$.

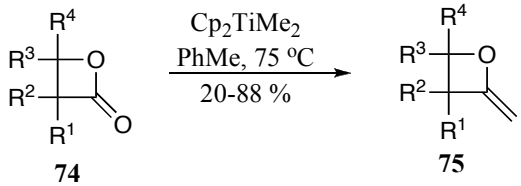
In the same way as the Tebbe reagent, DMT can also selectively methylenate aldehydes and ketones in the presence of less electrophilic carbonyl groups including esters, amides and carbamates. In the case of DMT more functionalised derivatives, such as α,β-unsaturated esters, lactones, as well as vinylogous esters are smoothly methylenated. A particularly impressive example is methylenation of cyclobutenedione derivative **72** to give *exo*-methylene compound **73** (Scheme 22).[64]



72 **73**

Scheme 22

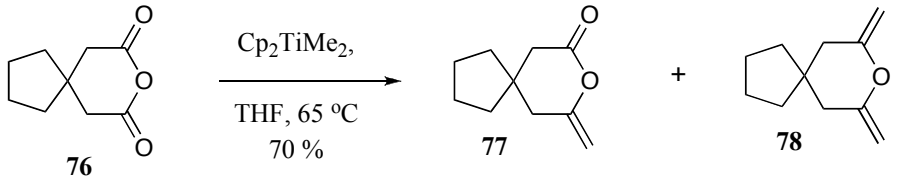
In cases where Tebbe methylenation has proven unsuccessful, Petasis methylenation has proceeded with excellent chemoselectivity.[65] Highly strained β-lactones **74** undergo transformation into enol ethers **75** under Petasis methylenation but not under Tebbe methylenation conditions, possibly due to the greater Lewis acidity of the Tebbe reagent (Scheme 23).[66]



74 **75**

Scheme 23

A variety of other carbonic and carboxylic acid derivatives are also converted into synthetically useful hetero-substituted alkenes with DMT. These include: silyl esters, thioesters, selenoesters, and acylsilanes. Similarly, anhydrides, carbonates, amides and imides give the corresponding enol ethers or enamines.[64] In the case of anhydrides and imides, excess of the reagent gives the bis-methylenation products while smaller amounts give primarily the mono-methylenation products. For example the selective methylenation of the anhydride **76** was achievable giving enol ether **77** with very little double methylenation product **78** (Scheme 24).[67]



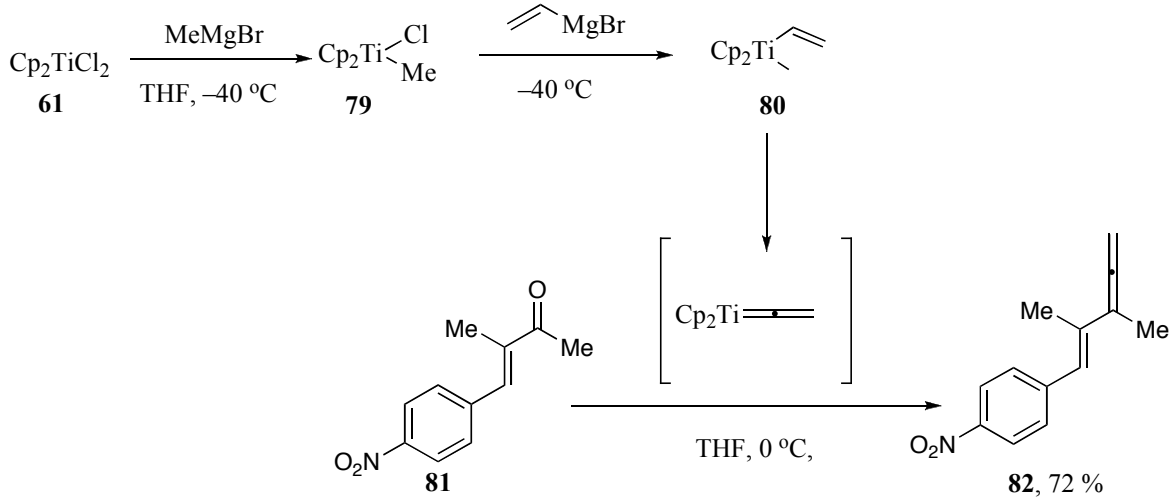
1 eq. of Cp_2TiMe_2	10	:	1
2 eq. of Cp_2TiMe_2	2	:	1
4 eq. of Cp_2TiMe_2	0	:	1

Scheme 24

The popularity of Petasis methylenation stems from excellent properties of the DMT reagent; it is easy to prepare, is relatively robust (briefly stable to air and moisture) and will methylenate a wide range of carbonyl groups effectively and cleanly (titanium-containing impurities are easily removed *via* precipitation and filtration).[68] The reaction conditions are also non-basic (unlike the Wittig reagent) so the epimerization of chiral centres can be avoided. The absence of Lewis acid (present in the Tebbe reagent) means that a wider range of functional groups can be tolerated.

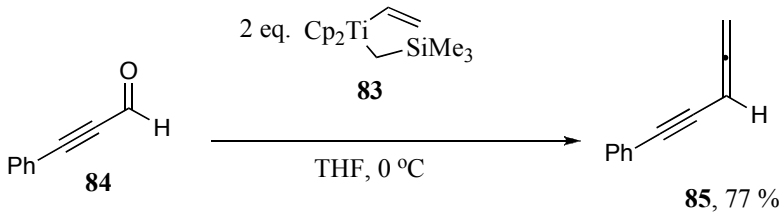
Functionalised Petasis reagents can also be prepared: *B*is(benzylic)titanocenes are easily generated from substituted and non-substituted benzylmagnesium chlorides and titanocene dichloride and upon heating effectively alkylidenate carbonyl compounds.[69] In addition, bis(vinylic)titanocenes can be synthesised from titanocene dichloride with two equivalents of an alkenyl-1-magnesium bromide at –40 °C, and warming to 0 °C to induce α-elimination, generates a titanium vinylidene. The titanium vinylidene is then capable of reaction with aldehydes and ketones to produce allenes.[70] α-Elimination from a vinyl group appears to be faster than from a methyl group, so titanocene dichloride **61** was converted first to methyl derivative **79** and then reacted with vinylmagnesium bromide to

give the Petasis reagent **80** (Scheme 25). Addition of ketone **81**, then gave allene **82** in good yield at 0 °C.



Scheme 25

Similarly, aldehyde **84**, gave allene **85** (Scheme 26), with Petasis reagent **83.**

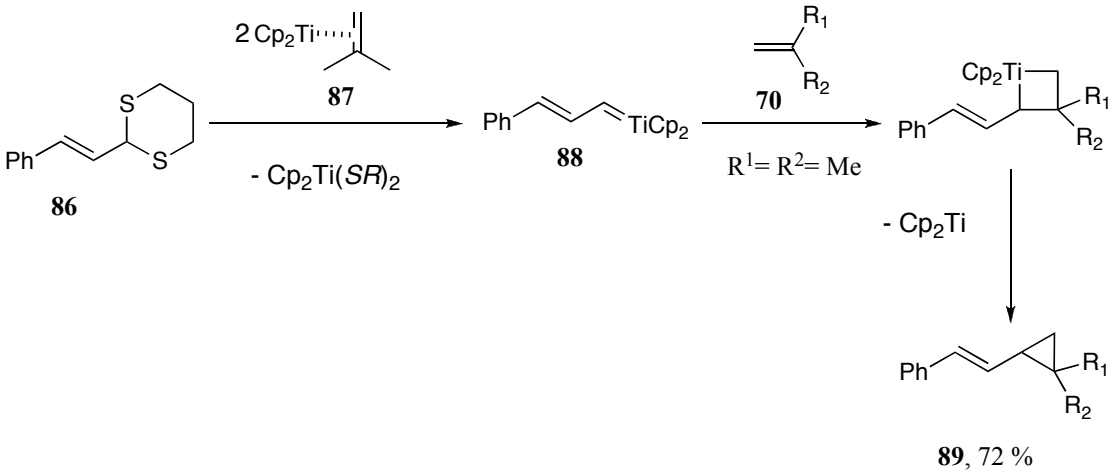


Scheme 26

However, the Petasis method has a limitation, the approach disallows the generation of titanium alkylidenes that have hydrogen atoms beta to titanium, as the process of β-elimination is faster than the α-elimination, required to generate the titanium alkylidene complex.

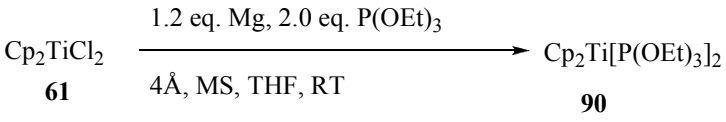
3.2.3 Takeda Reactions

Takeda and co-workers, while studying the preparation of organometallic compounds by the desulfurizative metallation of organosulfur compounds with low-valent metal species, noticed an unusual formation of cyclopropanes. They assumed that the thioacetal **86** had been reduced by the low-valent titanium reagent **87** to give the Schrock carbene **88**, which was then capable of rapid cyclopropanation of the terminal alkene **70,** to afford the alken-1-ylcyclopropane **89** (Scheme 27).[71]



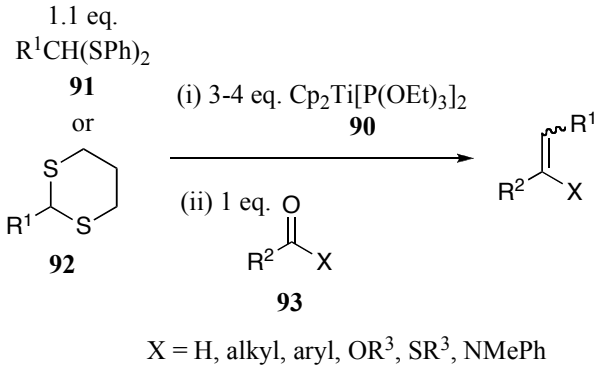
Scheme 27

In order to generate a low-valent titanium species for the desulfurization of thioacetals, the group also prepared $Cp_2Ti(PMe_3)_2$, first reported by Kool *et al*. by the reduction of titanocene dichloride with magnesium.[72] However the preparation of $Cp_2Ti(PMe_3)_2$ was problematic, the reagent took between 16 to 20 h to generate and required excess amounts of expensive PMe_3. The group then investigated the preparation of a low-valent titanium reagent using $P(OEt)_3$ as a ligand. The treatment of titanocene dichloride **61** with excess magnesium turnings and $P(OEt)_3$ in THF for roughly 12 h gave a black solution, which contained the low-valent titanium species **90**. However it was observed that the preparation was not completely reproducible and on occasion, the reaction would fail. Following the assumption that trace amounts of water retarded the reduction, they examined the use of a drying agent. They found that the reduction of titanocene dichloride was completed within 3 h in the presence of powdered molecular sieves (4Å) using a small excess of magnesium (1.2 equivalents) and $P(OEt)_3$ (2 equivalents) in dry THF (Scheme 28).[73]



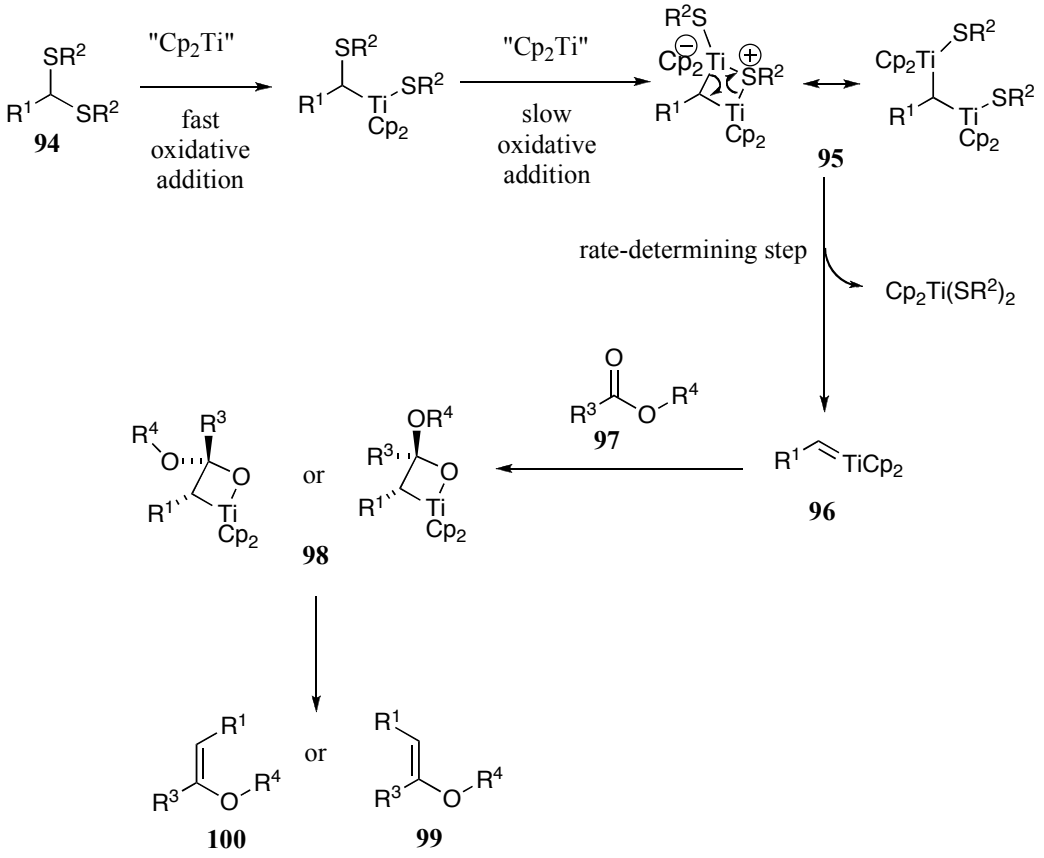
Scheme 28

Addition of low-valent titanium species **90** proceeded to reduce thioacetals and following treatment with aldehydes[73] or ketones,[73] produced alkenes. Thioacetal substrates for this reaction include diphenyldithioacetals **91** and 1,3-dithianes **92** (Scheme 29); although the former is more easily reduced.[74] The reaction was also successful with unsaturated thioacetals. Additionally alkenation could be achieved with carboxylic esters, thioesters[75] and *N*-methylanilides.[76] Lactones were transformed into cyclic enol ethers in a similar manner.[73] The application of their discovery, in the alkylidenation of a wide variety of carbonyl derivatives **93** represents a major breakthrough in the use of titanium alkylidene reagents.



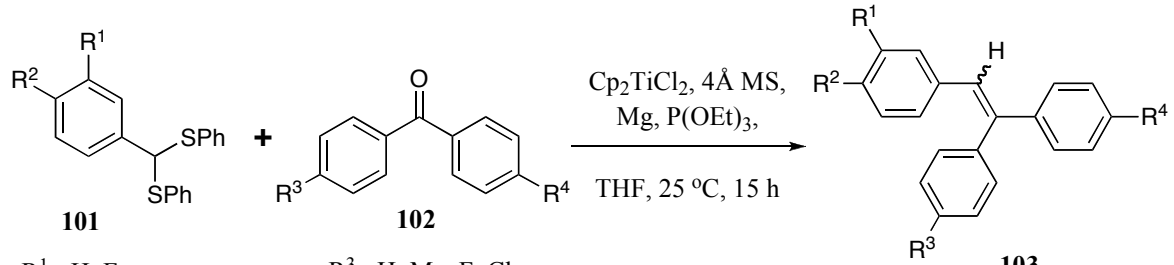
Scheme 29

Thioacetals **94**, easily prepared from corresponding aldehydes and ketones by treatment with thiols in the presence of a Lewis acid, are added to the low valent titanium species (Scheme 30).[53] Presumably, a geminal bimetallic species **95** is formed *en route* to the titanium alkylidene species **96**, which is capable of alkylidenating esters **97** *via* oxatitanacyclobutanes **98**. The ratios of Z and E alkenes **99** and **100** formed depends on the steric and electrostatic influences. Esters afford mostly *Z*-enol ethers **100**, [73] however the selectivity is often modest.



Scheme 30

An advantage of the Takeda method is that a wide range of titanium alkylidenes, [77, 78] with or without hydrogen atoms beta to the titanium atom, can be generated.[79] Thus, the main advantage of the Takeda alkylidenation is that the titanium alkylidene complex, unlike other titanium alkylidene reagents, can introduce functionality. Indeed, the Kanus group found that aryl halides **101** and **102** could be used in the synthesis of trisubstituted alkenes **103** (Scheme 31),[80] although it should be noted that aryl chlorides are only occasionally tolerated as dechloronation can often occur.[81]



101

R^1= H, F
R^2 = H, Me, SMe, F, Cl

102

R^3= H, Me, F, Cl
R^4 = Me, SMe, F, Cl

103

60 % - 74 %
(based on thioacetal)

Scheme 31

Hartley and co-workers recognised that a range of easily accessible functionalized thioacetals **104–112** (Figure 8) could be reduced by low valent titanium complex **90**, under Takeda conditions, to give a diverse range of alkylidenating reagents,[82, 83, 84, 85, 86] which could then be employed in the diversity-orientated synthesis of aromatic and non aromatic heterocycles (See Chapter 4).

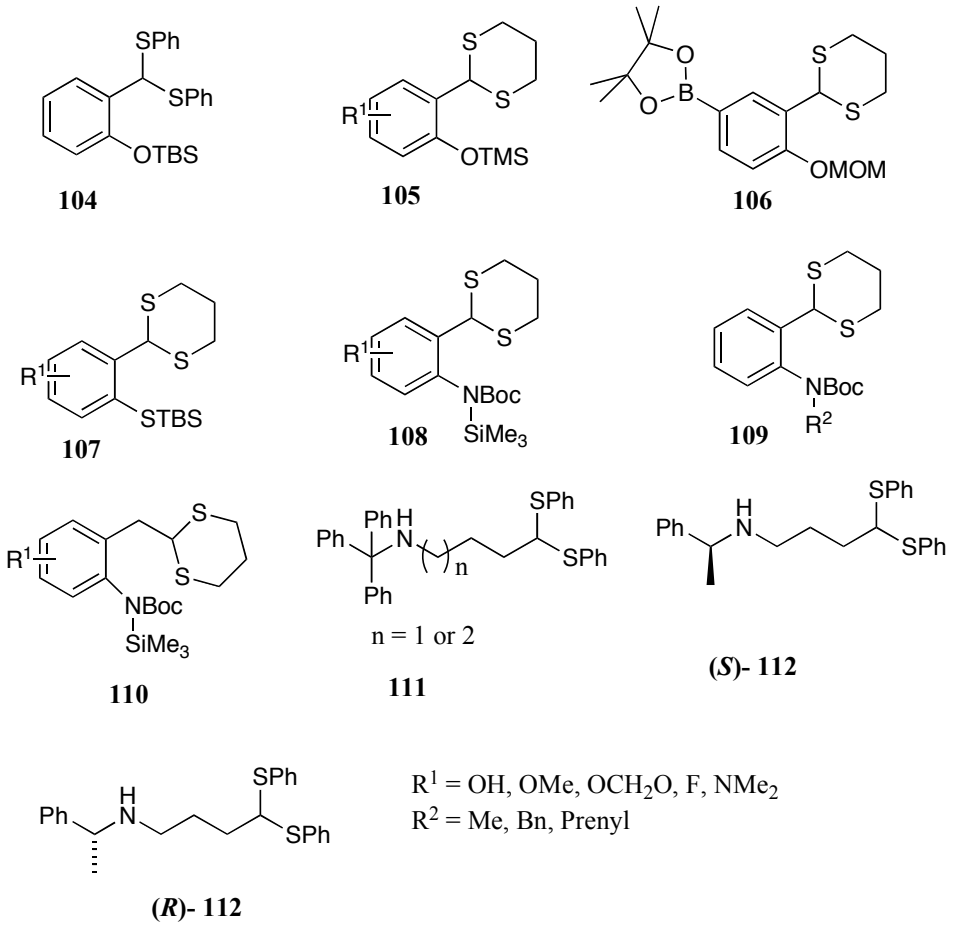
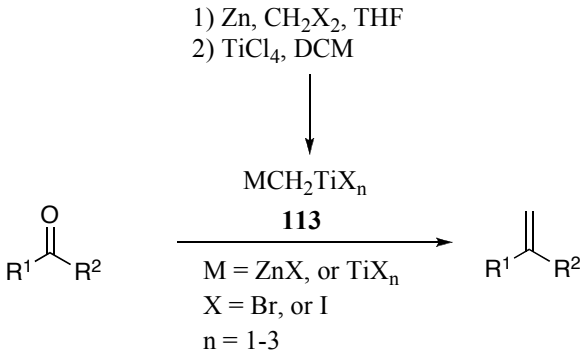


Figure 8

The few drawbacks of Takeda's method include poor stereoselectivity in the alkylidenation of ketones and aldehydes and methylenation is not possible. In addition, the requirement of an excess of titanocene (at least 3 equivalents) and triethylphosphite (at least 6 equivalents) can also lend itself to problematic product purification. Also, while the Takeda reaction does tolerate a broad spectrum of functionality, some groups cause problems within the reagent itself. Most notably unhindered amino groups prevent the formation of an effective alkylidenating reagent.[82]

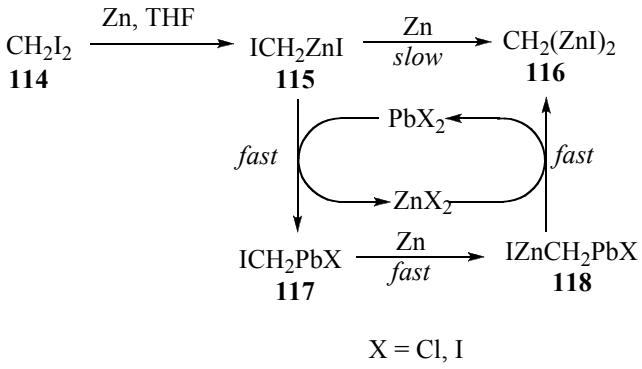
3.2.4 1,1 Bimetallic Reagents

Takai and co-workers were the first to report the methylenation of ketones at RT with a reagent generated from the addition of $TiCl_4$ to a suspension of dihalomethane and zinc in DCM. The reactive species is presumably a 1,1-bimetallic titanium carbenoid **113**, as alkene metathesis has never been observed with this or related reagents (Scheme 32).[87]



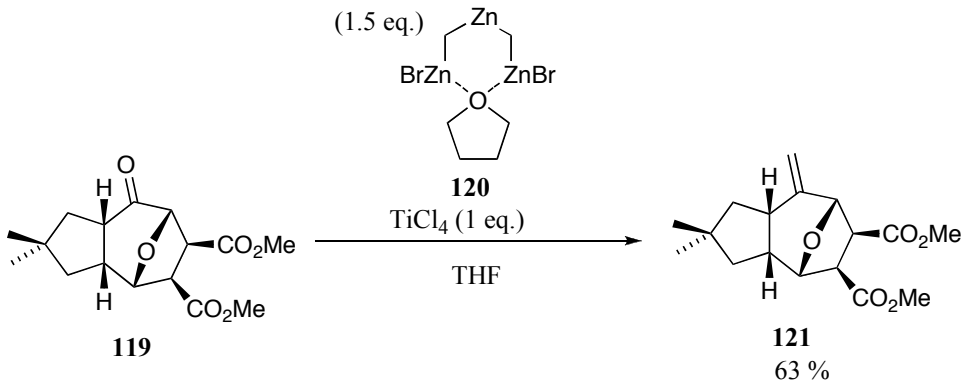
Scheme 32

It would seem that the reaction proceeds *via* double insertion of zinc into the C-I bonds of diiodomethane **114**. The first insertion takes place rapidly, but the second insertion to give geminal dizinc **116** is comparatively slow in the absence of lead. The conversion of diiodomethane **114** into geminal dizinc **116** is accelerated by the addition of lead(II) chloride, which acts as a catalyst.[88] Takai suggests that lead carbenoid **117**, a product of transmetallation from zinc to lead, is more easily reduced than the corresponding zinc carbenoid **115**, due to the greater covalent character of the Pb-C bond. Further reduction of carbenoid **117** by zinc gives rise to lead carbenoid **118** that after transmetallation from lead to zinc gives geminal dizinc **116** (Scheme 33),[56] which can form carbenoid **113** when treated with titanium(IV) chloride.



Scheme 33

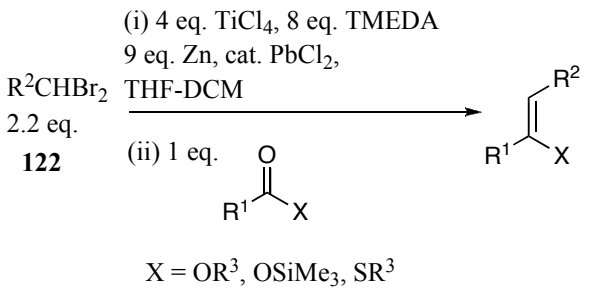
In 1995, the work by Tochterman and co-workers identified commercially available Nysted reagent **120** as a suitable replacement for the dihalomethane and zinc (and lead chloride) mix. Ketone **119** was methylenated, at room temperature, in the presence of Nysted reagent and $TiCl_4$, to give alkene **121** in good yield (Scheme 34).[89]



Scheme 34

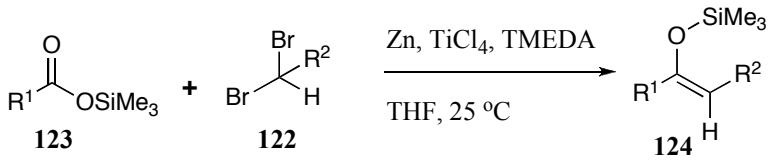
3.2.5 Takai Reagents

Takai reagents are also derived from $TiCl_4$ but differ in their preparation and reactivity. The reagents are prepared by the addition of 4 equivalents of titanium(IV) chloride ($TiCl_4$) to THF, followed by 8 equivalents of tetramethylethylenediamine (TMEDA), then 9 equivalents of zinc (containing trace lead) and finally 2.2 equivalents of 1,1-dibromoalkane **112** (Scheme 35).[88] Although the reaction mechanism is still to be established, it is reported that trace amounts of lead(II) salts are vital to the success of the reaction. As lead is often found in commercial zinc powder as a contaminant, the quantities vary; therefore a small quantity of lead(II) chloride is added to ensure success.



Scheme 35

A definitive procedure for the preparation of this reagent has been published and in comparison to the Tebbe reagent offers superior alkenation.[53] Takai reagents alkylidenate esters to give enol ethers in excellent yields and will convert thioesters into vinyl sulfides with good Z-selectivity.[90] They are also capable of alkylidenating other carboxylic and carbonic acid derivatives.[56] Stereoselectivity is generally governed by steric interactions, where enol ethers are generated from esters with a branch in R^1 α to the carbonyl group, near-total *Z*-selectivity is observed. Silyl esters **123** are also effectively alkylidenated to give the corresponding silyl enol ethers **124**, (Scheme 36) with comparable Z-selectivities to those found for alkyl esters (Table 1). [91]



Scheme 36

R^1	R^2	Yield (%)	**Z/E**
Ph	Me	90	**73:27**
Me	$PhCH_2$	79	**92:8**
PhCH=CH	Bu	79	**100:0**

Table 1

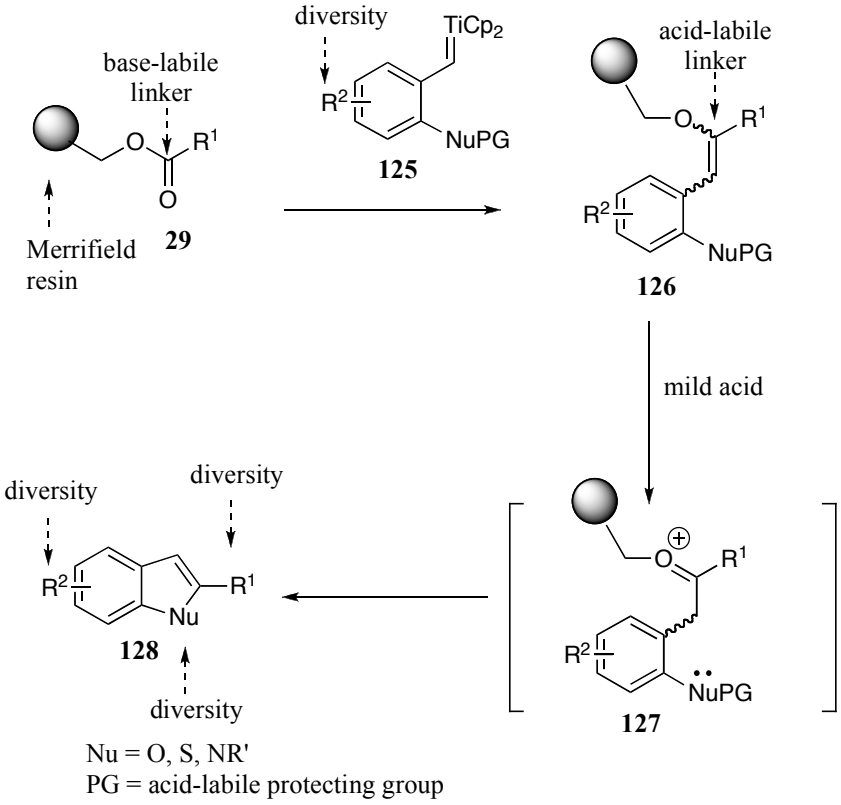
Takai and co-workers report that alkylidenation is generally superior to methylenation. There are however no examples of the alkylidenation or methylenation of aldehydes and only one example of reaction with a ketone.[92] The Takai alkylidenation/ methylenation of esters tolerates many functional groups in the ester substrates, including aryl and vinyl halides, alkenes, ethers, silyl ethers and acetals.[93,94] The reagent itself, believed to be a Schrock carbene because it occasionally induces metathesis,[95,96] may also contain functionality although this has only been demonstrated with THP acetals[97] and in the trimethylsilylmethylenation of esters.[98]

A main drawback to the Takai reagent has been the difficulty in accessing 1,1 dihaloalkanes, however there are now good methods for the preparation of 1,1-dibromoalkanes.[99,100]

CHAPTER 4 – Privileged Structures: Hartley Team Strategy

Barrett and co-workers introduced the term "chameleon catch strategy" to describe their work in which the Tebbe reagent switches an acid-stable ester linker into an acid-sensitive enol ether linker (see section 2.2.4 Schemes 11, 12 and 13).[40,41] However, their approach was limited by the choice of the Tebbe reagent, which only allows methylenation and cannot introduce additional functionality.

The Hartley team envisaged that the application of Takeda's method would allow the generation of functionalized titanium alkylidene reagents that would in turn lead to new synthetic strategies. Principally, resin-bound esters **29** would undergo benzylidenation reactions with titanium benzylidenes containing a masked nucleophile in the *ortho* position **125**. The acid-stable esters **29** would thus be converted into acid-sensitive enol ethers **126**. Treatment with acid would then generate oxonium ion **127** resulting in cleavage from resin with concomitant cyclisation to give heterocycles **128** in one clean step (Scheme 37). The switched nature of the linker would ensure the purity of the products **128** released from the resin, as any unreacted ester **29** would remain attached to the resin.[81]

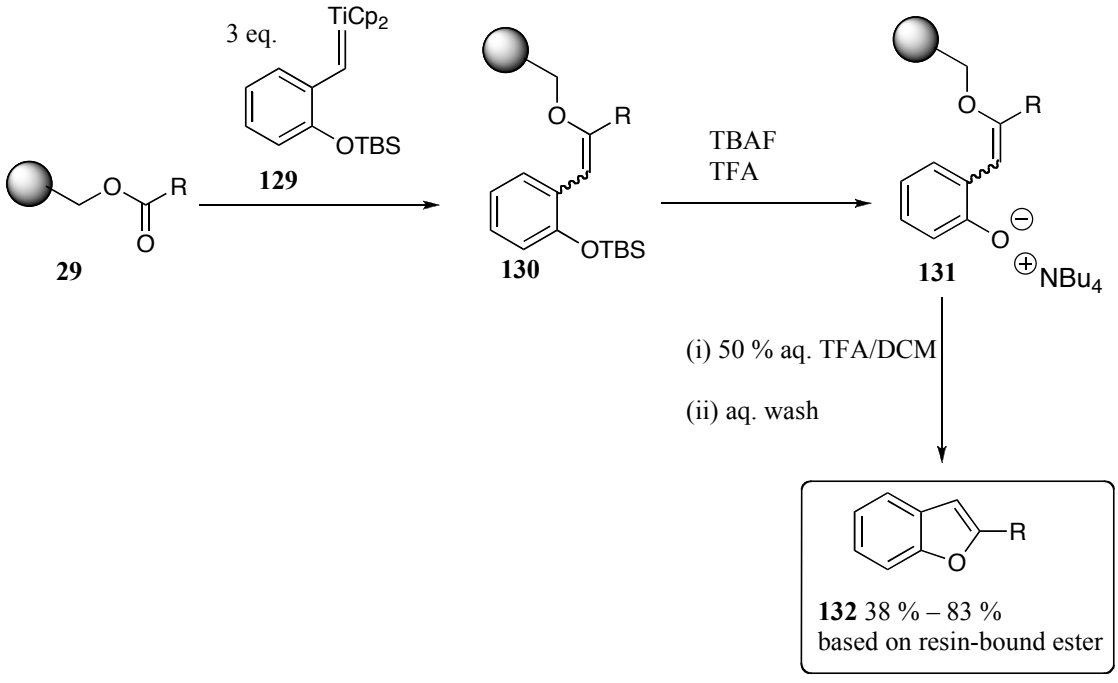


Scheme 37

4.1 Benzofuran Synthesis

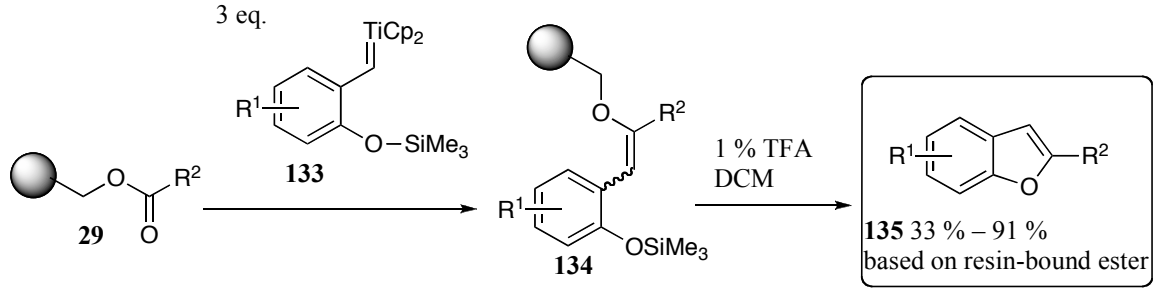
Emma Guthrie was the first of the Hartley team to demonstrate this synthetic strategy, proving that Takeda alkylidenation could be achieved on solid phase. This not only highlighted the advantage of being able to easily purify the products of alkylidenation but also showed the neat introduction of functionality in the alkylidenation step. Emma Guthrie developed the early strategy in the SPS of the bicyclic heterocycle, benzofuran.[101]

The benzofurans were synthesised utilising a titanium benzylidene **129** with a masked oxygen nucleophile in the *ortho* position (Scheme 38), generated under Takeda conditions (Section 3.2.3). Salicylaldehyde was converted into the corresponding diphenyldithioacetal and the hydroxy group silyl protected with *tert*-butyldimethylsilane (TBS) to give thioacetal **104 (**Figure 8, page 31). Following Takeda's procedure, the appropriate titanium benzylidene reagent **129** was generated. Reaction of titanium benzylidene **129** with a range of Wang resin-bound esters **29** gave the corresponding resin-bound enol ethers **130**. Treatment of the enol ethers **130** with tetrabutylammonium fluoride (TBAF) removed the *tert*-butyldimethylsilyl (TBS) protecting group to produce phenoxide **131**. Finally, addition of acid brought about cyclisation and cleavage from resin to give a range of benzofuran products **132** in modest to good yield and high purity. One significant draw-back however was that the presence of the tetrabutylammonium salt produced in the cleavage mixture, which had to be removed by an aqueous wash, leading to reduced yields (Scheme 38).[101]



Scheme 38

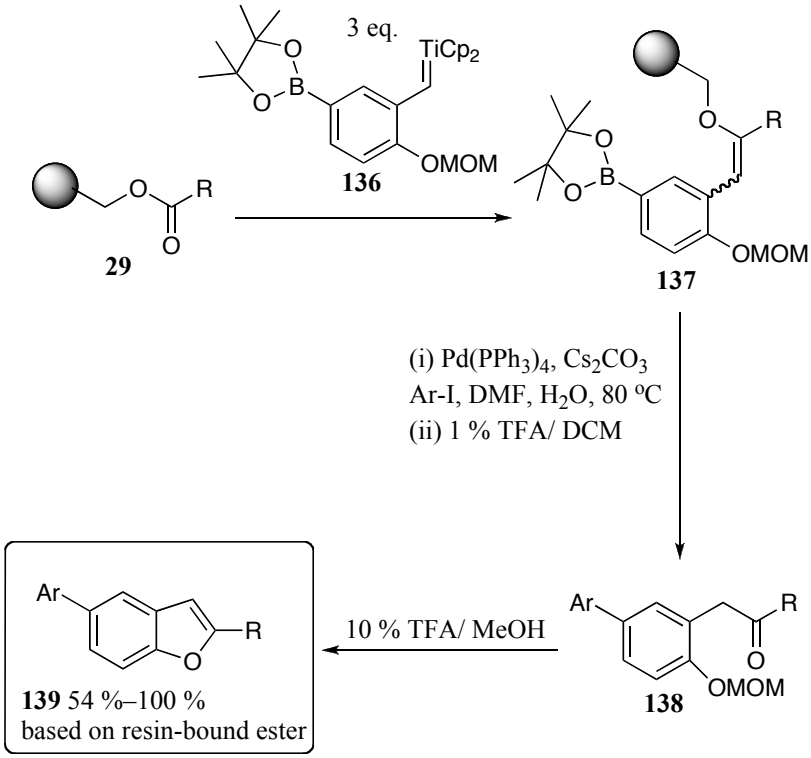
Optimisation and expansion on Emma Guthrie's early work was placed in the hands of Gordon McKiernan. Gordon found that trimethylsilyl (TMS) protected salicylaldehyde derived 1,3-dithianes **105** (Figure 8) were successfully desulfurized by the low valent titanium species **90**.[81] The resulting titanium benzylidene reagent **133** was then capable of alkylidenating resin-bound esters **29** to give the corresponding resin-bound enol ethers **134**. Cleavage from resin and cyclisation under mildly acidic conditions gave benzofurans **135** in good yields and excellent purities (Scheme 39). The previous issues encountered by Emma Guthrie had been avoided and the volatile silyl-containing side products were removed upon removal of solvent under reduced pressure.[81]



Scheme 39

Although successful, there was a limitation in Gordon's strategy in that no additional diversity was added after the switch of the linker. Gordon overcame this, by incorporating a boronate group in the titanium benzylidene reagent **136**.[83] Suzuki cross-coupling between resin-bound boronates **137** produced using this reagent and a variety of aryl iodides allowed access to a range of ketones **138**, which upon treatment with acid cyclised to give 2,5-disubstituted benzofurans **139** (Scheme 40). On the other hand, attempts at using dithianes bearing aryl bromides to produce titanium benzylidenes bearing a halide group for palladium-catalyzed cross-coupling reactions had to be abandoned. Unfortunately, under Gordon's conditions, aryl bromides and aryl chlorides were reduced whilst generating the low valent titanium species **90** i.e. $Cp_2Ti[P(OEt)_3]_2$.[81]

It should be noted that the immobilisation of the arylboronate component is advantageous as aryl halides are more widely and cheaply available in comparison to arylboronates.

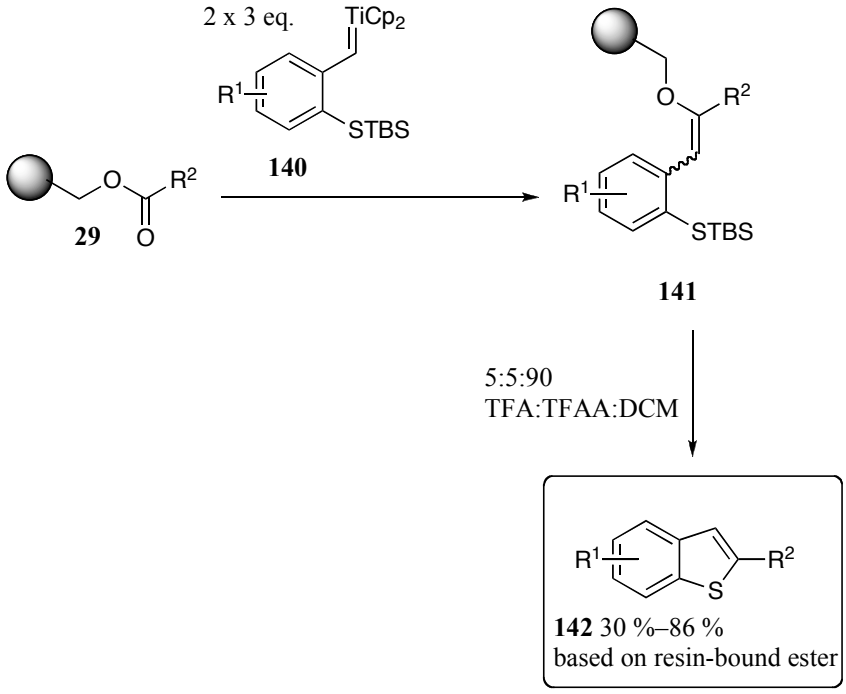


Scheme 40

Silyl protection had been employed to good effect in the original synthesis of the 2-substiuted benzofuran derivatives, however silyl ethers were unable to withstand the cross-coupling conditions in the synthesis of 2,5-disubstituted benzofurans. Therefore, a more robust protecting group was required and MOM protection proved effective.

4.2 Benzothiophenes

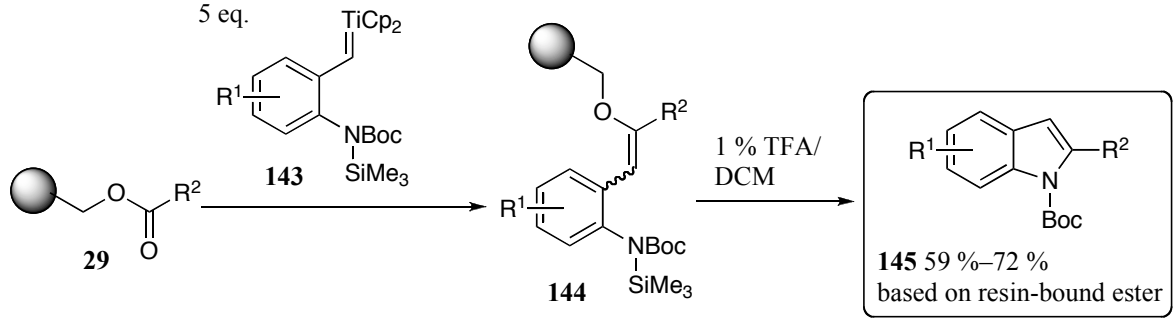
After the success of the benzofuran work accomplished by Emma Guthrie and Gordon McKiernan, the challenge was to explore other heterocyclic motifs using the same strategy. Christine Roberts was charged with the task of synthesising 2-substiuted benzo[b]thiophenes **142** from a novel masked sulfur-containing titanium benzylidene **140** (Scheme 41).[84] Titanium benzylidenes **140**, bearing the masked sulfur nucleophile in the *ortho* position, were generated from dithianes **107** (Figure 8) and the low valent titanium species **90** formed under Takeda conditions. Addition of the titanium benzylidene reagent **140** to Merrifield resin-bound ester **29** produced the desired conversion to enol ethers **141,** conversion being maximised by repeating the alkylidenation reaction. Subsequent treatment of the resin-bound enol ethers **141** with a 5:5:90 mixture of TFA, trifluoroacetic acid anhydride (TFAA) and DCM led to deprotection of the *tert*-butyldimethylsilyl protecting group, concomitant cleavage from resin and cyclisation. The material concentrated from the DCM wash contained, in excellent purities and modest to good yields, the desired 2-substitued benzothiophenes **142** (Scheme 41).



Scheme 41

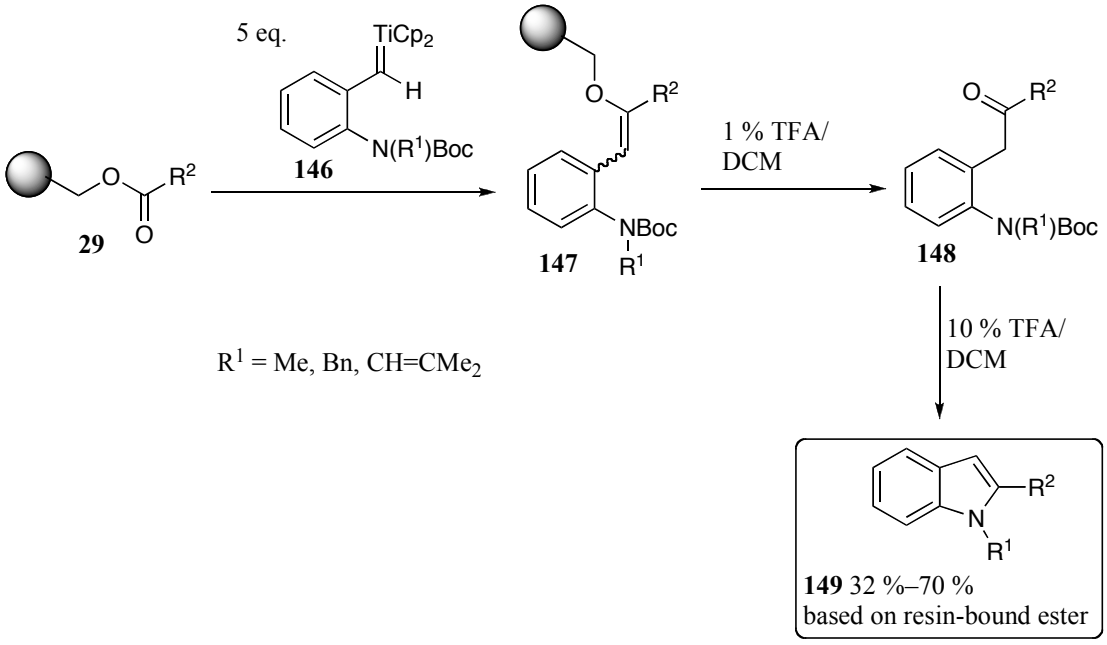
4.3 Indoles and Quinolines

Having successfully used the route to make benzofurans and benzo[b]thiophenes, the group focused their attentions on the solid-phase synthesis of nitrogen-containing heterocycles such as indoles and quinolines (Scheme 42, 43 and 44). Calum Macleod adapted the methodology developed by Emma Guthrie and applied it to the synthesis of 2-substituted indoles.[82]



Scheme 42

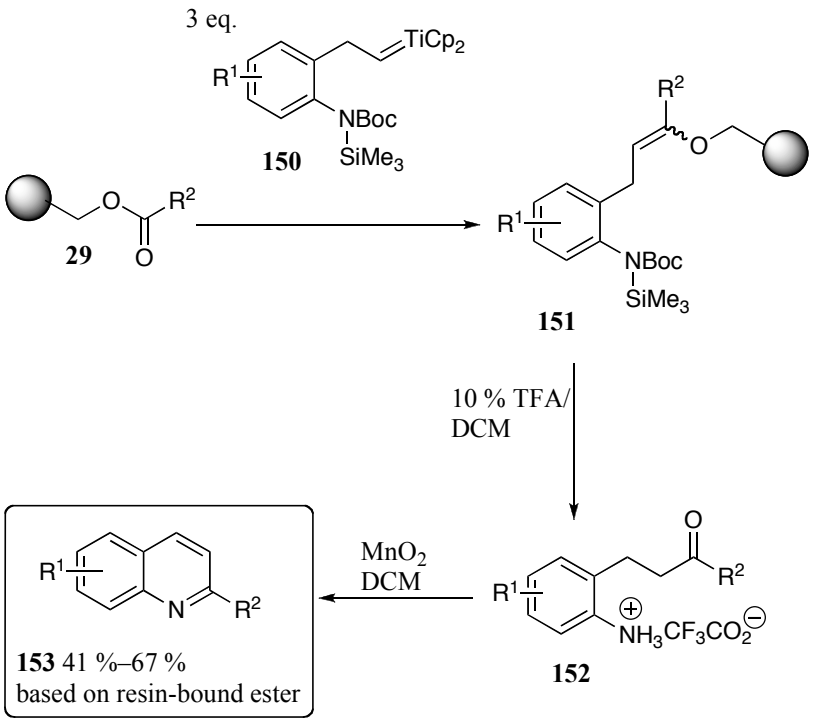
To prevent the possibility of intramolecular proton transfer, the carbamate derivates were deprotonated and silylated to yield *N*-Boc-silylated species **108** (Figure 8). The *N*-silylated carbamates **108** were used to produce titanium benzylidenes **143**, which converted resin-bound esters **29** into resin-bound enol ethers **144,** from which a number of *N*-Boc indoles **145** were generated in good yields and high purities (Scheme 42).[82]



Scheme 43

The *N*-methyl, *N*-benzyl and *N*-prenyl Boc-protected benzylic dithianes **109** (Figure 8) were also converted into the corresponding titanium alkylidene reagents **146**, and employed in the conversion of resin-bound esters **29** into resin-bound enol ethers **147** for the synthesis of *N*-alkyl indoles **149** *via* intramolecular cyclisation of ketones **148** (Scheme 43).[81] As demonstrated previously the chameleon catch strategy ensured high purity of the indole products.

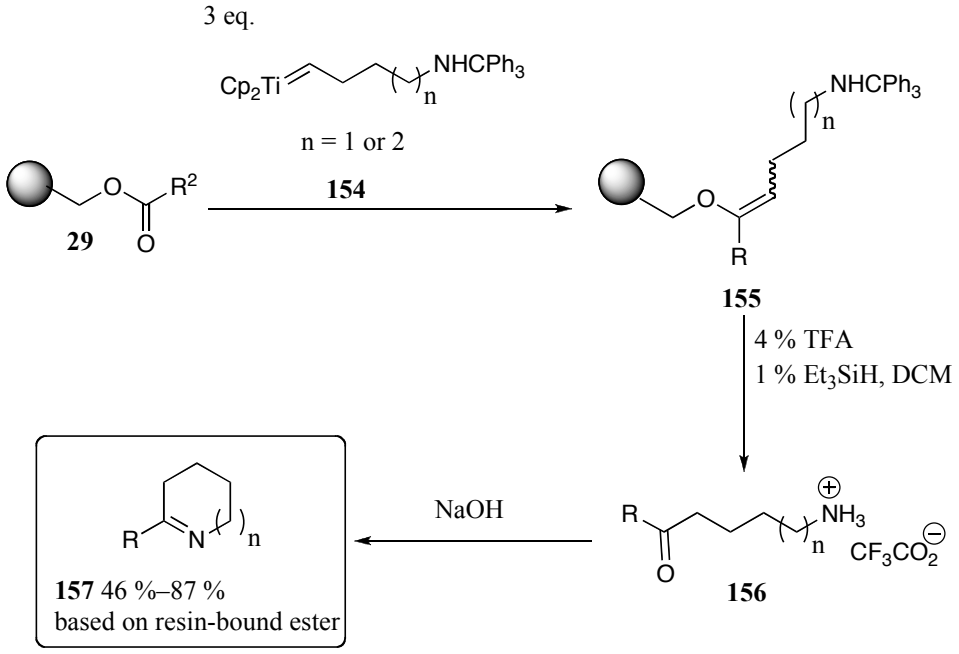
The above methodology was then adapted to the synthesis of a number of quinoline derivatives **153** (Scheme 44).[85] Titanium benzylidene reagent **150** alkylidenates resin-bound esters **29** to give the corresponding resin-bound enol ethers **151**. Cleavage from resin with TFA then produced the TFA salts **152**. Treatment with oxidative conditions converted the TFA salt **152** successfully into the desired quinoline derivatives **153**, in now customary high purity and modest to good yields.



Scheme 44

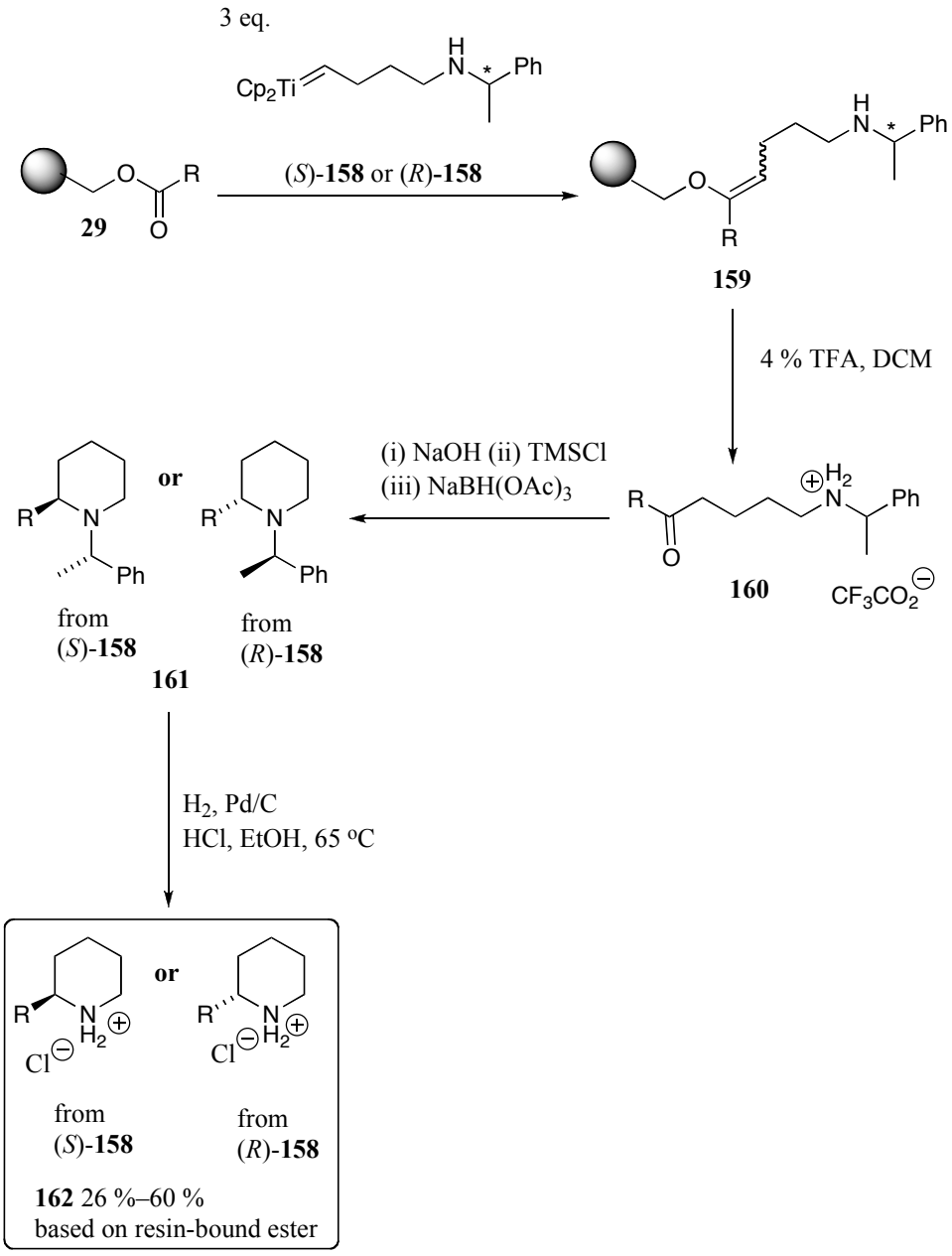
4.4 Piperidine Alkaloids

Carolyn Austin, having previously worked with Calum on the SPS of quinolines using functionalized titanium benzylidene reagents, turned her attention to the formation of titanium alkylidene reagents for the SPS of cyclic imines (Scheme 45). To access imines, Merrifield resin-bound esters **29** were first treated with the titanium alkylidenes **154**. The resulting enol ethers **155** were cleaved with mild acid in the presence of Et_3SiH and the solvent removed to give ammonium salts **156** (Scheme 45). The addition of Et_3SiH was required to reduce the trityl cation during cleavage so that the only side product was Ph_3CH. This was easily removed by washing the ammonium salts with hexane. Treatment with NaOH then generated imines **157** in good yields. [86, 102]



Scheme 45

Prior to Carolyn's work on cyclic imines, Mairi Gibson also of the Hartley group had been using enantiopure titanium alkylidene reagents for the conversion of resin-bound esters into chiral piperidines. This project was later taken up by Louis Adriaenssens, who optimised the synthesis and successfully developed a method for the stereodivergent diversity-oriented synthesis of piperidine alkaloids in high enantiomeric and diastereomeric purity[86] (Scheme 46).



Scheme 46

Asymmetric synthesis of piperidines **162** was achieved using the enantiopure titanium alkylidene compounds (*S*)-**158** and (*R*)-**158**. Alkylidenation of the resin-bound esters **29**, and acid-induced cleavage of the resulting enol ethers **159** gave the ketones **160**, which were cyclised and reduced stereoselectively to give the piperidines **161** (Scheme 46). Cyclisation to the iminium salt using trimethylsilyl chloride (TMSCl) provided a chloride counterion and gave only volatile side products. Removal of the chiral protecting group, 1-phenethyl (chosen as both enantiomers of 1-phenethylamine are commercially available) gave (*R*)- and (*S*)-2-substituted piperidines **162** as hydrochloride salts with high *ee* values. All were obtained in excellent purity in good yields (Scheme 46).[86]

4.5 From Merrifield Resin to Heterocyclic Privileged Structures *via* Titanium Carbenoids.

The application of novel titanium benzylidene reagents capable of converting Merrifield resin into exciting heterocyclic structures is one of the Hartley team's key aims. From cheap, commercially-available Merrifield resin, the team can generate a diverse range of privileged heterocyclic motifs (both aromatic and non-aromatic). Recently in the case of piperidine synthesis, this has been achieved with enantioselective control (Figure 9).[86]

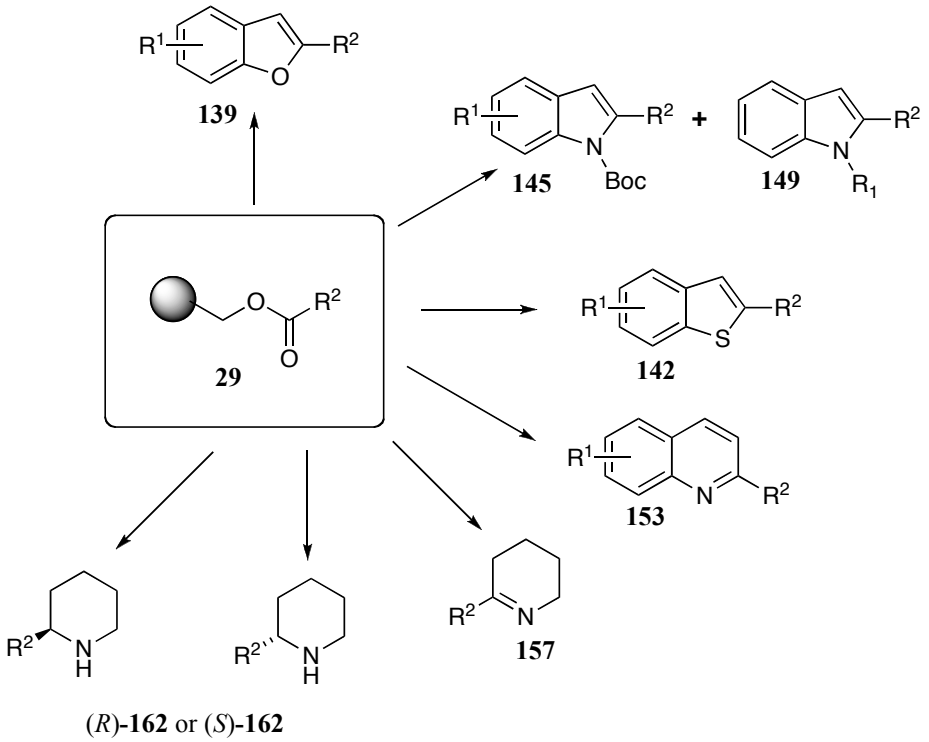


Figure 9

My first contribution was to further the methodology, by demonstrating a strategy to introduce extra diversity into the indole series. My primary goal was to introduce diversity after the switch of the linker. Although this had been achieved in the benzofuran series, the analogues synthesis would prove more demanding but more rewarding, due to the importance of indoles as privileged structures. To achieve this I would need to generate a boronate-bearing titanium benzylidene reagent. Once this reagent had been tested, I would use it at GlaxoSmith Kline to prepare a library of 96 diverse 2,5 disubstituted indoles. In the following chapters, I will discuss literature synthetic strategies for the preparation of indoles with particular emphasis on SPS of 2-substiuted indole derivatives, before discussing my own results.

CHAPTER 5 – Indoles

The fusion of a benzene ring onto the C-2/C-3 positions of pyrrole formally gives rise to the corresponding benzopyrrole known more commonly as *indole* an acronym from *ind*igo (the natural dye) and *ole*um (used for isolation) (Figure 10).[103]

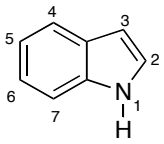


Figure 10

Indole is composed of a ten-π electron system, eight from the four double bonds and two from the lone pair of the nitrogen atom. As with pyrrole, delocalisation of the electron pair from nitrogen atom is required for aromaticity, conforming to the (4n+2π electrons) Hückel rule (Figure 11).[104]

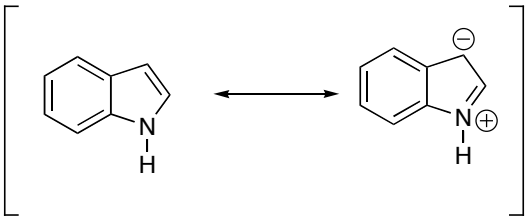
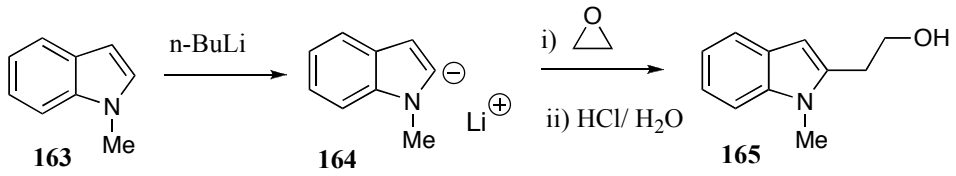


Figure 11

5.1 Reactivity of the Indole

A consequence of the delocalisation of the nitrogen lone pair is that the lone pair is not available for protonation under moderately acidic conditions. Thus, like pyrrole, indole is not a basic heterocycle. Similarly the 'electron-rich' heterocycle easily undergoes aromatic electrophilic substitution. However, in an important difference to pyrrole, indole will only substitute selectively at the C-3 position. The explanation is that the attack at C-2 results in disruption of the aromaticity of the benzenoid ring. In many ways, indole tends to react like an enamine towards nucleophiles, with substitution occurring at the C-3 position. In order to gain access to the corresponding C-2 position, the C-3 position or the nitrogen must be blocked. For example, when the nitrogen is blocked, treatment of indole **163** with strong bases such as butyl lithium, Grignard reagents or metal hydrides produces the indolyl anion **164**, capable of reacting with electrophiles to give introduction of functionality to the C-2 position, *e.g.* with ethylene oxide to give indole **165** (Scheme 47).[104]



Scheme 47

5.1.1 Biologically Active Indoles

The indole nuclei, a 'privileged structural' motif, can be found in a wide range of natural compounds possessing a spectrum of physiological activities.[105] The Indole moiety is one of the most commonly occurring heterocycles in nature, predominantly in the form of the essential amino acid tryptophan **166**.[106] Tryptophan is the key precursor in the biosynthesis of tryptamine **167**, from which is produced serotonin **168**, an important neurotransmitter in mammals. Indoles are also found in plants, *e.g.* as the plant growth hormone heteroauxin **169** (Figure 12). [107]

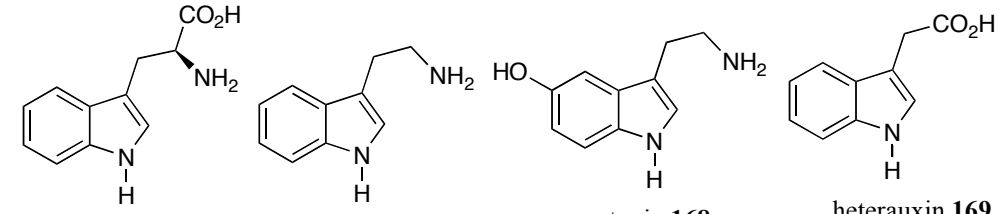
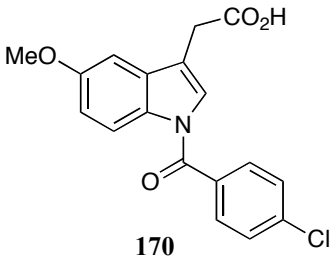


Figure 12

Historically, interest in indoles arose with the isolation and characterisation of members from an enormous family of indole alkaloids, commonly those found in fungi known for their psychoactive effects.[104] Following on from the observation that certain indoles, such as lysergic acid derivative lysergic acid diethylamide (LSD), had potent central nervous system activity, it was quickly established that indole derivatives may posses interesting and more-over useful biological activity. Although indole alkaloid chemistry is still very much an active area of natural product chemistry, more interest has been focused on the

preparation of indole derivatives as drug candidates, such as Merck's anti-inflammatory drug, Indomethacin **170** (Figure 13).[108]

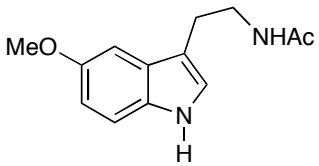


170

Indomethacin
anti-inflammatory drug

Figure 13

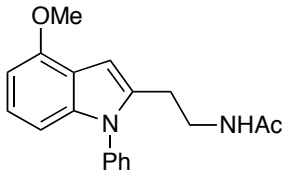
In addition to the more abundant, naturally occurring, 3-substiuted indoles, like the ones mentioned earlier, various 2-substituted indoles exhibit interesting pharmacological properties. An excellent example of this comes from the biological properties of the 2-substituted analogues of the hormone melatonin **171** (Figure 14).[109,110]



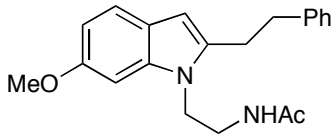
melatonin **171**
hormone

Figure 14

The hormone melatonin, endogenous to mammalian systems, regulates circadian rhythms and sleep processes. Regulatory imbalance of the hormone is thought to lead to sleeping disorders such as insomnia and also to increased risk of hypertension.[109, 111] Melatonin acts with high affinity on the G-protein membrane methoxytryptamine receptors MT_1 and MT_2.[111] The 2-substituted melatonin analogue **172** (Figure 15) has higher affinity for the MT_1 receptor than the native hormone melatonin.[109] Additionally, indole **173** (Figure 15) exhibits an affinity similar to that of melatonin for the MT_1 receptor, but it has lower affinity for the MT_2 receptor.[111] It is therefore the hope that 2-substituted melatonin analogues may eventually become useful drugs to help with disorders associated with melatonin imbalance.



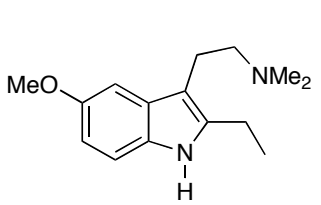
172



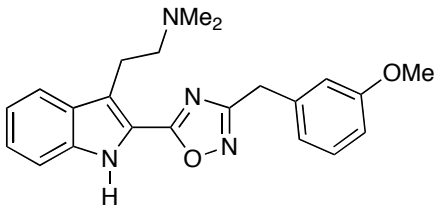
173

Figure 15

In the mammalian system, the neurotransmitter serotonin **168** (5-hydroxytryptamine, 5-HT) is synthesized from the amino acid tryptophan **166** by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). Serotonin acts on the serotonin/ 5-HT receptors classified into one of several different families 5-HT_1–$5HT_7$.[112] Of particular interest is the 5-HT_6 receptor, a member of the G-protein superfamily, this particular receptor is found primarily in the central nervous system (CNS). Although the exact clinical significance of 5-HT_6 receptors is not fully understood at this time, interest was sparked upon the observation that antipsychotic agents and tricyclic antidepressant bind with high affinity to the 5-HT_6 receptors.[113] Therefore 5-HT_6 ligands might be of value in the treatment of anxiety and mood related disorders.[114] Additional studies of the 5-HT_6 receptor suggest involvement in motor function, mood-dependent behaviour and the early growth process involving serotonin.[115] A study of 2-substitued analogues of serotonin identified indole **174** as the most selective 5-HT_6 agonist reported, [110] with another 2-substitued analogues **175** acting as an antagonist (Figure 16).[116]



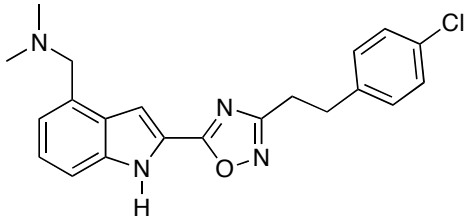
174



175

Figure 16

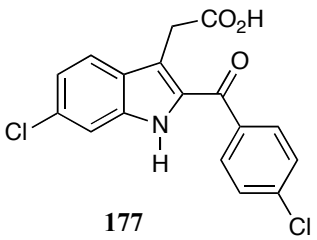
Other bioactive 2-substituted indoles recently reported include indole derivative **176** (Figure 17), identified as a novel antagonist for the G-protein coupled receptor ORL1.[117] Although the ORL1 receptor is known to have a 47 % overall identity to classical opioid receptors (μ, ∂, κ), native opioid peptides and synthetic agonists for μ, ∂, κ receptors show no significant affinity for ORL1 receptors.[118] The discovery of the affinity of indole **176** to the ORL1 receptor raises the possibility of a new class of drug for disorders involving pain and anxiety.



176

Figure 17

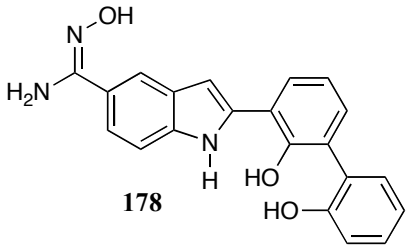
Selective cyclooxygenase-2 (COX-2) inhibitors are known for being very effective nonsteroidal anti-inflammatory drugs, however many produce undesirable gastric effects, including peptic ulceration. The potent COX-2 inhibitor indole, **177** (Figure 18), was reported as a potential lead candidate for an anti-inflammatory without the associated side effects.[119]



177

Figure 18

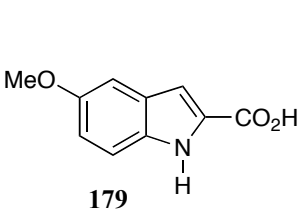
Recently, 2,5-disubstituted indoles have emerged as intriguing potential candidates in the search for therapeutic agents. Indole **178** was observed to be an inhibitor of the proteases involved in coagulation e.g. factor VIIa inhibitors, for the treatment and prevention of thromboembolic disease, including deep vein thrombosis and pulmonary embolism (Figure 19).[120, 121]



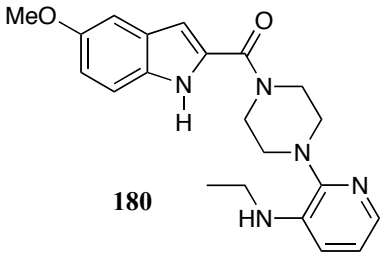
178

Figure 19

Peakdale's, 2,5-disubstituted indole derivative **179** has been shown to be an extremely useful intermediate in the preparation of a wide range of pharmaceutical intermediates.[122] A production-scale synthesis of the non-nucleoside reverse transcriptase inhibitor Atevirdine mesylate **180** was reported utilising indole **179** (Figure 20).[123]



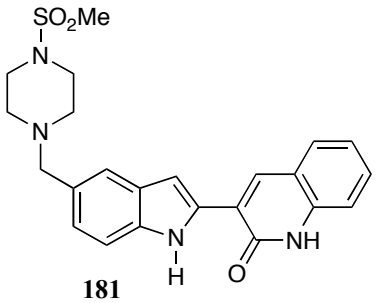
179



180

Figure 20

Anti-angiogenesis chemotherapy is an emerging field in clinical oncology and studies have highlighted vascular endothelial growth factor (VEGF) as a primary mediator in tumour-induced angiogenesis.[124] As such, the inhibition of VEGF action is now an ongoing priority in angiogenesis research. Recently, a screening campaign against the tyrosine kinase, KDR, found indole **181** as a selective and potent KDR inhibitor. The binding of VEGF to its receptor leads to KDR activity in endothelial cells. Thus, this recent discovery represents an early breakthrough for inhibitors of tumour-induced angiogenesis (Figure 21).[125]

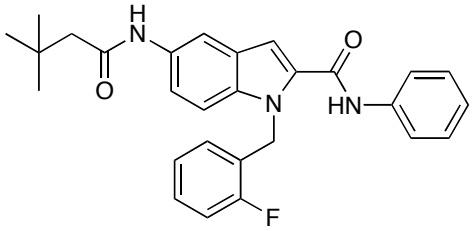


181

Figure 21

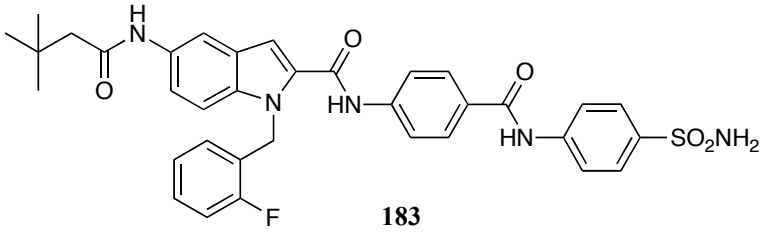
Endothelin (ET-1), discovered in 1998, has been the subject of considerable attention for the past decade, investigation of its metabolism and its potential implication in several diseases has lead to numerous attempts to produce antagonists to the ET-1 receptors.[126] Blockade of ET-1 receptors by ET-1 receptor antagonists have been widely studied both in animal models and clinical trials in order to evaluate the treatment of various diseases including hypertension, congenitive heart failure and cancer.[127] ET-1 is the product of cleavage of its precursor big-ET *via* the action of endothelin-converting-enzyme (ECE). Over the years, several inhibitors of ECE have been described, as an attractive target to modulating ET-1 levels. The majority contain structural motifs such as thiols and phosphonates. These particular pharmacophoric groups are very important for binding to the zinc-containing catalytic centre of ECE, and hence their ability to inhibit the enzyme, but they are known to lead to detrimental pharmacokinetic properties.[128] Thus there is a real need to discover novel lead structures for ECE inhibitors that do not posses such groups.

Bayer Health Care AG, have recently identified one such lead candidate from a high throughput screening (HTS) programme. Indole **182** is a potent ECE inhibitor, with what appears to be no obvious zinc chelating components (Figure 22).[129] From an intensive solid-phase combinatorial synthesis and screening of compounds based on the original indole **182**, indole derivative **183** was found to have optimal *in vitro* inhibitory activity on ECE, having a 50-fold increase in activity in comparison to the original indole. Currently, indole **183** is being used to further investigate the unexpected binding mode to the enzyme (Figure 22).[130]



182

Lead from HTS



183

Optimised lead

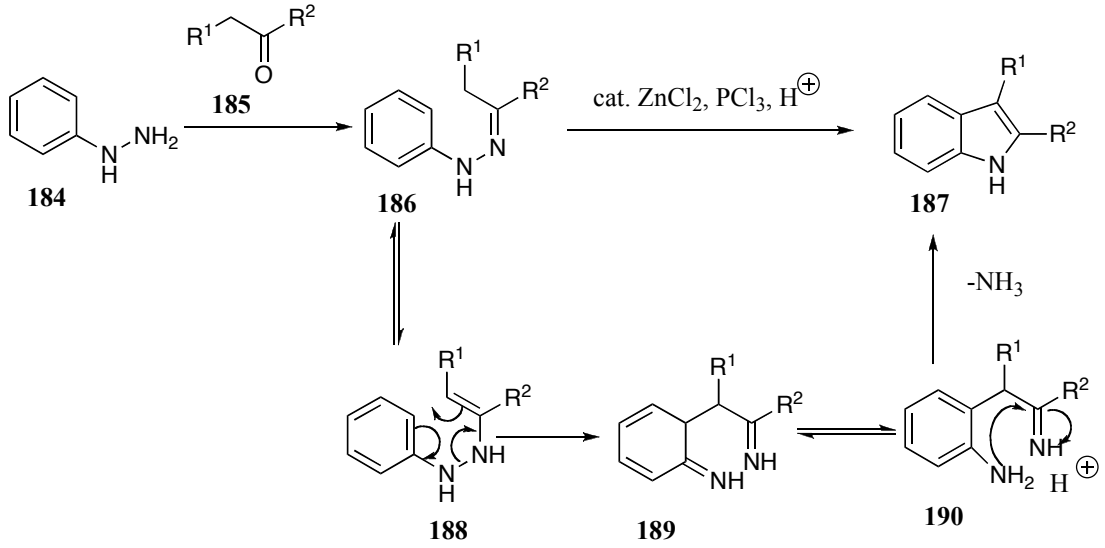
Figure 22

5.2 SPS of Indoles

Indoles and indole derivatives are considered to be the archetypal privileged structure and as such lend themselves to belonging within any class of pharmacologically active compounds.[131] Consequently the rapid generation of indole libraries is very attractive to both synthetic and medicinal chemists. New methods for the construction and modification of indole moieties are continually being reported, as such the volume of synthetic strategies, both in SPS and solution phase synthesis, is extensive.[108, 132] Therefore, I will focus on comprehensively reviewing the construction of 2-substituted indoles by solid-phase synthesis. Additionally, although many groups have constructed small-molecule libraries based on the decoration of pre-formed indole scaffolds, [133] I will concentrate on those methods used in construction of the indole moiety on resin.

5.2.1 Fischer Indole Synthesis

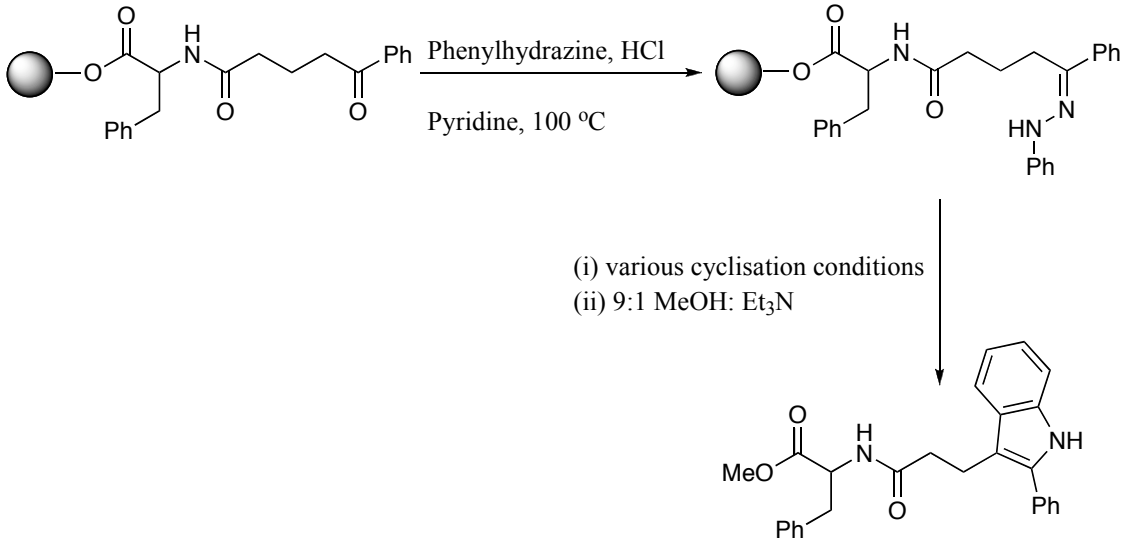
First developed in 1883, by Emil Fischer, the Fisher indole synthesis remains as probably the most widely used method for the solution-phase synthesis of indoles (Scheme 48). It is noteworthy, that suppliers of pharmaceutical intermediates still to this day utilise this method in preference to any other indole synthesis.[104]



Scheme 48

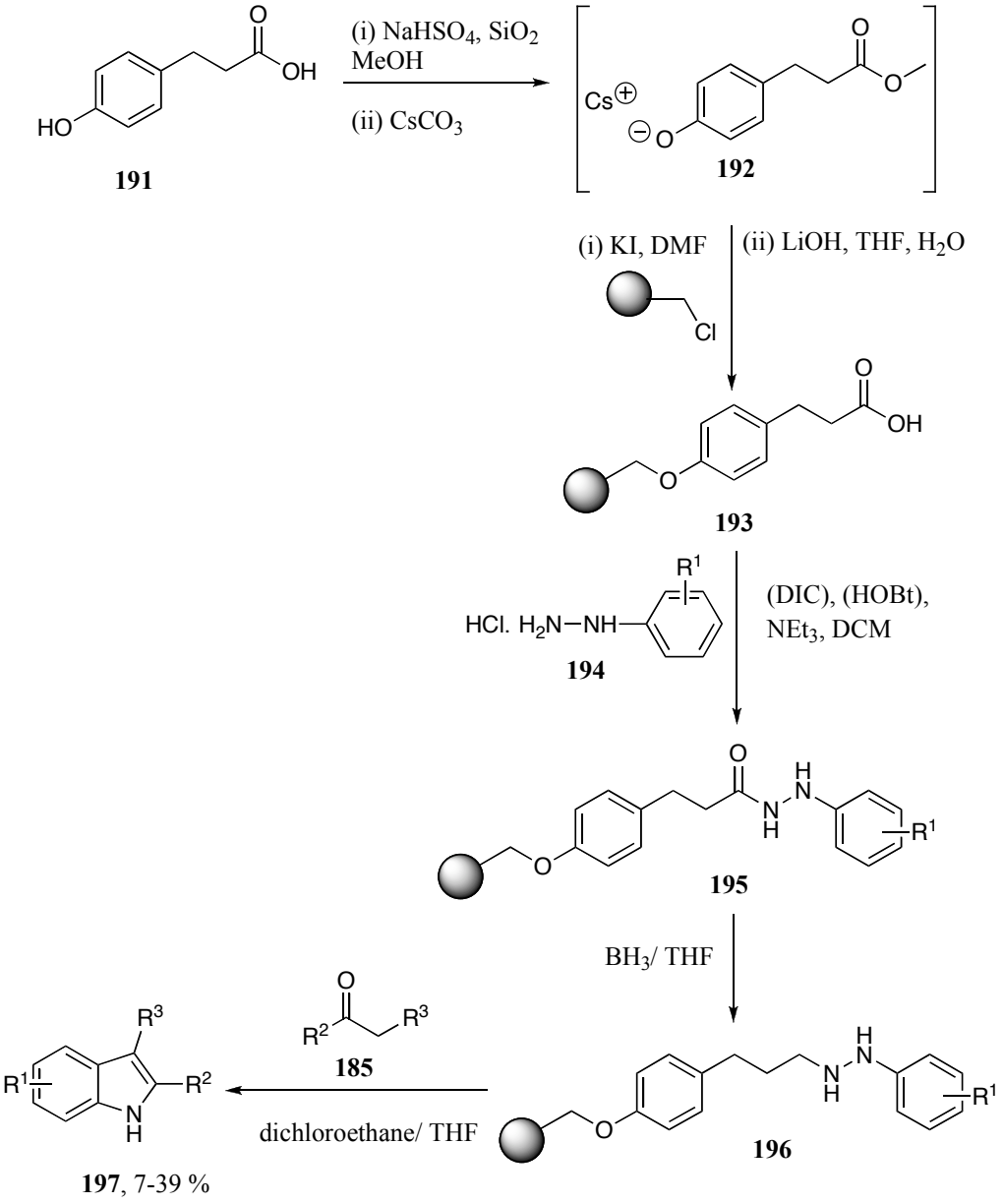
The Fischer indole synthesis proceeds with the condensation of aryl hydrazine **184** with a ketone **185**. The next step is the acid-catalysed equilibration between hydrazone **186** ene hydrazine **188**. The hydrazine **188** undergoes a [3,3] sigmatropic rearrangement, forming a strong C-C bond and breaking the relatively weak N-N bond. The resulting imine **189** re-aromatises by tautomerisation to aniline **190**. Finally acid-catalysed elimination of ammonia forms indole **187**.

In 1996, the Fischer indole synthesis was adapted to SPS by Hutchins *et al*. (Scheme 49). The method allowed only one avenue to introduce diversity, *via* different hydrazine hydrochlorides, the yields and purity were variable and the synthesis was not traceless, leaving an ester at the site were resin was attached.[134]



Scheme 49

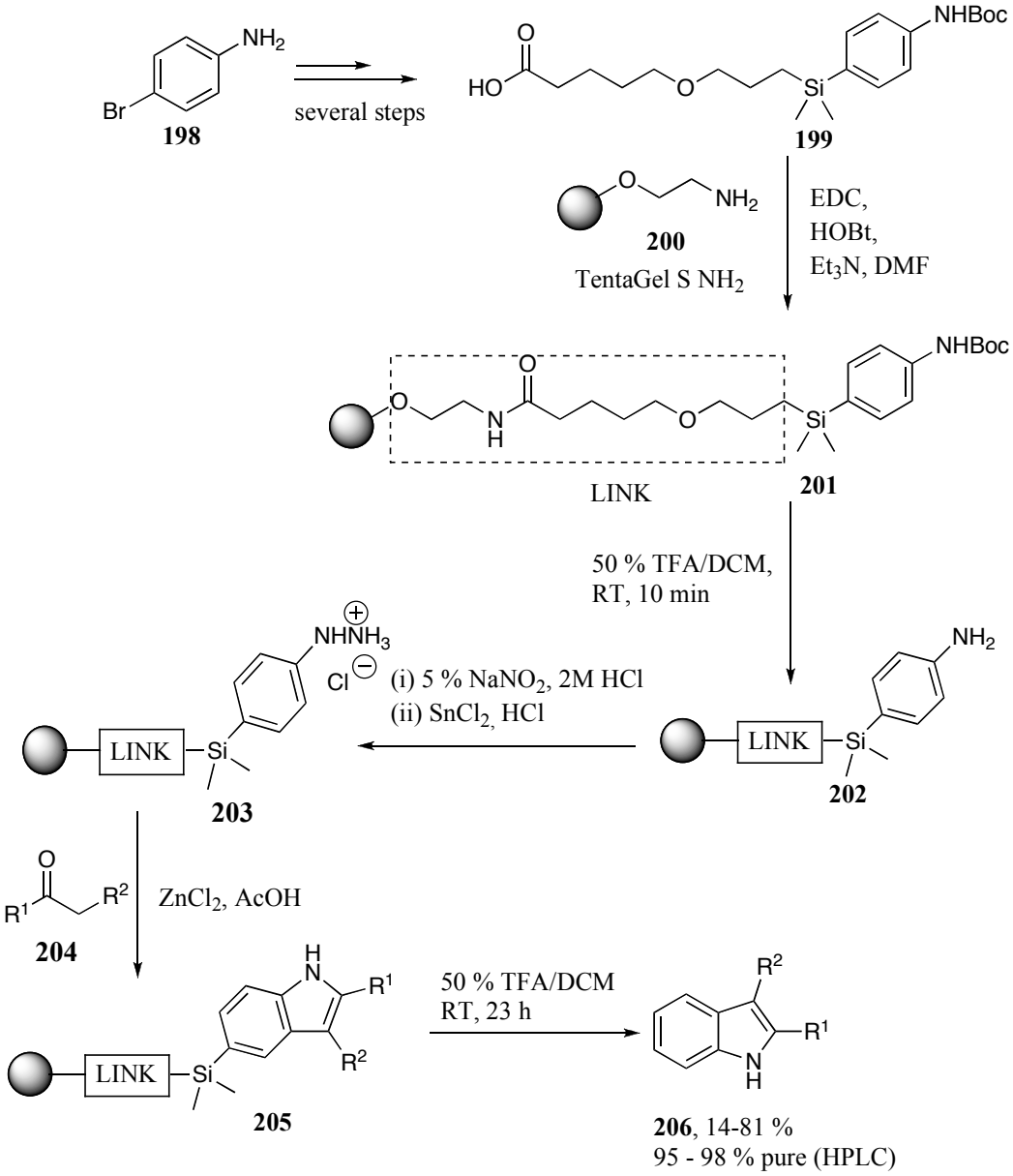
Since then many improved techniques, including the traceless Fischer indole SPS, have emerged. The strategy developed by Rosenbaum *et al*. employs solid supported hydrazines **195** to which a number of ketones **185** can be added (Scheme 50).[135] The supported hydrazines **195** were prepared starting with the conversion of *para*-hydroxyphenylpropionic acid **191** into the methyl ester followed by deprotonation to give phenolate **192**. Nucleophilic attack on Merrifield resin followed by hydrolysis proceeded to yield the resin-bound carboxylic acid **193**. This was coupled with various hydrazines **194** using diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) to give resin-bound amides **195**, which were reduced to give hydrazines **196**. A number of ketones **185** were then reacted with the solid-supported hydrazines **195**. Under typical conditions for the Fischer indole synthesis, the resulting [3,3] sigmatropic rearrangement and intramolecular attack of the formed aniline, leads to the traceless release of indole derivatives **197** from the polymeric carrier. In total eleven, 2-susbstituted and 2,3 disubstituted examples were synthesised in modest yield after chromatography.



Scheme 50

Recently, Mun and co-workers presented a traceless Fisher indole strategy from solid phase for the synthesis of 2,3 disubstituted indoles (although the method could be adapted to synthesis of 2-substituted indoles).[136] As in the previous case, the group envisaged solid-supported hydrazine precursors for indole synthesis, however this method employs a modified Ellman silicon-based traceless linker. The original silicon traceless linker first reported by Ellman *et al*. consists of a carbon chain, as the spacer group, between resin and the silicon-bound reagent.[137] Although initially used by Mun and co-workers, they found that they could not form the diazonium salt due to problems with solvation. The inclusion of an oxygen group mid-way into the carbon chain, spacer group, was seen to enhance solvation.

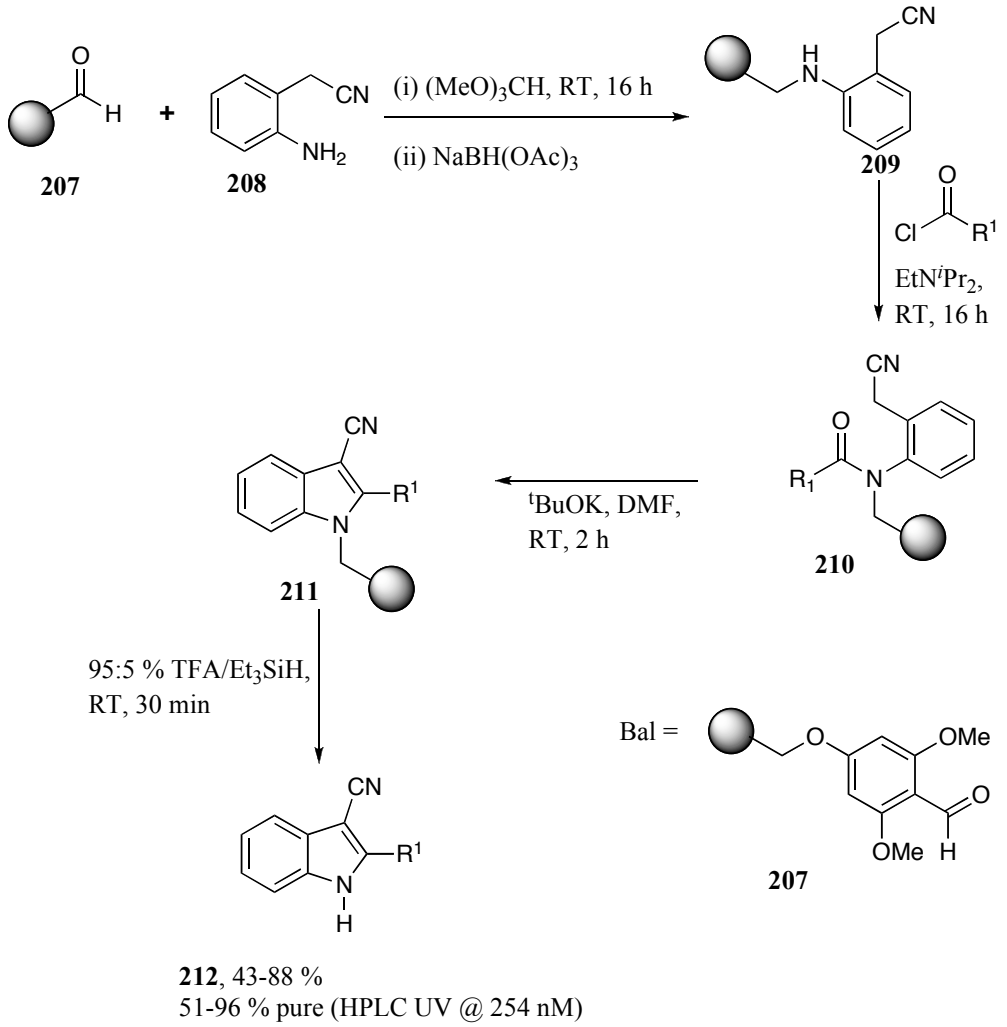
The traceless linker **201** was prepared by coupling a carboxylic acid **199,** derived from 4-bromoaniline **198**, with TentaGel S NH_2 resin **200** swollen in DMF using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Scheme 51).[136] The Boc-group was then removed by only short exposure (10 min) to TFA in DCM so as to avoid silicon-carbon bond cleavage. The resulting resin-bound aniline **202** was then converted into the corresponding hydrazine **203**, the process being monitored *via* the ninhydrin test to establish presence of amine. The hydrazine **203** underwent Fischer indole synthesis upon addition of ketones **204** having an α-methylene group. The resulting solution was shaken for 23 h at 70 °C to give resin-bound 2,3-disubstituted indoles **205**, before finally being exposed to TFA/ DCM (1:1) for 23 h. Cleavage of the silicon-carbon bond released the 2,3-disubstituted indoles **206** in excellent purity. In total sixteen, 2,3-disbstituted indoles were obtained in moderate to good yields (Scheme 51).



Scheme 51

5.2.2 Madelung Indole Synthesis

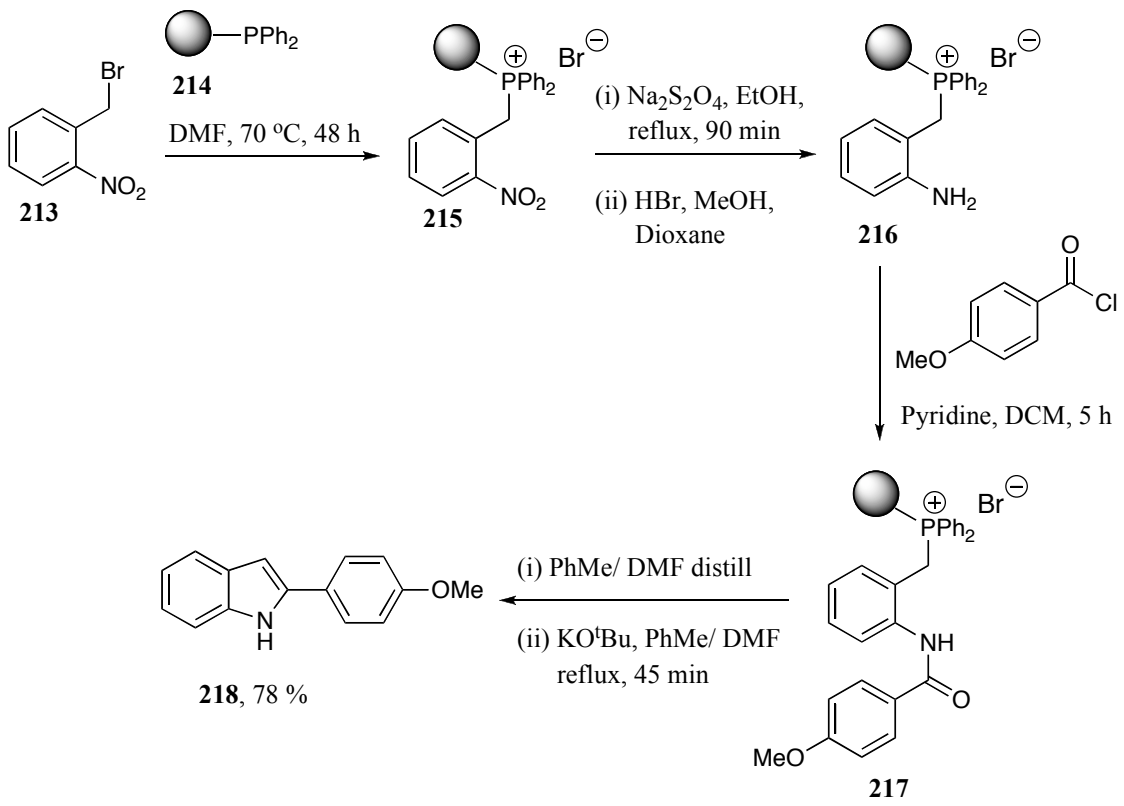
The Madelung indole synthesis has also been adapted to solid phase, the first reported case of a solid-phase Madelung indole synthesis comes from the work by Wacker *et al.*[138] Aniline **208** was loaded onto Bal-resin **207**. The resulting imine was reduced to a secondary amine **209** and then acylated (Scheme 52). The resulting resin-bound amides **210** were then converted into resin-bound indoles **211**, *via* an intramolecular cyclisation-dehydration step, and cleaved from resin under strongly acidic conditions to give 15 examples of 2-subsitiuted 3-cyanoindoles **212**.[138]



Scheme 52

5.2.3 Wittig Indole Synthesis

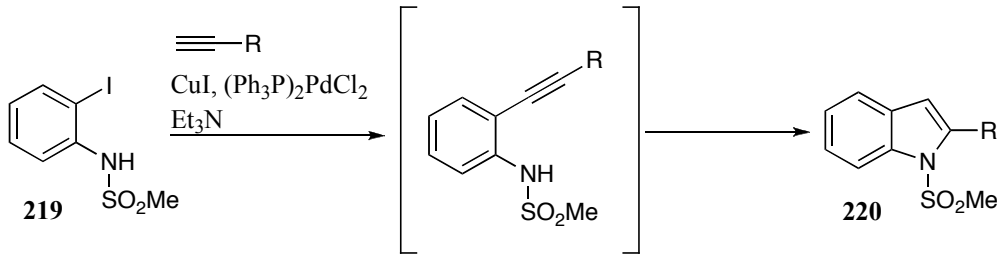
Hughes developed an intramolecular Wittig reaction, involving a resin-bound phosphonium salt bearing an internal amide **217**, to give a traceless SPS of 2-substituted indole **218** (Scheme 53).[139] The phosphonium salt was easily generated from commercially available benzylic bromide **213** and resin-bound triphenylphosphine **214**, to give resin-bound phosphonium group **215** that was sufficiently stable to a range of conditions, allowing its use in subsequent reactions as a traceless linker. The nitro group was reduced to an amine with sodium dithionite, and this was followed by HBr treatment to regenerate the bromide counter ion. In the only example, the resulting resin-bound aniline **216** was then acylated to give amide **217**. Finally, intramolecular Wittig reaction, under anhydrous conditions, produced 2-substituted indole **218**. Although a very novel method to the traceless creation of an indole derivative, only one such example *via* this method exists.



Scheme 53

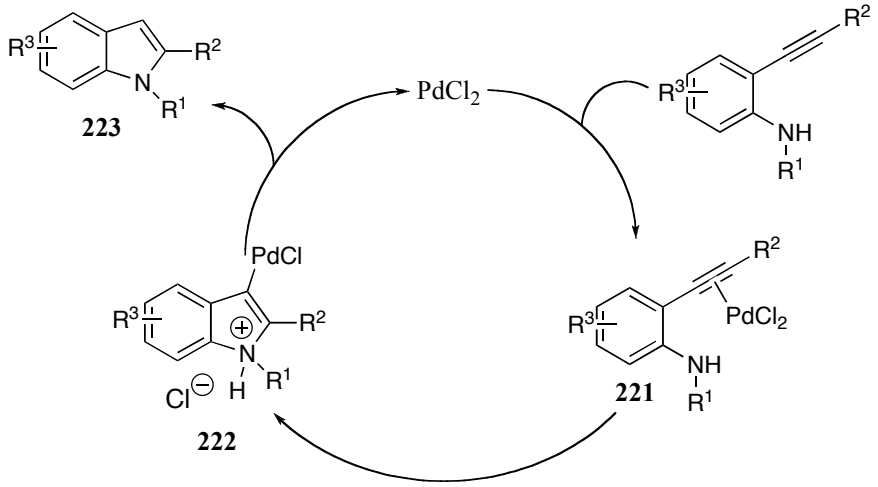
5.2.4 Palladium-Mediated Indole Synthesis

Arguably, the most popular method for the formation of indoles on solid-phase involves the palladium catalysed heteroannulation of terminal or internal alkynes.[103] The first solution-phase example of palladium-catalysed cyclisation of an *ortho*-alkynylanilide to give an indole was by Taylor and McKillop[140] in the mid-1980's. Their procedure however has rarely found application in indole synthesis, most probably due the toxicity of the reagents used. A significant improvement in palladium-mediated indole synthesis came from Yamanaka and co-workers, who observed that treatment of 1-alkynes with *ortho*-iodo-*N*-mesylanilides **219** under Sonogashira conditions could directly afford indoles **220** in a single operative step; through a domino coupling cyclisation process with the palladium catalyst involved both in the coupling and in the cyclisation reaction (Scheme 54).[141]



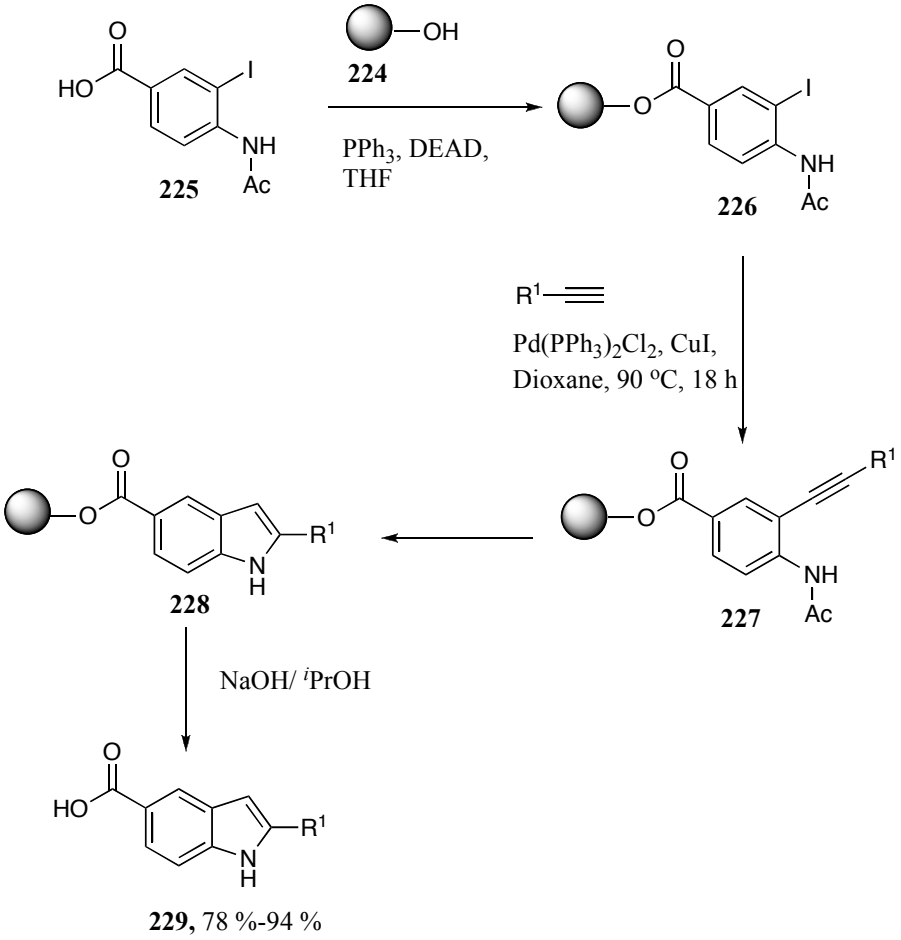
Scheme 54

The proposed reaction mechanism for the palladium-catalysed cyclisation, is comprised of the following steps: (i) initial formation of a π-alkynepalladium complex **221**, (ii) intramolecular nucleophilic attack of the nitrogen nucleophile onto the activated carbon-carbon triple bond to give the σ-indolylpalladium complex **222**, (iii) proton transfer with loss of palladium(II), which enters a new catalytic cycle, and formation of indole **223** (Scheme 55).[103]



Scheme 55

SPS of indole derivatives for the generation of indole-based libraries were then developed, the solid-phase part of the process involved tethering the *ortho*-iodo aniline, usually in the 5-position, by either Rink amide AM®[142], TentaGel-S®[143] or Wang[144] resins and cleaving with acid or base. In the example from Bedeschi *et al*. commercially available TentaGel-S resin in the OH form **224** was coupled with 3-iodo-4-acetamidobenzoic acid **225** under standard Mitsunobu conditions to provide resin-bound derivatives **226** (Scheme 56).[143] The resin-bound substrates were then coupled with alkynes using standard conditions to yield the polymer-bound alkynes **227**, which cyclise *in situ* to indoles **228**. Indoles **228** were then cleaved from the resin in 1M NaOH/ *i*-PrOH to give 2,5-disubstituted indoles **229**.



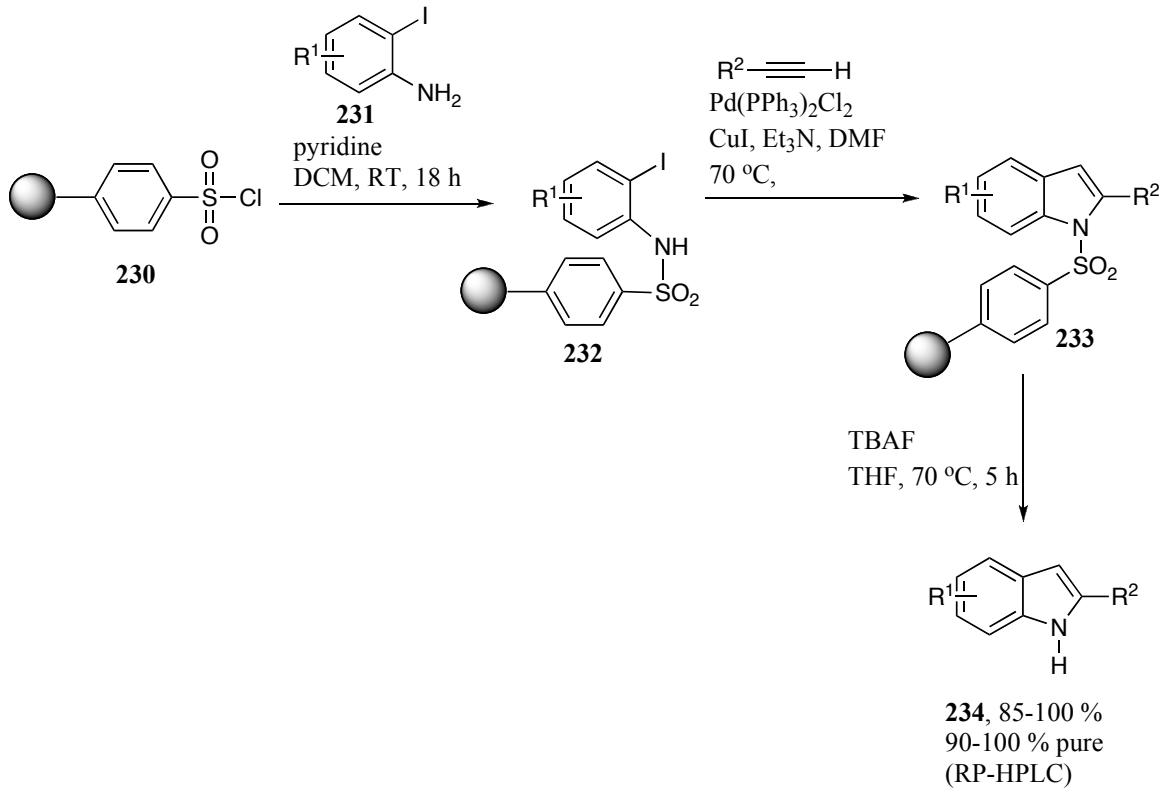
Scheme 56

The method was also adapted to include further diversity by introduction of a vinyl group, from a vinyl triflate, during the cyclisation step, incorporation of the vinyl group into the 3-position gave after cleavage 2,3,5-trisubstituted indoles. Additionally, alkylation of the *N*-H core was easily achieved with NaH and alkyl halide to give ultimately a 1,2,3,5-tetrasubstituted indole.[144] These methods were straightforward, the conditions mild so theoretically suitable for automated combinatorial array, yields satisfactory and purities high. However there was one very inconvenient draw back in every case. The cleavage strategies all left polar substituents at the site where the resin was previously attached. Polar groups such as carboxylic acids and carboxyamides are known to affect structure activity relationships and thus limit the application of this method for the synthesis of libraries for drug discovery.

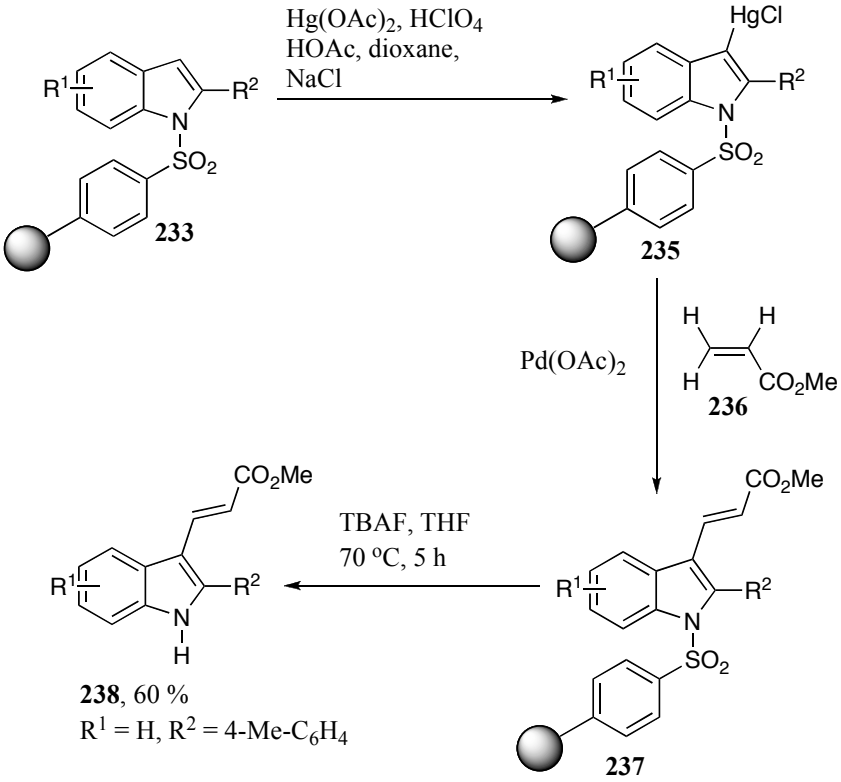
Zhang and co-workers developed a traceless method[145] based on Yamanaka's cyclisation procedure. Resin-bound arylsulfonyl chloride **230** was reacted with a range of anilines **231** to give sulfonamides **232**. Reaction with a range of terminal alkynes then gave resin-bound indoles **233**. Treatment with fluoride then released the indoles **234** from resin (Scheme 57).

The sulfonamide group played two roles in this SPS: firstly, it acted as an easily cleaved traceless linker (the cleavage conditions tolerating both acid- and base-sensitive substituents) and secondly, its low pKa allowed the *in* situ formation of a better nitrogen nucleophile for the cyclisation.[146]

This method produced ten diverse 2-substituted indoles **234** in excellent yield and purity (Scheme 57). The terminal alkyne can deliver diverse functionality in the form of alkyl, ether, thioether, alcohol, acetyl, aryl with electron-donating or electron-withdrawing substituents and even heterocycles. Substituents on the resin-bound 2-iodoaniline **232** can also be electron-donating or electron-withdrawing. The sulfonyl linker also proved effective during mecuration, organomercurial species **235**, generated from resin-bound indole **233**, was coupled with methyl acrylate **236** in the presence of $Pd(OAc)_2$, and after cleavage of **237** with TBAF, 2,3-disubstiuted indole **238** was isolated in good yield (Scheme 58).

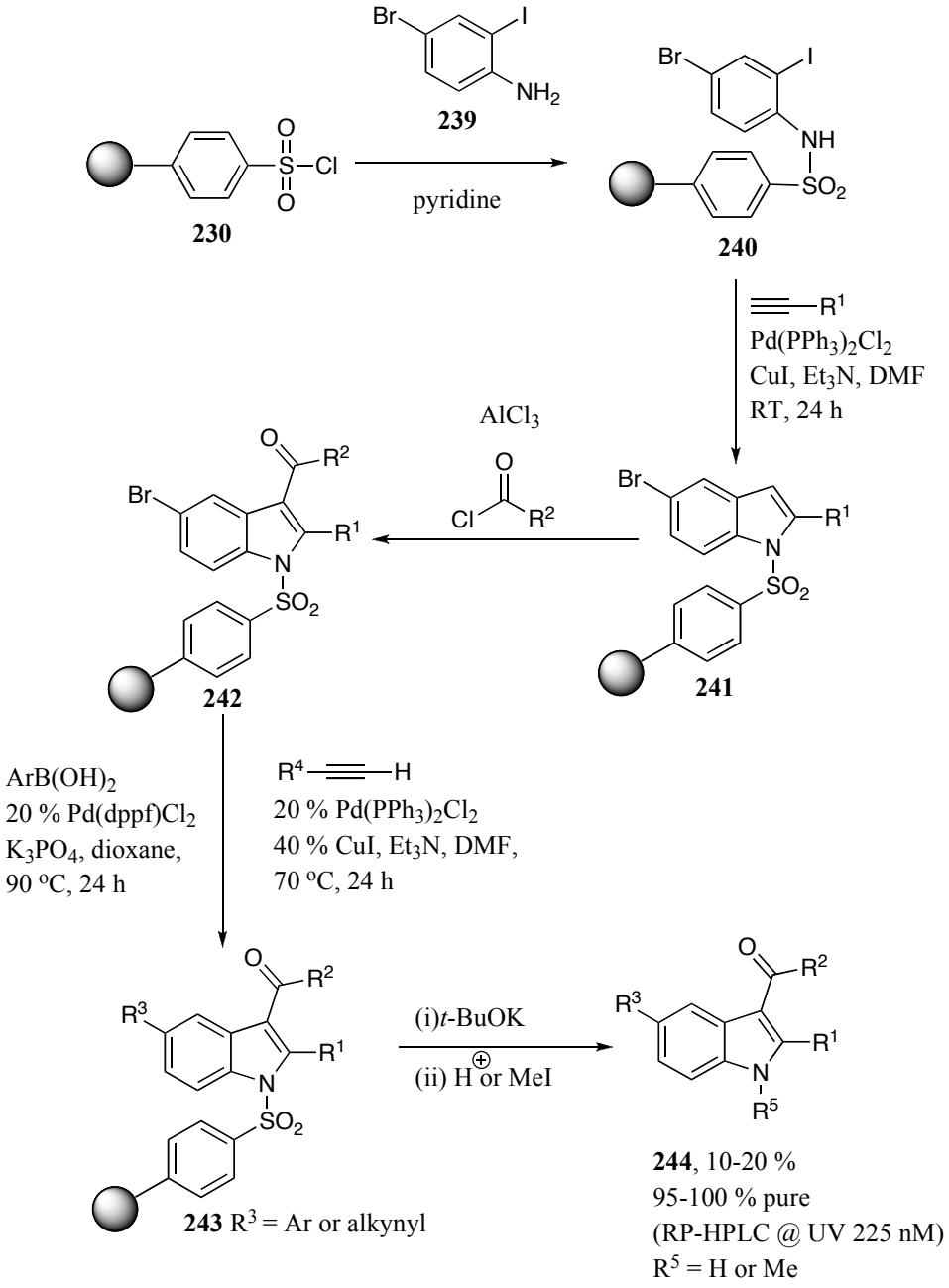


Scheme 57



Scheme 58

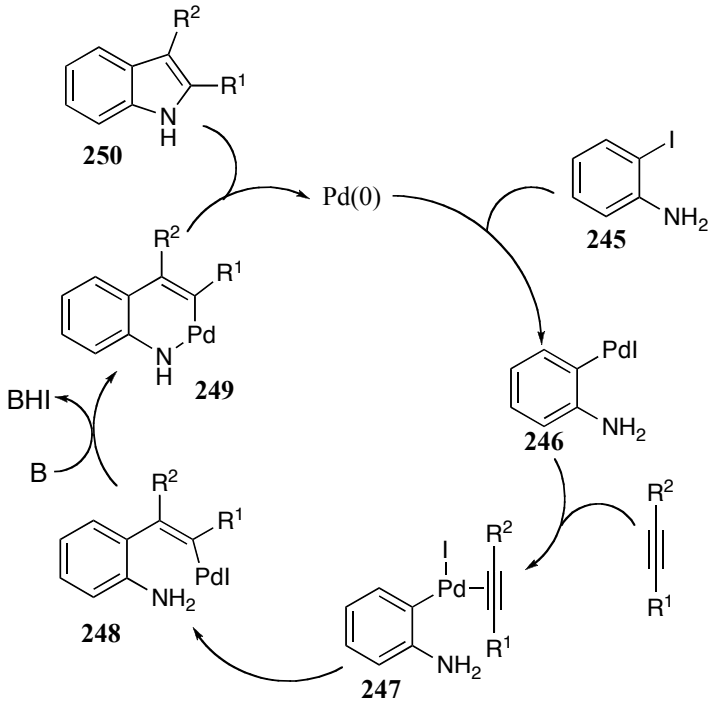
The same resin (PS–TsCl resin) **230** was used to excellent effect by Wu and colleagues, utilising a slightly modified approach. This approach, as before, introduces functionality by a palladium-mediated coupling of the resin-bound aryl iodide with terminal alkynes followed by intramolecular cyclisation to form the indole core. Although the Wu group initially used Zhang's original conditions, it was observed that reaction occurred with both the 2-iodo and the 4-bromo groups of their resin-bound sulfonamide **240** derived from aniline **239**. Conditions needed to be selective for the coupling of terminal alkynes to the aryl iodide, as the bromo-substituent was required in later steps to introduce functionality. By lowering the reaction temperature and extending the reaction time to 24 h, they managed to overcome this problem. Functionality was introduced to the C-3 position of the resin-bound indole **241** *via* acylation with an acid chloride in the presence of a Lewis acid catalyst to give indole **242**. Further functionality was then delivered, either by Sonogashira coupling with terminal alkynes or Suzuki coupling with aryl boronic acids to the resin-bound aryl bromide, to add diversity to the C-5 position of the indole **243**. Cleavage was then affected by saponification of the sulfonamide linker upon treatment with *t*-BuOK, at room temperature. Finally, *N*-methylation of the indole could be accomplished by carrying out the cleavage in the presence of methyl iodide **244** (Scheme 59).[147]



Scheme 59

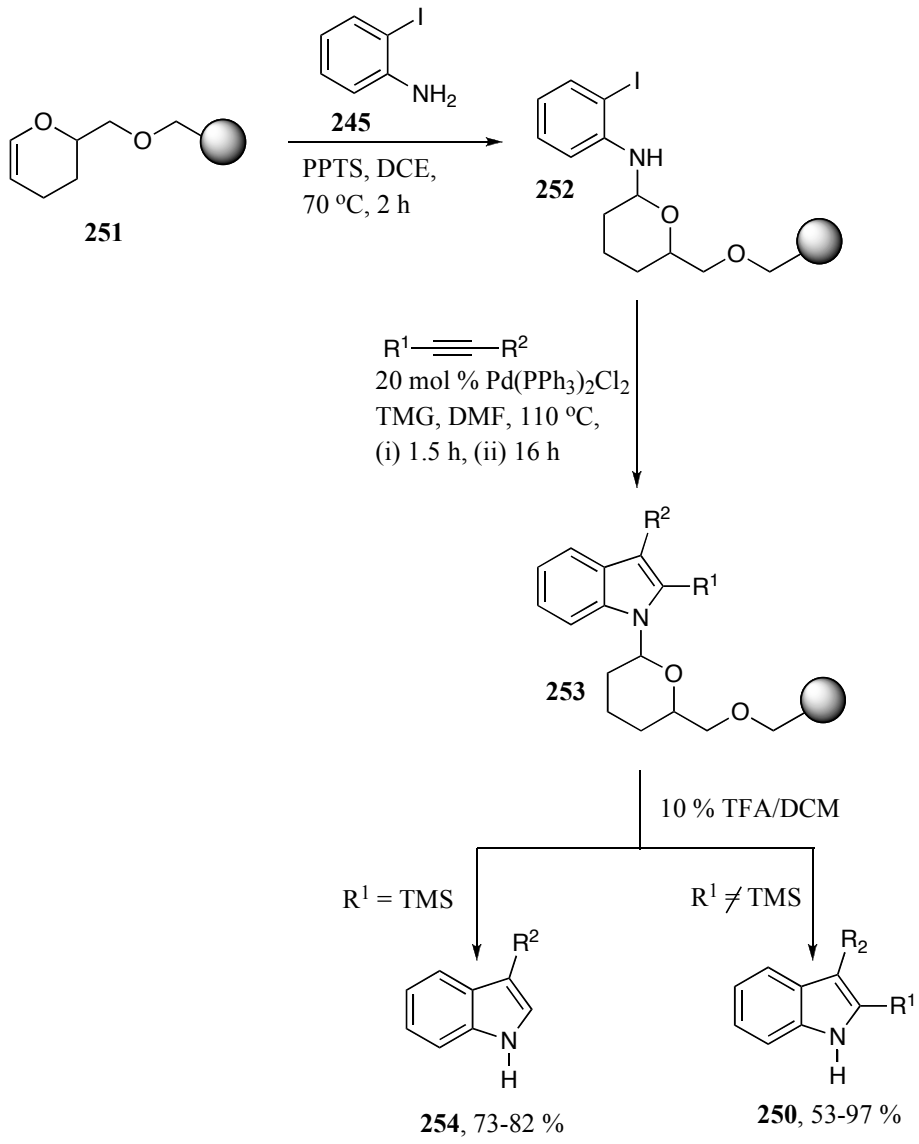
This route represents one of the most rewarding methods for introduction of diversity and traceless cleavage from resin in a SPS of indole derivatives. The application of IRORI MicroKan^{TM} technology allows for automated combinatorial synthesis and thus production of a library of potential drug candidates. However, the process has its limitations, yields range from 10 %–20 % (based on resin-loading of aniline), the methodology is restricted to aryl, acyl and alkynyl substituents at the 2-, 3- and 5-positions respectively. Substitution to either the 4-, 6- or 7- positions using differently substituted anilines from aniline **239** has not yet been demonstrated, possibly due to difficulty in accessing these substrates, also methylation has been the only successful alkylation in the *N*-1 position.[147]

A similar but mechanistically different palladium-mediated indole synthesis from the one reported by Yamanaka *et al*. is the coupling originally developed in the solution phase by Larock (Scheme 60).[148] As before 2-iodoanilines **245** and their derivatives are the starting materials but these are reacted with internal alkynes. Oxidative addition of palladium to the aryl iodide **245** gives arylpalladium complex **246**, which coordinates to the alkyne to give complex **247**. Carbopalladation then yields complex **248**. Intramolecular halide displacement from the palladium then occurs to form a nitrogen-containing palladacycle **249**, which subsequently affords the indole product **250** *via* a reductive elimination step, regenerating the catalyst.



Scheme 60

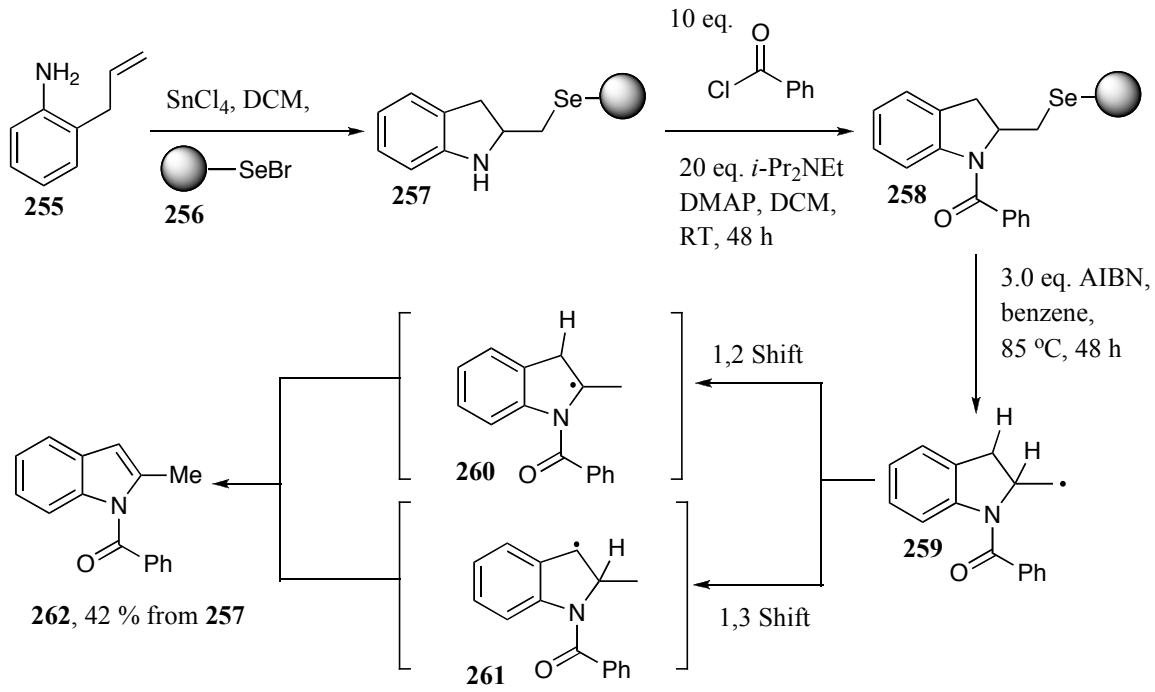
This was adapted to SPS route by Smith *et al*,[149] 2-Iodoaniline **245** was successfully loaded onto Ellman's THP resin[150] **251** through PPTS mediated aminal linkage to give resin-bound **252** (Scheme 61). Coupling with internal alkynes used $Pd(PPh_3)_2Cl_2$ as the catalyst and tetramethylguanidine (TMG) as base. Repeated applications of the coupling conditions were necessary to drive the reactions to completion to afford resin-bound indoles **253**. Treatment with 10 % TFA gave the free indoles **254** or **250**. Regioselectivity appeared to be generally high (5:1) with the bulkier substituent preferentially ending up in the 2-position of the indole. It should be noted, that complete regioselectivity was only achieved when R^1 = TMS. In total, six indoles were isolated however information on purities was not supplied.


I
NH2
245
PPTS, DCE,
70 °C, 2 h
251
252
NH
O
O
R1
R2
20 mol % Pd(PPh3)2Cl2
TMG, DMF, 110 °C,
(i) 1.5 h, (ii) 16 h
253
10 % TFA/DCM
R1 = TMS
R1 ≠ TMS
254, 73-82 %
250, 53-97 %

Scheme 61

5.2.5 Cycloaddition Route to Indole Synthesis

K.C. Nicolaou and co-workers have also developed a strategy to access 2-substitued indole derivatives in a traceless manner from solid phase.[151] The method is an extension of their previous work: the selenium-based approach for the solid phase combinatorial synthesis of benzopyran derivatives.[152] Given the versatility of their cycloaddition strategy they sought to apply it the generation of other heterocycles, namely indolines and indoles. Preliminary solution phase studies showed unprotected *ortho*-allyl anilines smoothly underwent a selenium-mediated cyclisation with PhSeBr in the presence of a suitable Lewis acid catalyst (such as AgOTf or $SnCl_4$). They then attempted the corresponding reaction using a resin-bound equivalent of phenylselenyl bromide. Treatment of a suspension of the selenenyl bromide resin **256** and aniline **255,** with $SnCl_4$ (3 equivalents) at –20 °C in DCM, results in rapid decolourisation, signalling successful attachment to resin. With the now resin-bound indoline scaffold **257** in place, the amino group could be converted into an amide, a carbamate or a sulfonamide. In one example, benzoyl bromide was used to give amide **258**. Treatment with AIBN (3 equivalents) in refluxing benzene gave, 2-methyl indoles **262** in satisfactory yield over 2 steps (Scheme 62).[151] Presumably, the primary alkyl radical intermediate **259** rearranges by 1,2 shift or a 1,3 shift to give the more stable radicals **260** and **261**, and this is followed by loss of a hydrogen atom to another radical species.

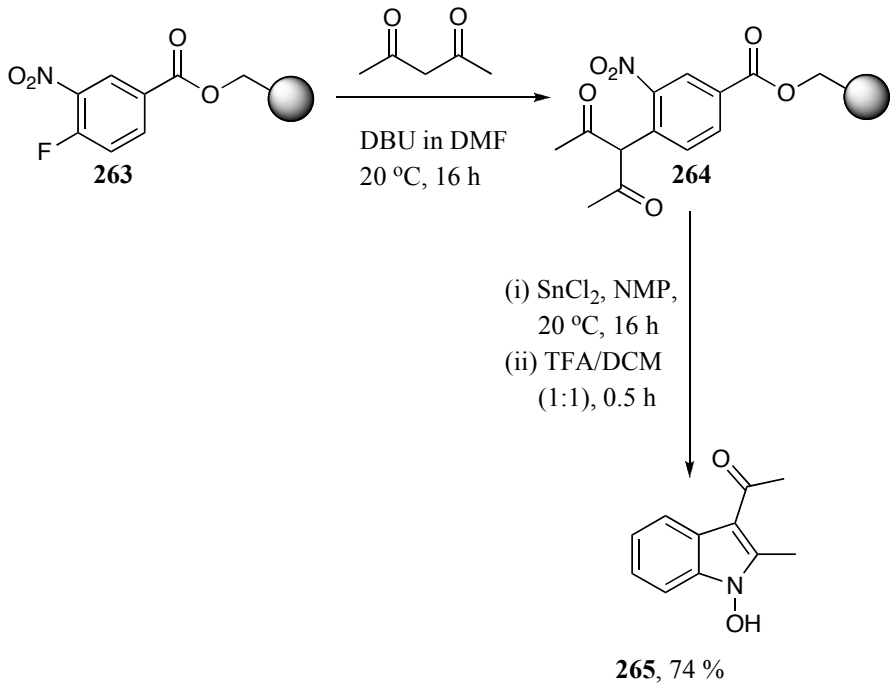


Scheme 62

K.C. Nicolaou stated in the work that 2-methyl indoles are targets for a template library design. There was no further elaboration on whether additional functionality may be introduced, *via* a selenium-mediated reaction, so as to further derivatise the 2-position of the indole. Therefore, for the time being the method lends itself to only introducing methyl functionality into the 2-position of the indole ring from resin. [151]

5.2.6 *C*-Arylation Route Towards Indole Synthesis

Stephenson and Zaragoza employ carbon-arylation in their strategy for solid-phase combinatorial synthesis towards indole compounds.[153] Three examples of the SPS of *N*-hydroxyindoles were presented. In the best example, acetylacetone reacted smoothly with Wang resin-bound 4-fluoro-3-nitrobenzate **263**, resulting resin-bound intermediate **264** was then exposed to tin(II) chloride in methyl-2-pyrrolidinone so as to reduce the nitro group. Treatment with acid then brought about cleavage from the Wang resin and formation of *N*-hydroxyindole **265**. Various attempts were made to reductively cleave the N-O bond but none were successful (Scheme 63).



Scheme 63

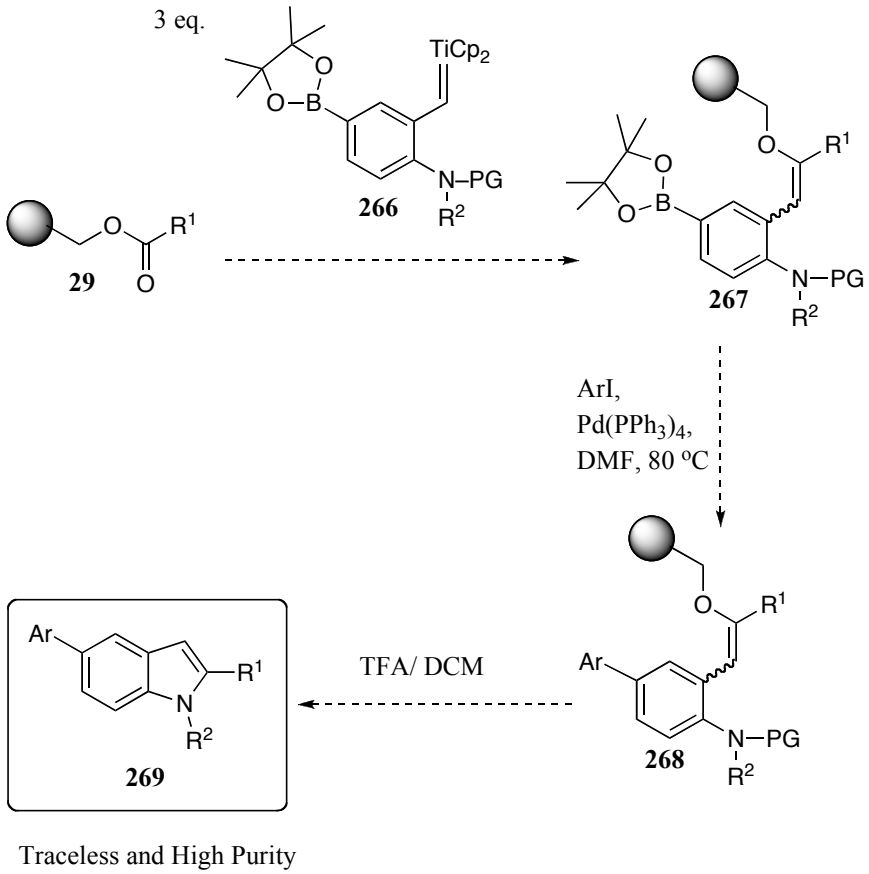
5.3 Conclusion

Some powerful and robust methods for the traceless synthesis of indole and indole derivates on the solid phase exist. With this in mind it should be noted the conversion of simple resin-bound esters into a range of heterocycles, including indoles (see Chapter 4.5), is still unique to the Hartley team. The Nenitzescu indole synthesis[154] and Heck directed indole synthesis[155] also belong to the many methods that can be employed by the synthetic chemist in the combinatorial approach to indole libraries. However these approaches were not discussed as they predominately introduce functionality to the 3-position of the indole ring.

CHAPTER 6 – Solid Phase Synthesis of 2,5-Disubstituted Indoles

6.1 Introduction

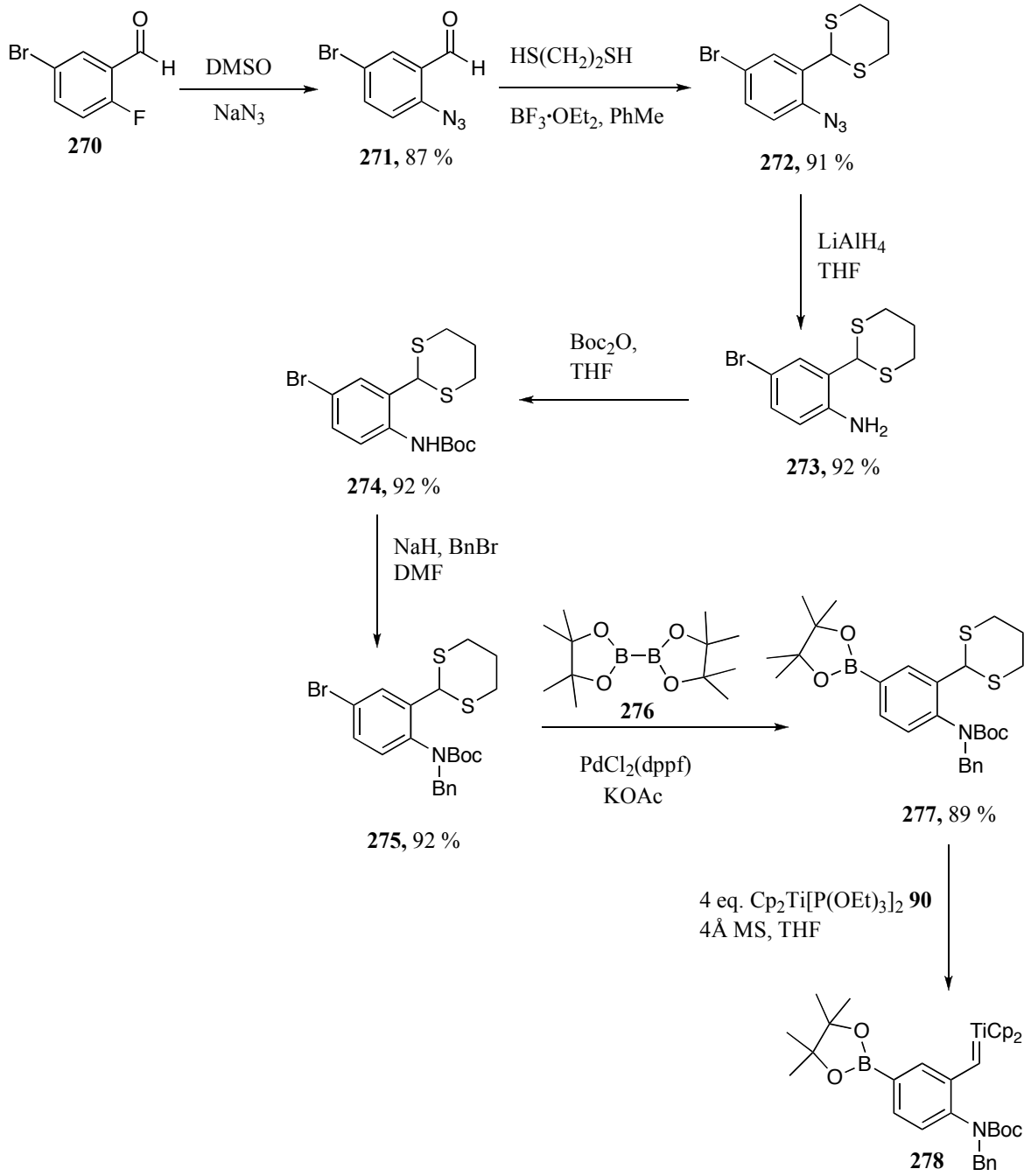
This project was centred on extending the range of boronate-bearing titanium benzylidenes. Previous work within the group had led to the successful completion of a small library of 2,5-disubstituted benzofurans from a boronate-bearing titanium benzylidene reagent.[83] We wished to demonstrate a similar strategy for introducing diversity in the indole series. We would firstly develop an efficient and scalable route to a boronate-bearing titanium benzylidene reagent **266**, with the intention of using this reagent for the SPS of 2,5-disubstituted indoles **269** from resin-bound esters **29** (Scheme 64). This would involve formation of enol ethers **267** and cross-coupling with aryl iodides to give enol ethers **268** followed by cleavage to give the indoles **269**. Once we had established conditions for the sequence, we would prepare a 96-member library of indoles **269** to illustrate the power of the method.



Scheme 64

6.2 Preparation of a Boronate-Bearing Titanium Benzylidene

The first aim was to investigate the synthesis of the titanium benzylidene reagent **266**, having an appropriate protecting group on the nitrogen atom. Hanna Petersson was the first to synthesise such a boronate-bearing titanium reagent. In her route she chose commercially available 5-bromo-2-flurobenzaldehyde **270** as the starting material for the synthesis. Adapting the method of Kuo *et al*. for the aromatic nucleophilic displacement (S_{NAr}) of fluoride by sulfide,[156] fluoride was displaced to introduce azide. The electron-withdrawing effect of the aldehyde group *ortho* to the fluoride group ensured a high yield **271.** Aldehyde **271** was then smoothly converted into dithiane **272**.[157] Reduction of the azide gave aniline derivative **273**,[158] which was then converted into carbamate **274**. *N*-Benzylation under the conditions developed by Calum Macleod gave aryl bromide **275**. Miyaura cross-coupling[159] then introduced the boronate **276**, in high yield, completing the synthesis of a dithiane **277**. Treatment of dithiane **277** with excess freshly prepared Takeda reagent, $Cp_2Ti[P(OEt)_3]_2$ **90**, gave a titanium carbenoid, presumed to be titanium benzylidene **278** (Scheme 65).



270

271, 87 %

272, 91 %

273, 92 %

274, 92 %

275, 92 %

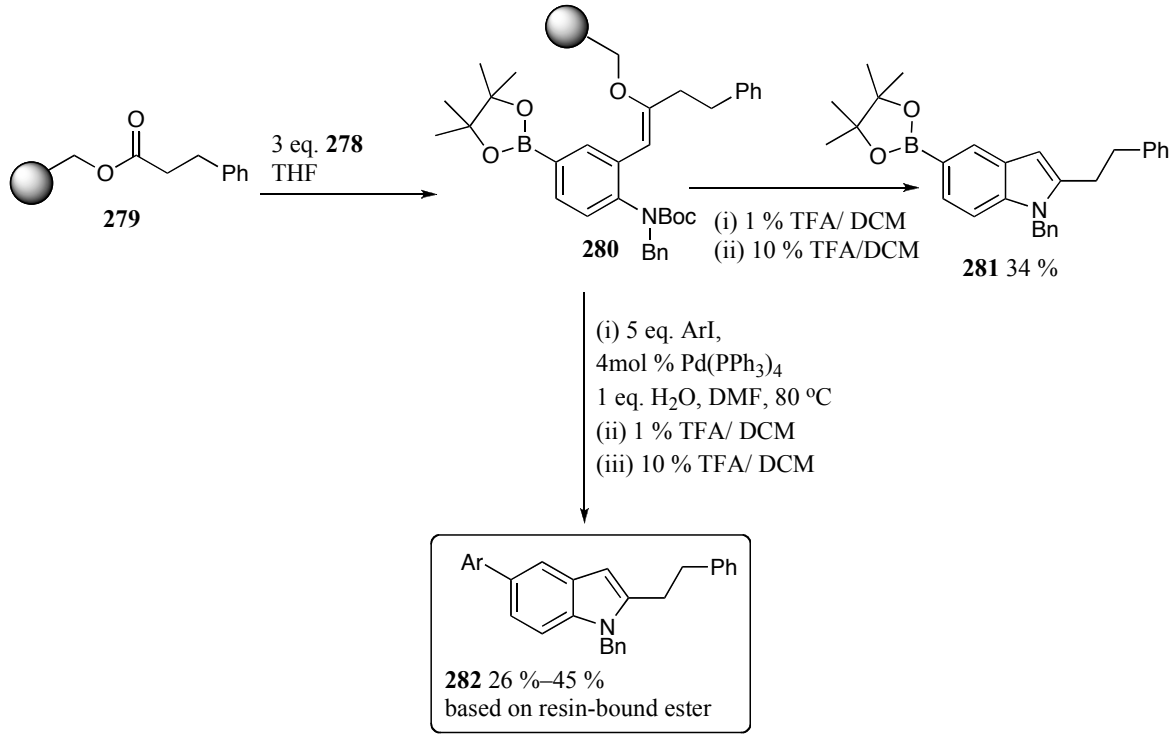
277, 89 %

278

Scheme 65

6.2.1 Alkylidenation and Cross-Coupling to give *N*-Benzyl Indoles

Hanna Petersson used boronate-bearing titanium benzylidene **278** immediately, without isolation, to benzylidenate resin-bound ester **279** (Scheme 66), prepared from Merrifield resin and contained within MacroKans™ (see chapter 6.3.2). Cleavage of the resulting resin-bound enol ether **280** with acid and cyclisation under published conditions[83] then gave boronate **281.** Alternatively, Suzuki cross-coupling between the resin-bound arylboronate **280** and aryl iodides, followed by release and cyclisation gave *N*-benzylindoles **282**.[160] The products were isolated in high purity without the need for chromatography.



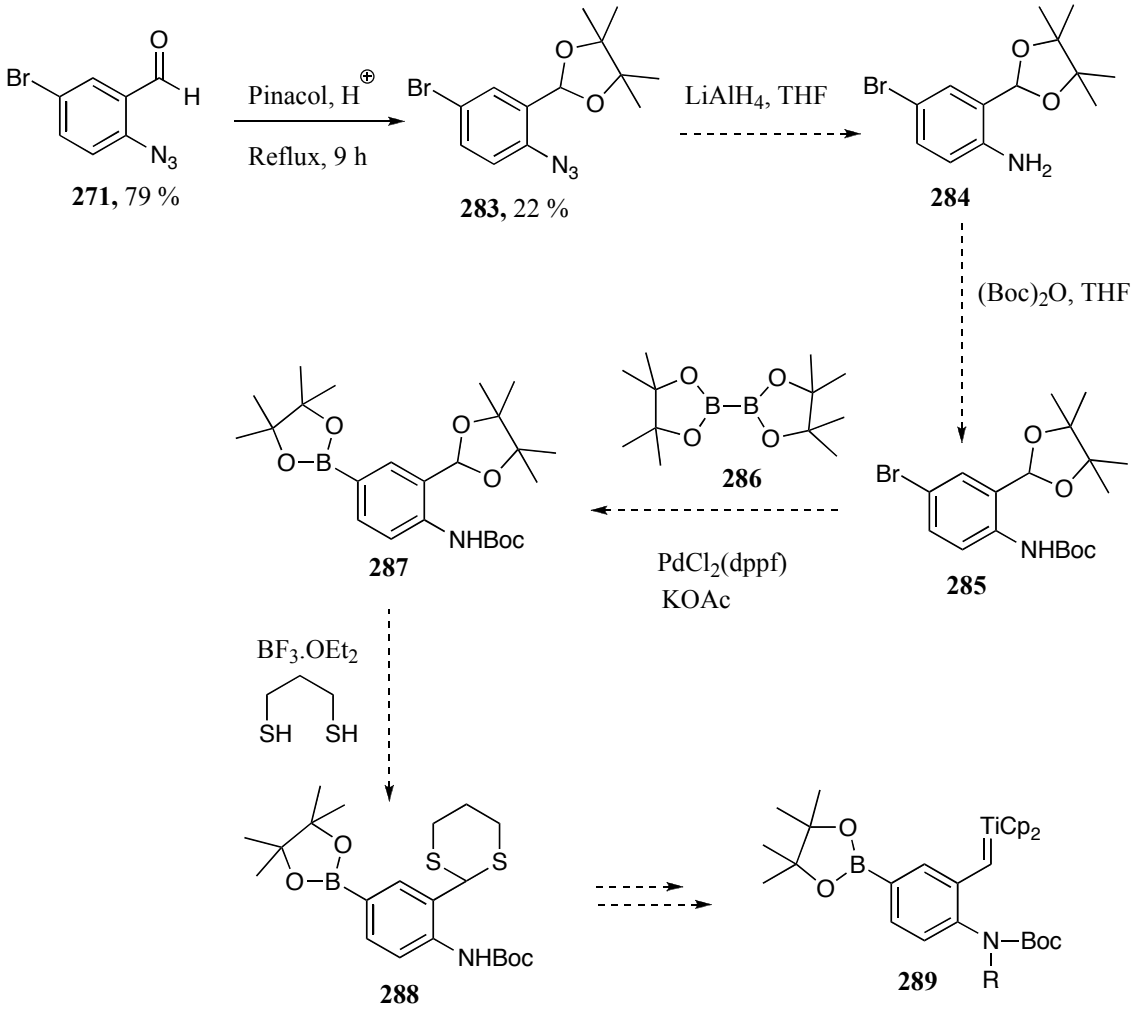
Scheme 66

Following this method, six 2,5-disubstituted indoles were reported. However there were problems with this approach. The boronate-bearing titanium alkylidene **278** gave only moderate yields and the benzyl group could not be removed under literature conditions.[161] The Miyaura cross-coupling failed when amine **273** or primary carbamate **274** was the substrate[162] and was only possible when both the benzyl and the boc groups were present. Presumably, coordination of palladium by the dithiane poisons the catalyst,[163] and this coordination is prevented by the bulky *tert*-butylcarbamate and the benzyl groups, which point above and below the planes of the aromatic ring.[81]

My contribution to the 2,5-disubstituted indole project started in collaboration with Hanna Petersson in exploring the possibility of performing the Miyaura cross-coupling without the need for the bulky *N*-*tert*-butylcarbamate protection. We hoped to develop a route to a boronate-bearing titanium alkylidenating reagent that would be capable of optimal alkylidenation and producing *N*-Boc protected indoles. As although there are reports in the literature that *N*-benzyl indoles can be deprotected to give indoles,[164] *N*-Boc protecting groups are more easily removed.[165]

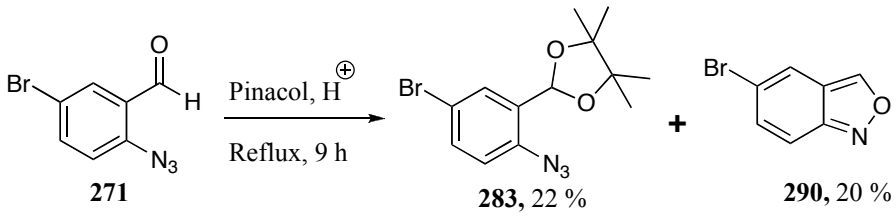
6.2.2 Proposed Route to a Titanium Benzylidene Reagent *via* Acetal Protection

The following scheme represents our initial approach to the synthesis of the boronate-bearing titanium benzylidene reagent with a Boc protecting group **289** (Scheme 67). I began with commercially available 5-bromo-2-fluorobenzaldehyde **270** and followed Hanna Petersson's previous route (Scheme 65) to obtain aldehyde **271**. I opted at this point to convert the aldehyde into dithiane **288** *via* acetal **283** (Scheme 67). McKiernan had shown, that similar acetals are easily transposed into 1,3-dithianes upon addition of propandithiol and $BF_3.OEt_2$.[83] The use of an acetal derivative should allow the introduction of the boronate ester *via* Miyaura cross-coupling: acetal **285**, derived from **284** would be coupled with diboronate **286**, after which the acetal **287** would be easily converted into the corresponding 1,3-dithiane **288**.[83]



Scheme 67

My investigation into the above scheme produced an intriguing result: formation of the acetal derivative **283** went in low yield with formation of a significant by-product **290**, which was isolated by column chromatography (Scheme 68). Crystallisation gave the compound as needles and the crystal structure[166] showed it was 5-bromoanthranil **290** (Figure 23).



271 **283,** 22 % **290,** 20 %

Scheme 68

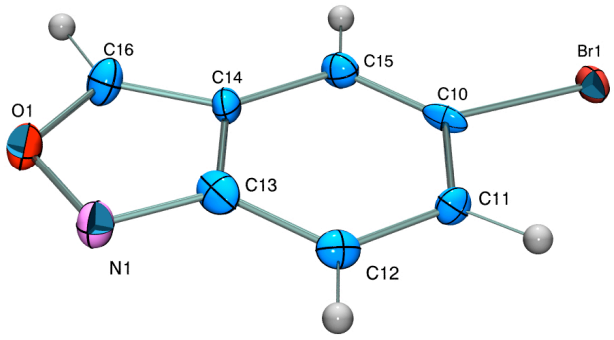
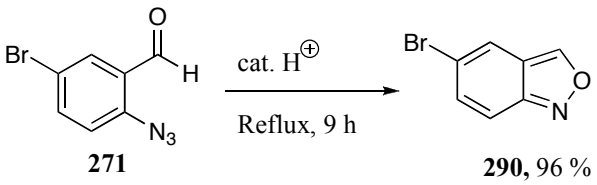


Figure 23

6.2.3 5–Bromoanthranil

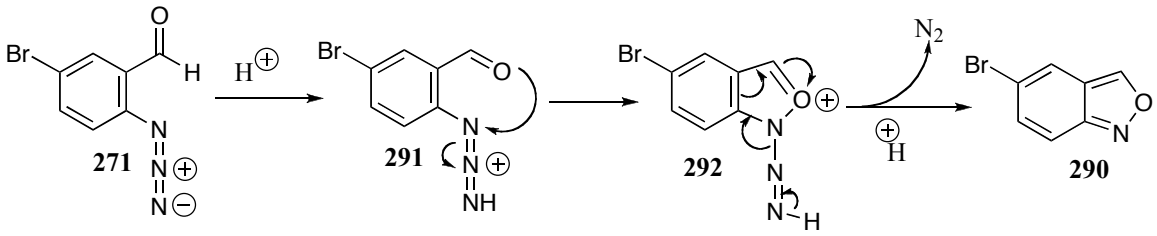
5-Bromoanthranil, which was first reported by Bamberger & Lublin[167] (1909) and more recently synthesised by Wünsch & Boulton[168] (1967), is a 10 π electron system; hence it is aromatic. Previously the highest yield of the compound was a modest 56 %. Repeating the above reaction in the absence of pinacol gave the compound in near quantitative yield (Scheme 69).



271 **290,** 96 %

Scheme 69

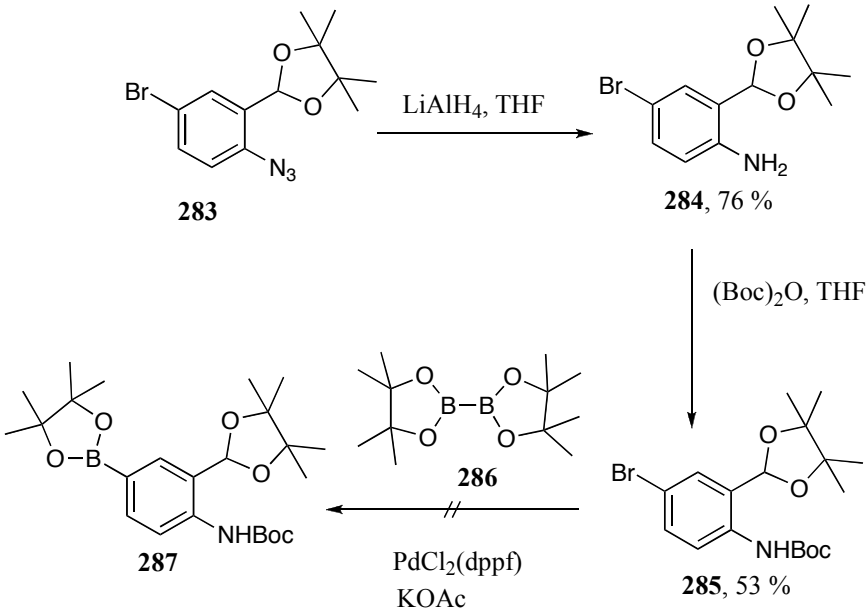
The mechanism of formation is straightforward. Protonation of azide **271** gives aldehyde **291,** which is activated for cyclisation to oxonium ion **292.** Loss of nitrogen gas then gives heterocycle **290** (Scheme 70).



Scheme 70

6.2.4 Acetal Protection Abandoned

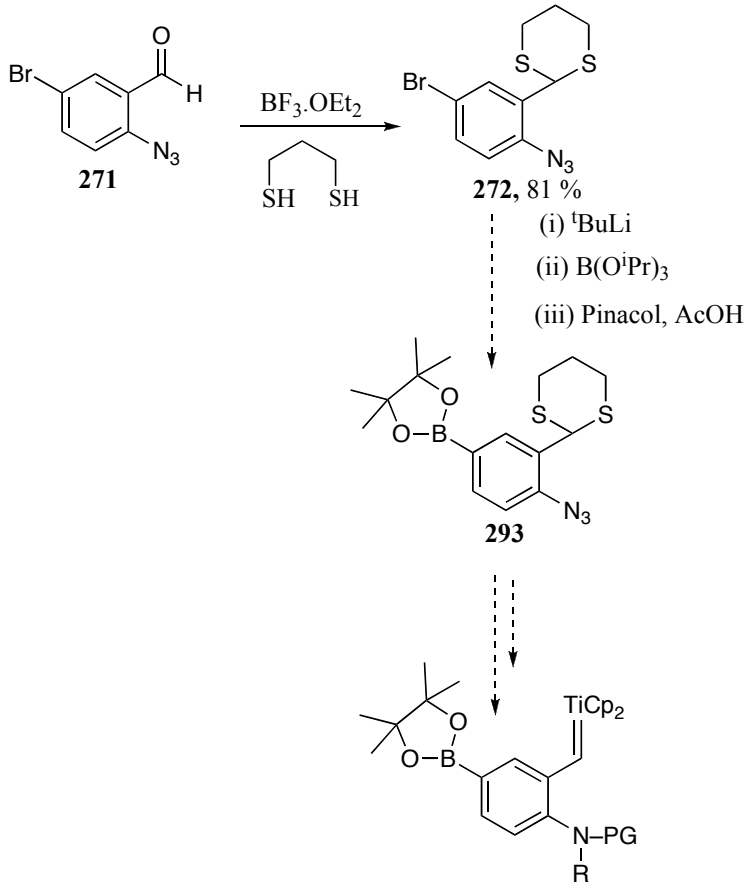
In the meantime, Hanna Petersson had proceeded to convert acetal **283** into carbamate **285** by reduction of the azide to the corresponding amine **284** and Boc protection. Unfortunately, the Miyaura cross-coupling of the aryl bromide **285** gave a mixture of products and the arylboronate **287** could not be isolated (Scheme 71).



Scheme 71

6.2.5 Revised Route

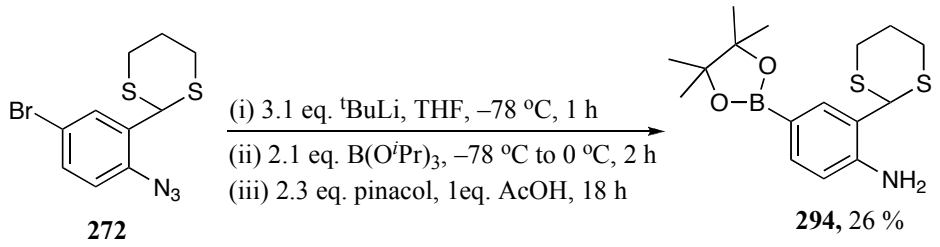
The decision was taken to remove the Miyaura cross-coupling step from the synthesis given its limited scope and the high cost of bis(pinacolato)diboron **286**. Arguably a better approach might be to introduce the boronate group *via* lithium-halogen exchange followed by quenching with $B(O^iPr)_3$ and transesterification with pinacol in one pot.[169] In this way, dithiane **272** would be converted into boronate **293** (Scheme 72). This alternative route would have the cost advantage over the Miyaura cross-coupling and would allow more versatility later in the synthesis. However, it carried considerable risk. The dithiane is sufficiently acidic to be deprotonated by organolithiums and the azide might not be stable to the reaction conditions. Nonetheless, aldehyde **271** was converted into dithiane **272** to allow this route to be investigated.



Scheme 72

6.2.6 Organolithium-Mediated Reduction of Azide

Hanna Petersson was the first to attempt the conversion of aryl bromide **272** into arylboronate **293**. In her hands, lithiation-boronation gave not the expected azide **293**, but amine **294** where the azide group had been reduced (Scheme 73).

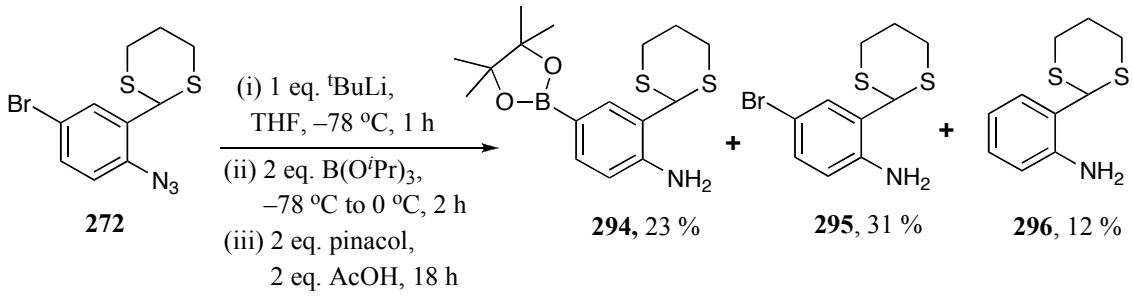


272 **294,** 26 %

Scheme 73

I investigated this reaction to gain more information on its mechanism. As the reaction involved moisture sensitive reagents it seemed prudent to absolutely ensure anhydrous reaction conditions. All glassware was oven-dried and flame-dried, solvents distilled, and *tert*-butyllithium freshly titrated before each reaction. Several experiments were then performed.

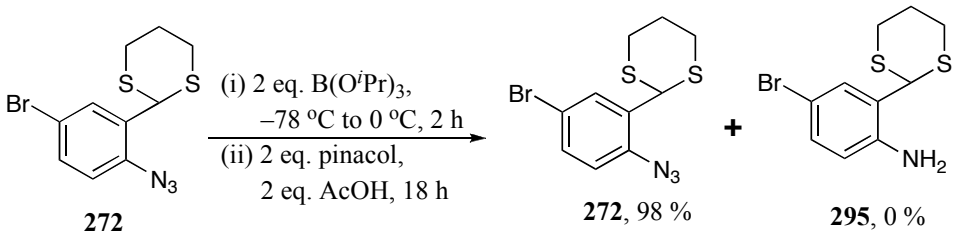
When azide **272** was treated with 1 equivalent of *tert*-butyllithium followed by $B(O^iPr)_3$ and then pinacol and acetic acid, a mixture of three compounds **294**, **295** and **296** was obtained, which were isolated in the yields shown (Scheme 74). The presence of brominated amine **295** (isolated in 31 % yield) indicated competition between lithium-halogen exchange and azide reduction with reduction of the azide preferred. It should be noted that aniline **295** could also be accessed by treatment of 5-bromoanthranil with 1,3-propanedithiol.



272 **294,** 23 % **295**, 31 % **296**, 12 %

Scheme 74

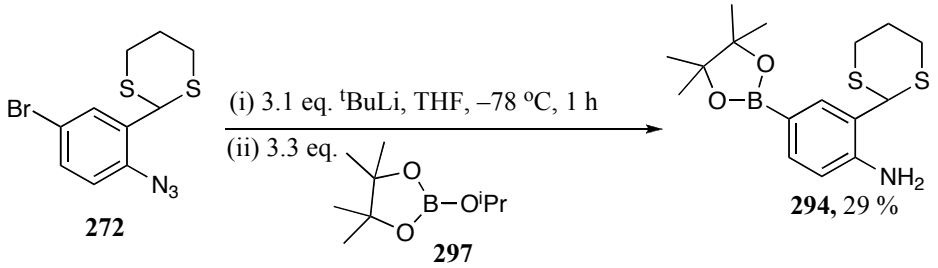
In order to clarify whether or not pinacol was involved in the reduction, pinacol, $B(O^iPr)_3$ and acetic acid (under the same conditions as previous) were reacted with dithiane **272** (Scheme 75). If indeed these reaction conditions reduced the azide, amine **295** would be produced. However the reaction failed resulting in the retrieval of starting material **272**. Evidently an acidic solution of pinacol could not reduce the azide.



272 **272**, 98 % **295**, 0 %

Scheme 75

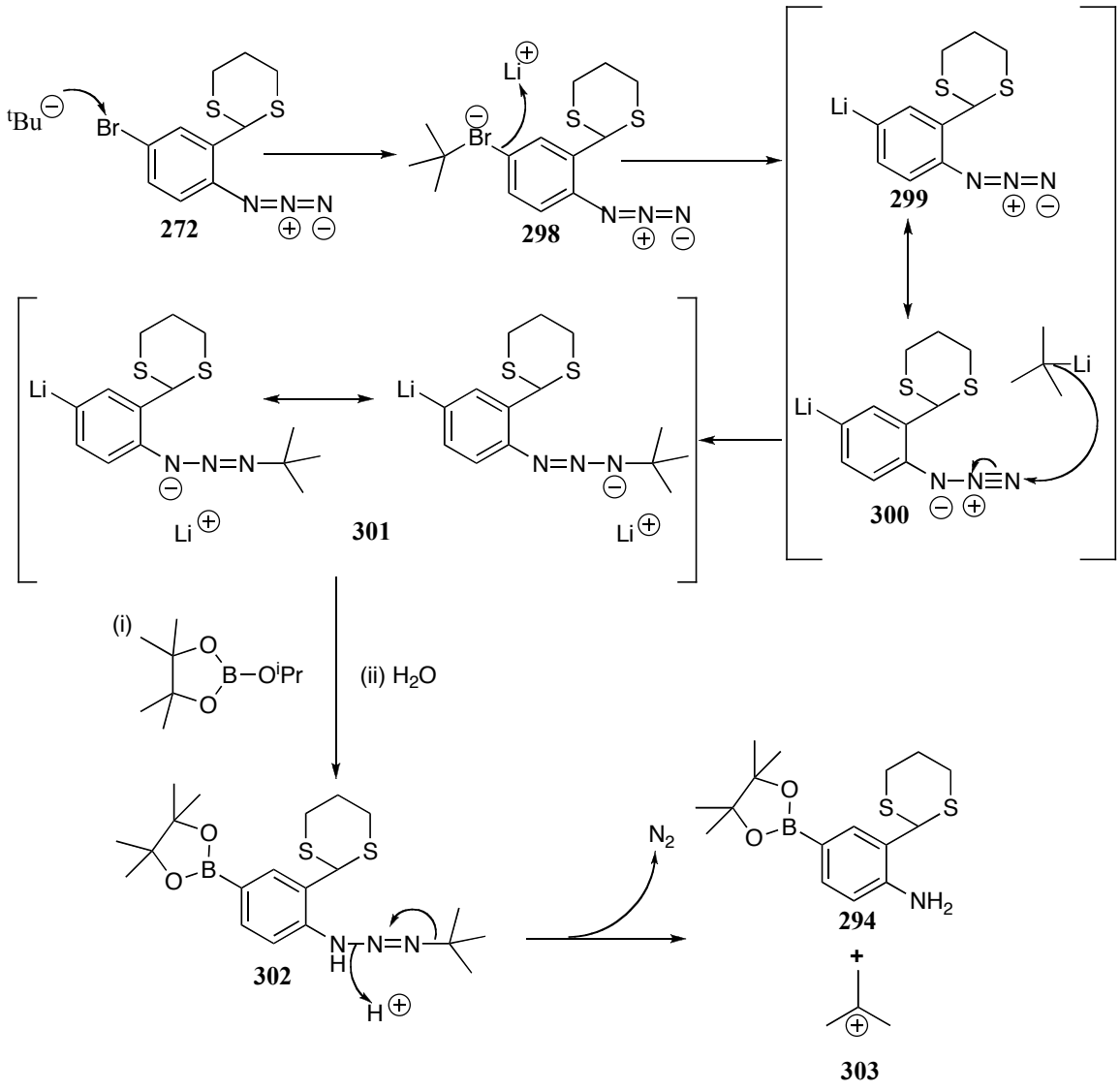
Replacing $B(O^iPr)_3$, pinacol and acetic acid with boronate **297** would reduce the number of variables. Hopefully, this experiment would remove any ambiguity that pinacol or any other reagent apart from ^{t}BuLi in this reaction was involved in the reduction of the azide to give the boronate ester **294**. Additionally, the reaction time was increased (2 h to 2.5 h), so as to allow sufficient time for reaction between lithiated species and the boronate.[170] Furthermore, quenching the reaction mixture with a pH 7 buffer was employed to avoid any possible loss of protonated amine into the aqueous layer upon work up (Scheme 76). With these new conditions the yield, after column chromatography, was improved to 29 %.



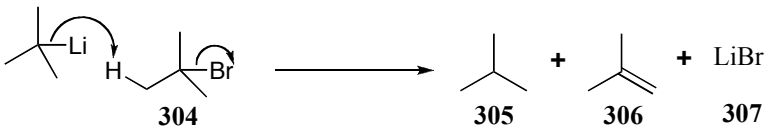
272 **294,** 29 %

Scheme 76

From a range of experiments, I discovered that 3 equivalents of *tert*-butyllithium was the optimal number for the reaction procedure. This is not surprising and can be explained by the following mechanism (Scheme 77). One of the three equivalents of *tert*-butyllithium is required to convert the aryl bromide moiety **272** into aryllithium **299** and another equivalent destroys the resulting *tert*-butyl bromide **304** into by-products **305**, **306** and LiBr **307** (Scheme 78). Organolithiums are known to attack the terminal nitrogen of aryl azides and alkyl azides to give 1-aryl-3-alkyltriazenes and 1,3-dialkyltriazenes, respectively;[171] therefore dilithiated triazene **301** is a likely intermediate. 1-Aryl-3-alkyltriazenes decompose in acid to the corresponding anilines with loss of nitrogen and formation of an alkyl carbocation. This process can be particularly fast when the carbocation is stabilised.[172] This type of decomposition appears to be induced by the Lewis acidic borate or the water. Thus, 1-aryl-3-*tert*-butyltriazene **302** or a similar intermediate collapses to give the amine **294**, nitrogen gas and a *tert*-butyl cation **303** (Scheme 77).



Scheme 77

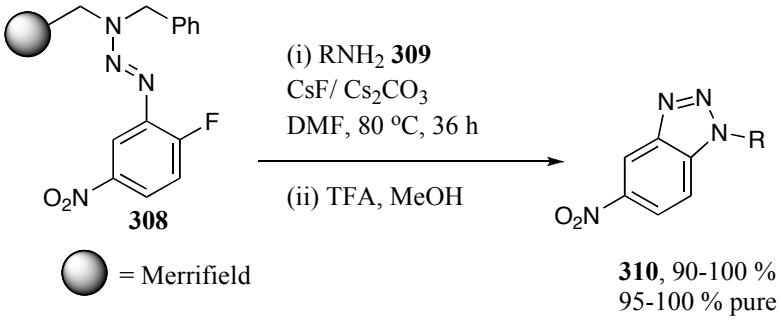


Scheme 78

6.2.7 Triazenes – Linkers in Solid Phase

Interestingly, 1,3-disubstiued triazenes are often employed as electrophile-cleavable linkers in solid-phase synthesis.[173] Bräse and co-workers demonstrated the rapid (10 min) synthesis of alkyl halides and alkyl esters from reaction between 1,3-disubstituted triazene-bound resins and trimethylsilyl halides and carboxylic acids respectively.[174]

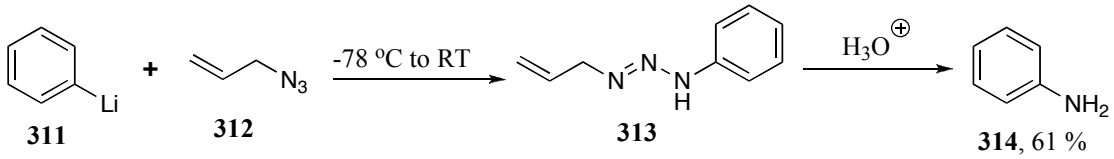
Trisubstituted triazenes have also been resin-bound and proven to be more popular and versatile than their 1,3-disubstituted triazene counterparts. Continuing their work Bräse's group, diazotised commercially available 2-fluoro-5-nitroaniline and coupled it to benzylaminomethyl polystyrene to yield the immobilised trisubstituted triazene **308**. Nucleophilic displacement of the fluoride with primary amines **309** furnished resin-bound anilines which cyclised in acid in a matter of minutes to give benzotriazoles **310** (Scheme 79). This was subsequently adapted to the successful synthesis of a 200-member library via automated synthesis.[175] Currently the group are designing routes, utilizing their resin-bound triazene toward traceless synthesis of indoles amongst other heterocycles.[176]



Scheme 79

6.2.8 Azide to Amine

Most commonly, anilines are synthesised from the reduction of nitrogen-containing aromatic compounds such as nitroarenes and aryl azides or by rearrangements of the corresponding carboxylic acid derivative.[177] Allyl azide **312** in combination with an aryllithium, e.g. phenyllithium **311**, is also an established route to the preparation of anilines **314** (Scheme 80).[177] Allyl azide **312** can be easily generated, in the presence of a catalytic quantity of tetrabutylammonium bromide (from sodium azide with allyl bromide in water).[178] The resulting allyl azide is preferably used without purification since organic azides are potentially explosive.[179] Reduction with phenyllithium gives 1,3-allylaryltriazene **313**. The addition of acid, then initiates acid-induced decomposition of the allylaryltriazene to give aniline **314** in modest yield.[177]



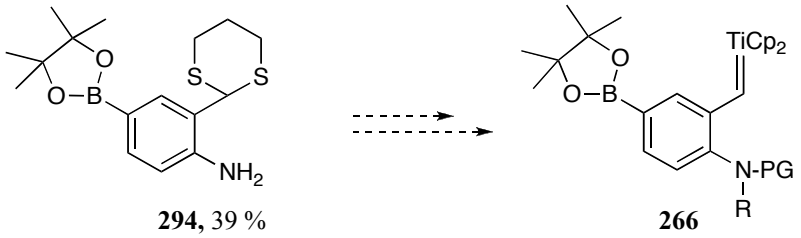
311 **312** **313** **314**, 61 %

Scheme 80

Although the reaction of allyl azide with aryllithiums, followed by acid-induced decomposition is a known method for preparing anilines, [177] the generation of an aniline derivative from aryl azides using *tert*-butyllithium is an exciting new discovery made by the group.

6.2.9 Summary

We had achieved conversion of azide to amine **294** under the conditions used to introduce boronate ester, *via* lithium-halogen exchange, in one pot without detriment to thioacetal. We now needed to investigate suitable protecting groups for the *ortho* amino group of aryl boronate **294** so as to allow its conversion into the boronate-bearing titanium benzylidene **266**, *via* the Takeda reaction (Scheme 81). Although we had set out to utilise a Boc protection strategy as discussed earlier, we were also interested in the trityl protecting group. This was prompted by a discovery within the group that trityl protection had proven successful in a related system.



294, 39 % **266**

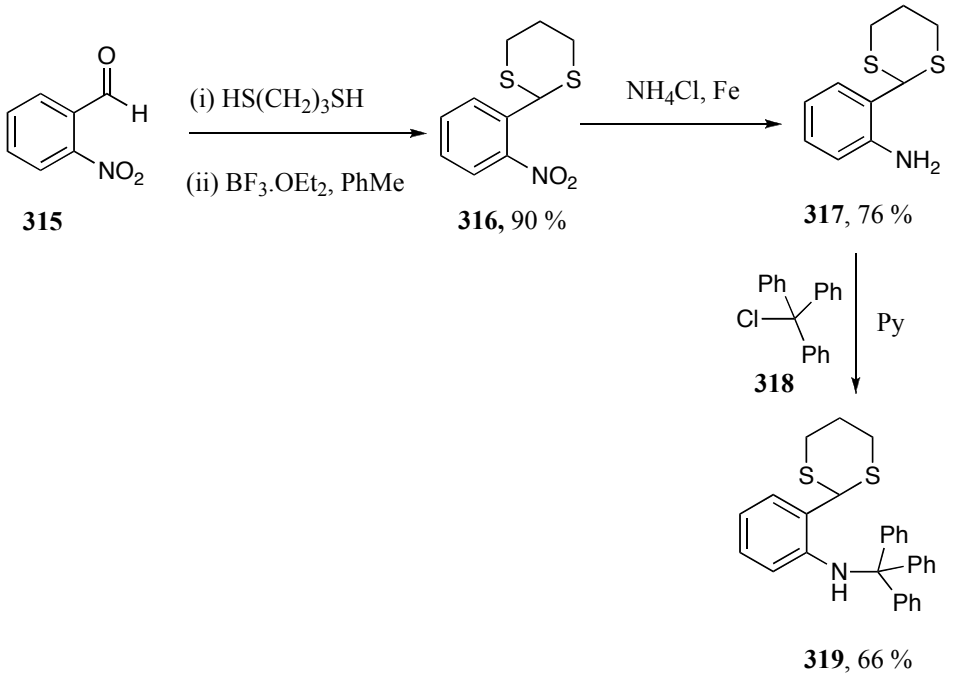
Scheme 81

6.3 Trityl Protection

Within the group Carolyn Austin in her work on the synthesis of cyclic imines had opted for trityl protection[180] of the amino group to allow generation of titanium alkylidene **154** (see chapter 4.4). Trityl protection fulfilled the criteria of a good protecting group: ease of removal under acidic conditions required for cleavage, purification of products without need for chromatography and more importantly had the added bonus of being relatively stable. Moreover she had demonstrated that the steric bulk of the phenyl rings successfully prevented the nucleophilic amino group interfering with the formation of a reactive titanium alkylidene. Consequently, I investigated using this protecting group in the synthesis of indoles.

6.3.1 Synthesis of Trityl-Protected Substrate

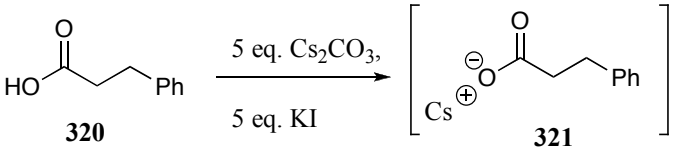
Before using the arylboronate **294**, we considered it wise to test out the trityl protection on a similar system. Aniline derivative **317** was prepared from *ortho*-nitrobenzaldehyde **315** by conversion to the dithiane **316** followed by reduction to the nitro group, employing the route of Calum Macleod.[82] Reaction between triphenylmethyl chloride **318** and aniline **317** gave trityl-protected amine **319** in good yield (Scheme 82).[181]



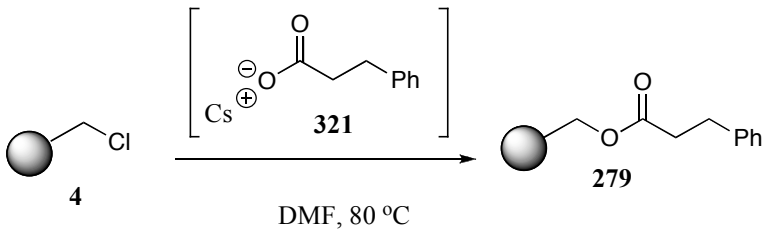
Scheme 82

6.3.2 Synthesis of Resin-Bound Esters

Before alkylidenation reaction, resin-bound ester **279** had to be prepared. Ester **279** was readily formed on Merrifield resin (cheapest polystyrene resin available), using standard methods, in which carboxylic acid **320** is converted to cesium carboxylic salt complex **321** (Scheme 83) and is used in excess with Merrifield resin **4**, to give resin-bound ester **279** (Scheme 84).[18, 182]



Scheme 83



Scheme 84

Merrifield resin **4** is swollen in DMF and then reacted with cesium carboxylate **321**. The cesium salt posses a large cation and in polar solvents such as DMF will readily dissociate from the carboxylate anion. The exposed carboxylate anion is now readily available to undergo nucleophilic (S_N2) attack on Merrifield resin resulting in a rapid rate of ester formation, compared with reaction when other metal counter ions are used (Scheme 84).

The Merrifield resin-bound esters **279**, were contained within small polypropylene reactor vessels called IRORI MacroKans™ that have an internal volume of 2.4 mL and a pore size of 74 μm. In each IRORI MacroKans™ (Figure 24)[183] there is 0.315 meq. of resin, with a loading of 1.97 meq. g^{-1}. The MacroKans™ allow easy handling and are suitable for use with standard lab glassware.

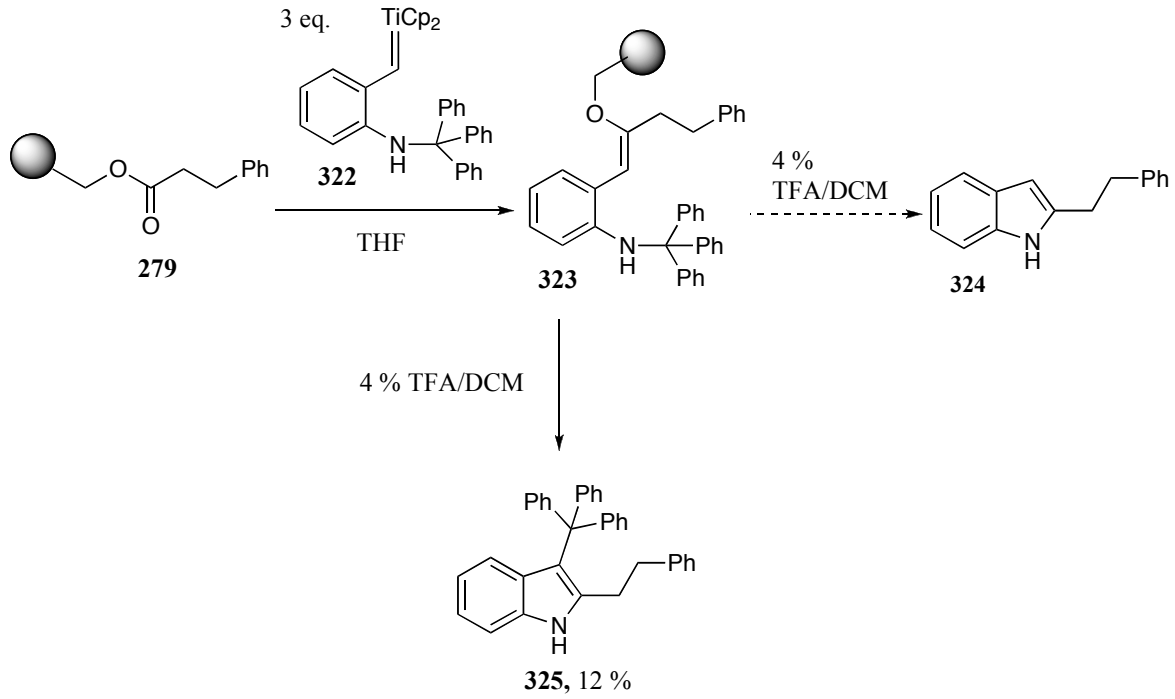
IRORI MacroKans™

Figure 24

6.3.3 Alkylidenation of Trityl-Protected Substrate

Treatment of dithiane **319** with 4 equivalents of freshly prepared Takeda reagent, $Cp_2Ti[P(OEt)_3]_2$, gave the titanium carbenoid reagent thought to be titanium benzylidene **322**. It should be noted that formation of $Cp_2Ti[P(OEt)_3]_2$ **90**, (Scheme 28, Chapter 3.2.3) is by no means a trivial operation. Many concerns are taken into consideration with particular emphasis on ensuring complete anhydrous and air free reaction conditions. Louis Adriaenssens formerly of the Hartley group recognised, during his work on 2-substituted piperidines, that trace amounts of moisture from the argon were a problem to the $Cp_2Ti[P(OEt)_3]_2$ reagent.[184] He developed a CaH_2/ CaO desiccant plug to go between the argon line and reaction vessel, in doing so he observed improved yields and purities in his final compounds. In the work reported here-in, all reactions were performed employing this method. Additionally, all glassware and molecular sieves were heated overnight, at a temperature of 250 °C to absolutely ensure moisture removal/ activation of the sieves, and then used directly the following morning.

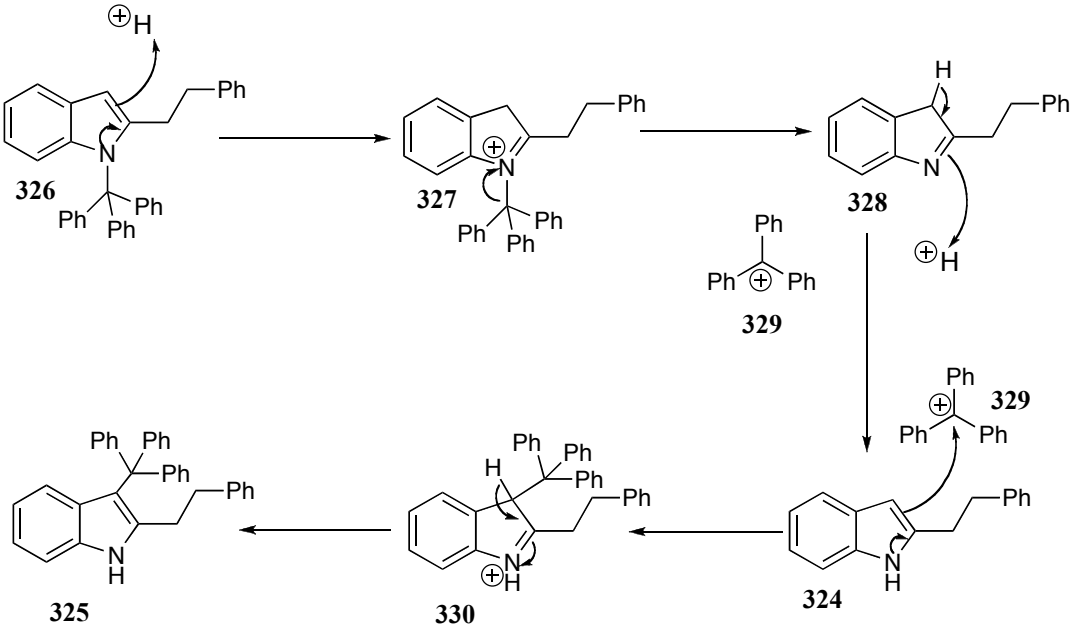
Titanium benzylidene **322** was used immediately without isolation to alkylidenate resin-bound ester **279** contained within an IRORI MacroKan^{TM}. Cleavage of the resulting resin-bound enol ether **323** with mild acid, under our standard conditions, [81] gave a mixture of compounds from the resin, with indole **325** isolated from column chromatography (Scheme 85).



Scheme 85

6.3.4 Trityl Bounce-Back

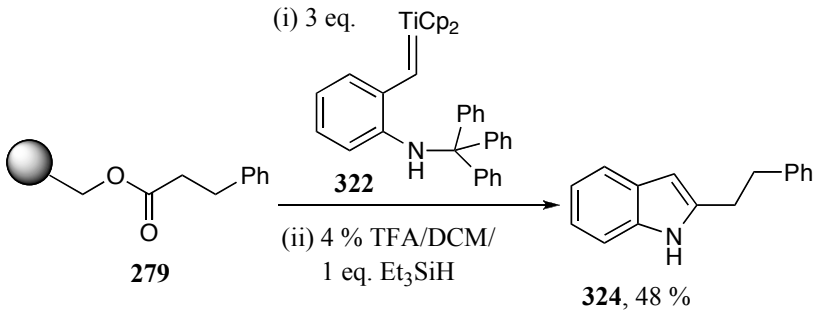
The bulky trityl group had prevented the nitrogen atom from co-ordinating intramolecularly with the titanium atom of the titanium benzylidene, however target compound **324** was not successfully synthesised. We had not factored the potential of trityl "bounce back". The major product was the 2,3-disubstituted indole **325** (isolated in 12 % yield following chromatography) and this compound is a result of the trityl carbocation[185] being attacked by the electrophilic C-3 of the indole ring, thus forming a 2,3-disubstituted indole species after deprotection as shown below (Scheme 86).



Scheme 86

N-Trityl-indole **326** is likely to be formed during or immediately after cleavage. Protonation gives the iminium ion **327**, which loses a trityl cation to give the imine **328**. Following tautomerisation to the indole **324** the trityl cation **329** alkylates the electron-rich C-3 position to give the iminium ion **330**, which loses a proton to give the indole **325** that was isolated.

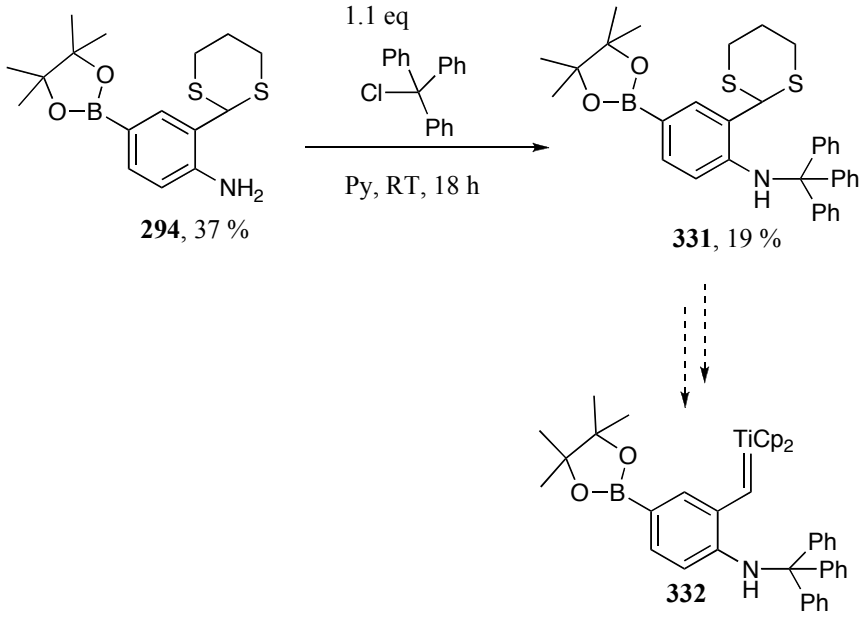
This phenomenon of "bounce-back" can be avoided. It is reported that introduction of triethylsilane during the cleavage of the protecting group leads to *in situ* reduction of the trityl cation, thus preventing further reaction.[186] Investigation into the efficacy of triethylsilane as a cation scavenger, introduced during the cleavage step, proved to be encouraging (Scheme 87) with indole **324** isolated in 48 % yield and in high purity without need for column chromatography.



Scheme 87

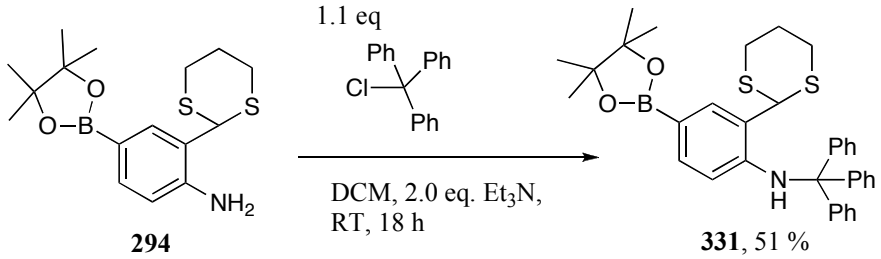
6.3.5 Synthesis of Boronate-Bearing, Trityl-Protected Substrate

Preliminary results with the trityl-protected derivative **319** and low valent titanium species had been encouraging, so I considered the use of trityl derivative **331** bearing a boronate group (Scheme 88). However, conversion of the arylboronate **294** into trityl-protected arylboronate **331** employing pyridine was difficult, recrystallisation was impossible and purification by column chromatography on deactivated alumina resulted in low yields. Thus, insufficient amounts of material are synthesised in this way to allow testing of dithiane **331** under Takeda conditions.



Scheme 88

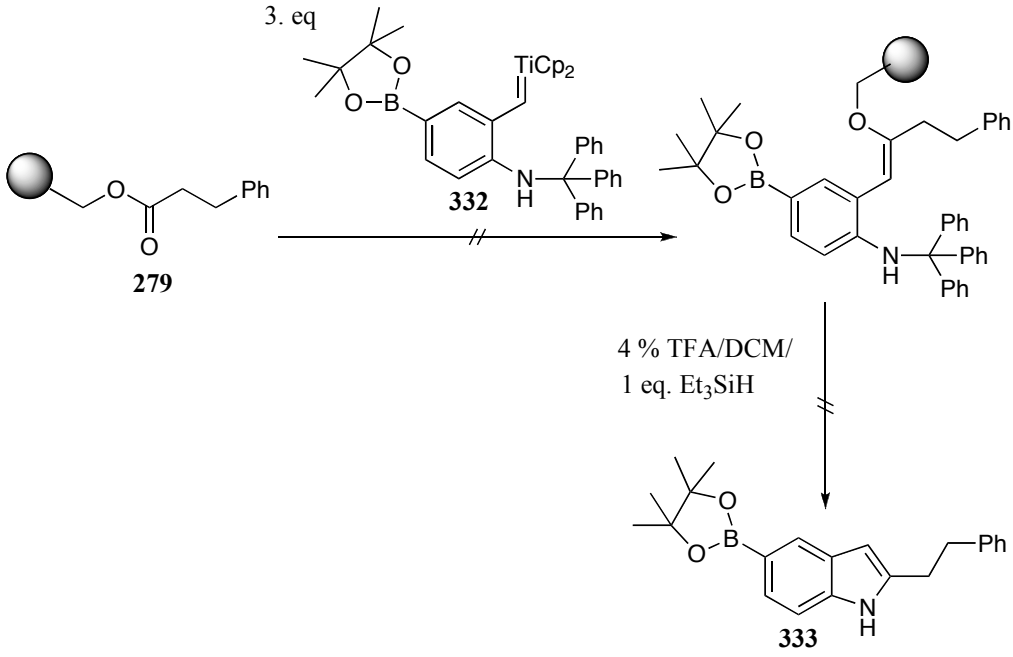
In order to acquire sufficient material for the alkylidenation to be tested, the reaction conditions were optimised, by simply changing the solvent and adding base,[187] recrystallisation from (hexane/ MeOH) of the crude material following work-up was possible. As a result, yields were significantly improved from 19 % to 51 % (Scheme 89).



Scheme 89

6.3.6 Alkylidenation Using Boronate-Bearing, Trityl-Protected Substrate

Trityl-protected arylboronate **331** was added to the low valent titanium species **90**, to synthesise the boronate-bearing titanium benzylidene **332**. This was used immediately in an attempt to alkylidenate resin-bound ester **279** contained within the IRORI MacroKans^{TM}. However treatment with TFA, failed to yield the expected boronate-bearing indole **333** (Scheme 90).



Scheme 90

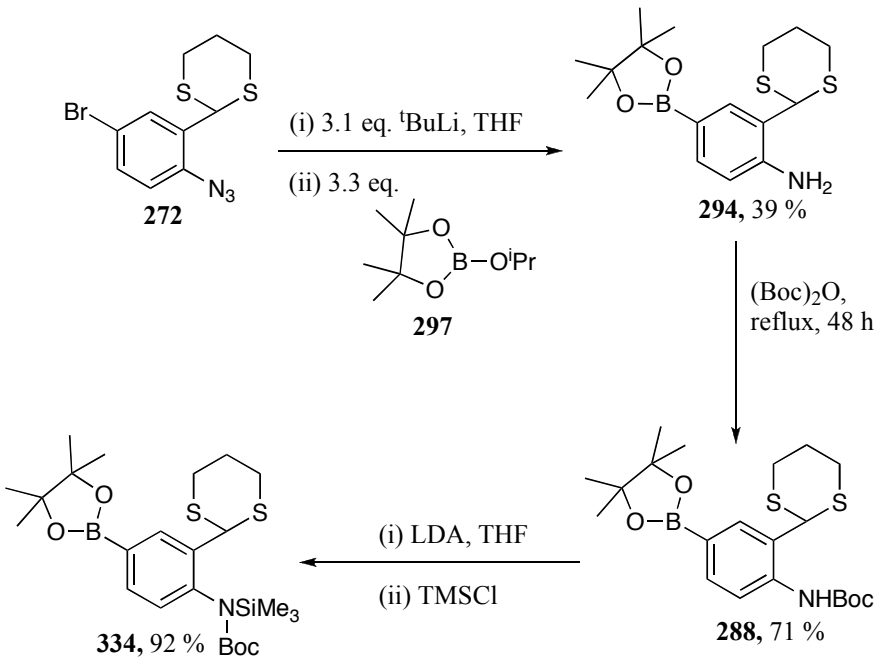
I concluded that titanium alkylidene **332** had not been successfully generated from the trityl-protected arylboronate by the low valent titanium species. This was slightly disappointing, as the free *N*H indole would have been accessed without need for further deprotection steps, however the silylcarbamate option was still open for investigation.

6.4 Synthesis of Silylcarbamate-Protected Substrate.

The first reported use of silylcarbamate protection of an NH_2 group comes from the work performed by Voyer, although not for the protection of anilines.[188] *N*-Silylcarbamate protection of an aniline derivative for titanium alkylidenation first came into the literature from work performed by Calum Macleod formerly of the Hartley group, [82] as described in Chapter 4.3 (Scheme 42).

At the end of Hanna Petersson's PhD, Hanna Petersson had prepared dithiane **334** with the *N*-silylcarbamate protecting group. However, due to lack of material and time constraints, Hanna Petersson never used this reagent to prepare indoles. Both the synthesis of amine **294** and Boc protection had proceeded in low yields in Hanna Petersson's hands (30 % each step, 9 % overall). I optimised the steps, tripling the overall yield as follows. In order to avoid column chromatography, the crude arylboronate **294** was recrystallised from hot pentane with a small quantity of ethyl acetate. The solvent system proved most effective, and arylboronate **294** was successfully crystallised to give a 39 % yield. In spite of the modest yield, the ^{1}H NMR spectrum of the crude mixture appeared to contain no other aromatic compounds.

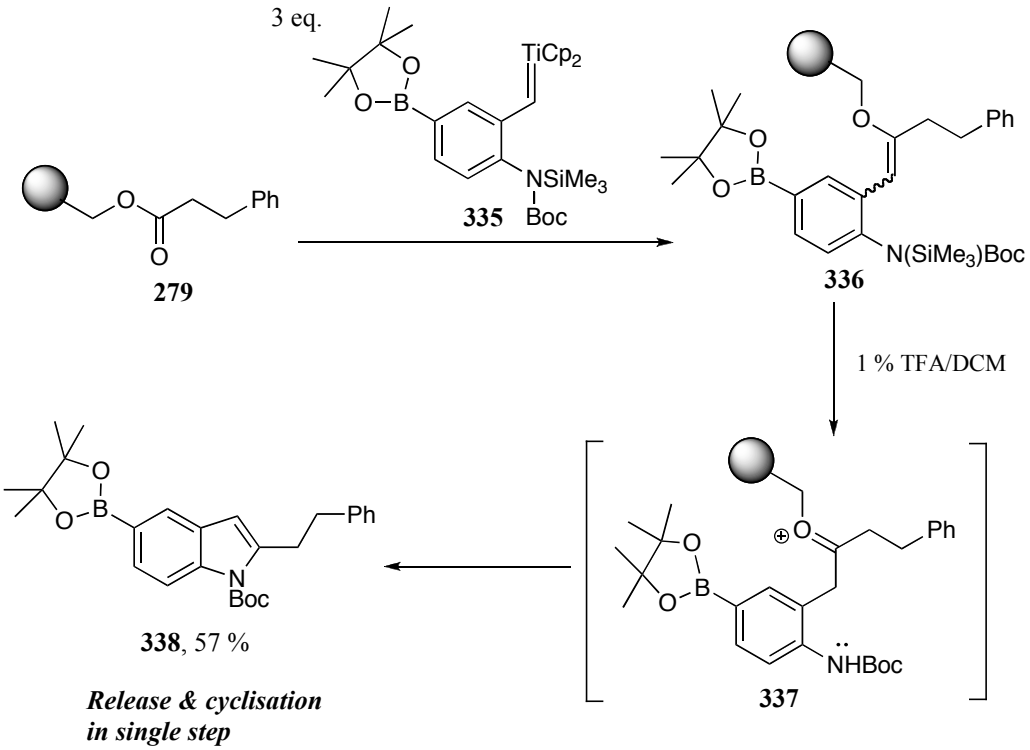
Mono-Boc protection proceeded under standard conditions, with a yield of 71 % after column chromatography. Addition of LDA to deprotonate the carbamate **288** followed by introduction of silyl chloride formed the corresponding silylcarbamate **334** in near quantitative yield. It is important to note that the same problems of instability experienced by Calum Macleod in the synthesis of his silylcarbamate derivative **108**[81] (Chapter 3.2.3, Fig 8, **108**) were also apparent in my synthesis. Indeed full characterisation of the compound was not obtained for this reason (Scheme 91).



Scheme 91

6.4.1 Alkylidenation and Cleavage to give Boronate-Bearing Indole

Addition of freshly prepared compound **334** to the low valent titanium species **90**, formed in the Takeda procedure, to generate the titanium benzylidene **335** went underway. Resin-bound ester **279** was then added, alkylidenation of the ester proceeded to give resin-bound, acid labile, enol ether **336**. When the resin was treated with acid, indole **338** was produced in good yield, presumably *via* the corresponding oxonium ion **337** (Scheme 92).



Scheme 92

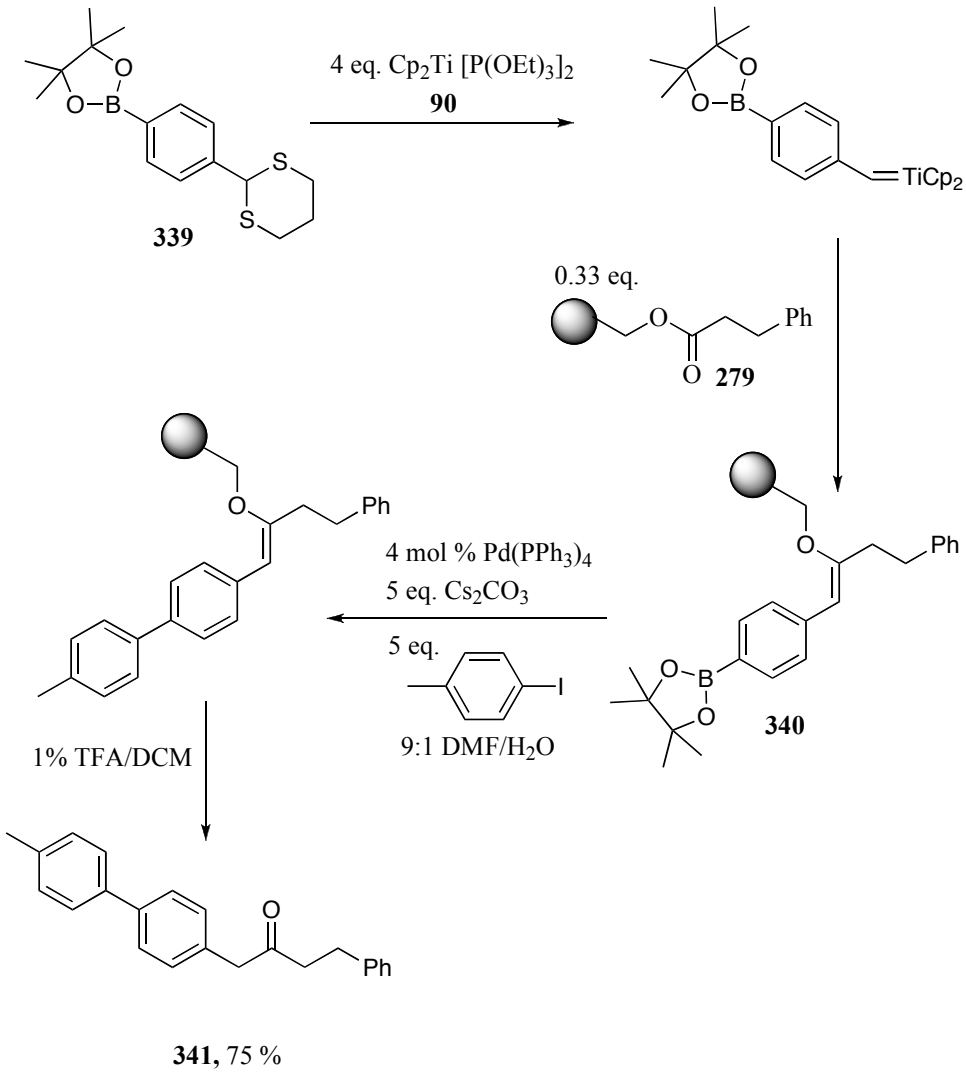
The boronate-bearing *N*-Boc indole **338** had been synthesised with functionality introduced from resin in the 2-position, in good yield. The resulting NMR spectrum of the crude material showed the indole derivative to be in excellent purity and chromatography was unnecessary, demonstrating the effectiveness of the chameleon catch strategy (see Appendix A for NMR spectrum of crude material).

6.4.2 Boronate-Bearing Substrates on Resin

A key advantage to an immobilised arylboronate is that aryl halides are more widely available and cheaper then their arylboronate counterparts. Piettre and Baltzer encouraged the application of resin-bound boronates by Miyaura palladium mediated cross-coupling to transform polymer-bound aryl halides into the corresponding boronates.[189] More recently Kondo *et al*. employed resin-bound boronates in the synthesis of bisindole alkaloids analogues.[190] Despite these examples, surprisingly, the vast majority of resin-bound Suzuki cross-couplings feature the aryl halide as the immobilised coupling partner.[191]

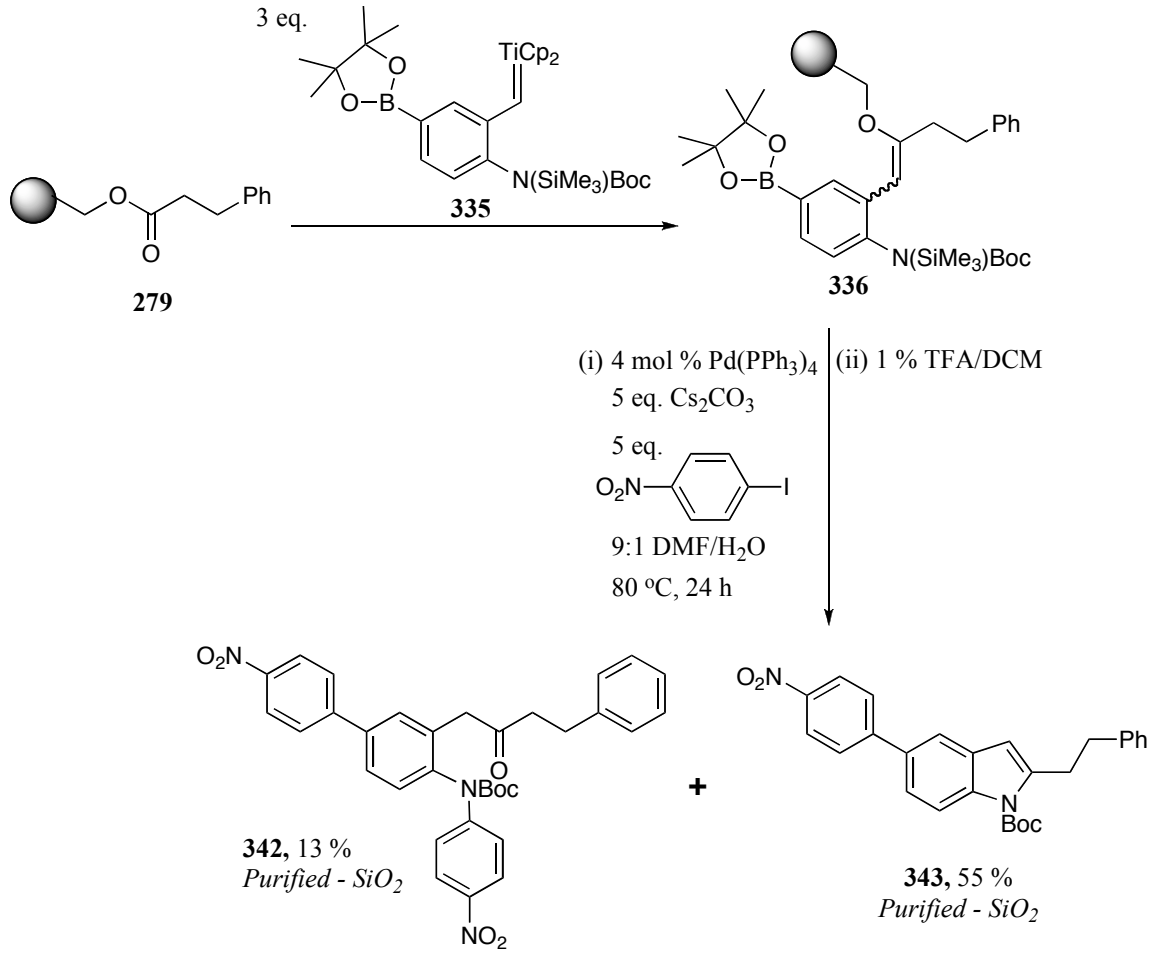
6.5 Suzuki Cross-Coupling on Resin

The success of the alkylidenation prompted investigation into cross-coupling with an aromatic partner under Suzuki conditions on resin.[192,193] A standard procedure for Suzuki cross-coupling was tested on an enol ether that lacked the added complexity of an *ortho*-group. This was prepared, using dithiane **339** which was available in the lab from Gordon McKiernan, under our now standard alkylidenation conditions. Cross-coupling proceeded with resin-bound enol ether **340**, 4 mol % $Pd(PPh_3)_4$, 5 equivalents of cesium carbonate and aryl iodide in DMF for 24 h at 80 °C, containing 1 equivalent of water, followed by cleavage in acid, to give ketone **341** (Scheme 93).[194]



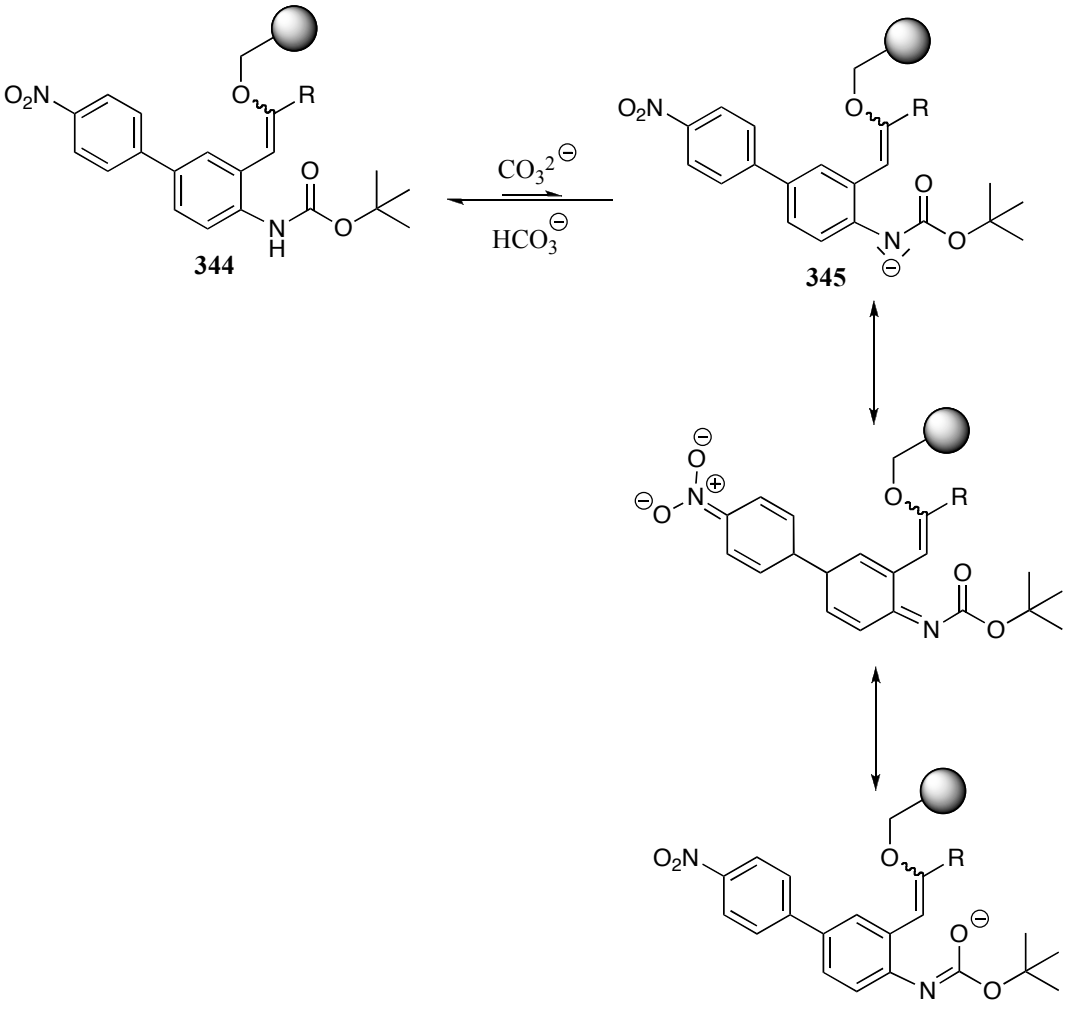
Scheme 93

With the results from the cross-coupling reactions in hand, we considered changing the aryl halide cross-coupling partner. We opted, to repeat the reaction with the resin-bound aryl boronate **336** under the same Suzuki conditions as before, this time with electron withdrawing halide, 1-iodo-4-nitrobenzene. This would hopefully prove successful, as the electron withdrawing nature of the nitro-group would promote cross-coupling between boronate and aryl halide.[195] The result was surprising upon purification *via* column chromatography not only was the expected cross-coupled compound **343** isolated but also ketone **342**. The latter is most likely a product of Buchwald-Hartwig coupling[196,197,198] (Scheme 94).

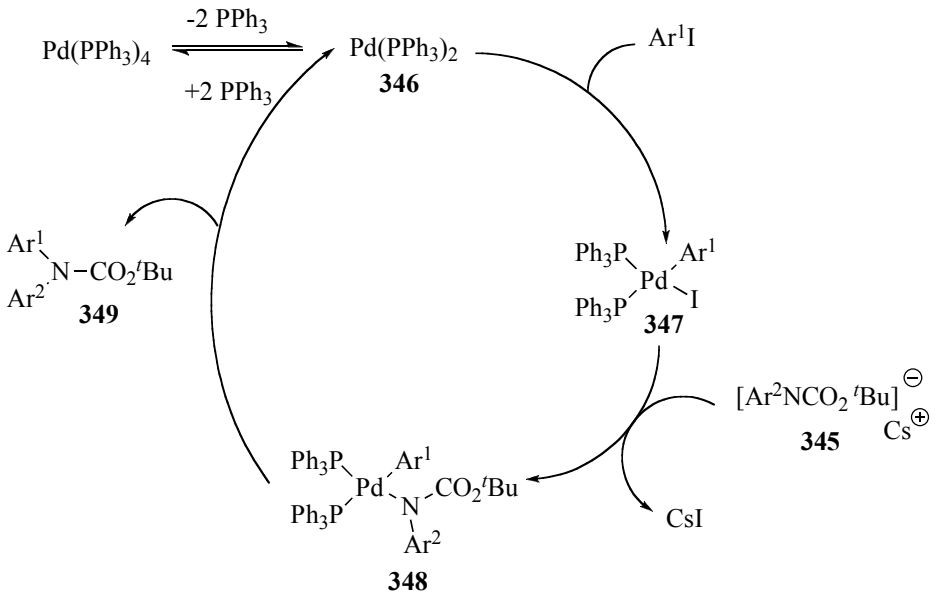


Scheme 94

The mechanism for the formation of the resin-bound precursor **336** to ketone **342** is shown in the following schemes (Scheme **95** and Scheme **96**).



Scheme 95



Scheme 96

Electron poor carbamate **344** will be in equilibrium with the deprotonated version **345**, in which the anion is delocalised over both the carbonyl and nitro groups (Scheme 95). The tetrakis(triphenylphosphine)palladium(0) is coordinatively saturated and probably dissociates to 14 electron complex **346** before reacting with aryl iodide to give the palladium(II) complex **347** *via* oxidative addition (Scheme 96). Displacement of the halide by the carbamate anion **345** then generates complex **348**, which undergoes reductive elimination to give the tertiary carbamate **349** and regenerating the active catalyst **346.**

Although a small set back in terms of finding optimal Suzuki conditions for target 2,5-disubstituted indoles, this result did present the possibility of introducing aryl functionality into the *N*-1 position of the final indole ring.[199] If we could control one mode of coupling over the other, we could have a viable route to 1,2,5-trisubstituted indoles. A number of trial reactions, varying stir times and numbers of equivalents of *para*-nitro-4-iodobezene were attempted. The results of which are presented in table 2.

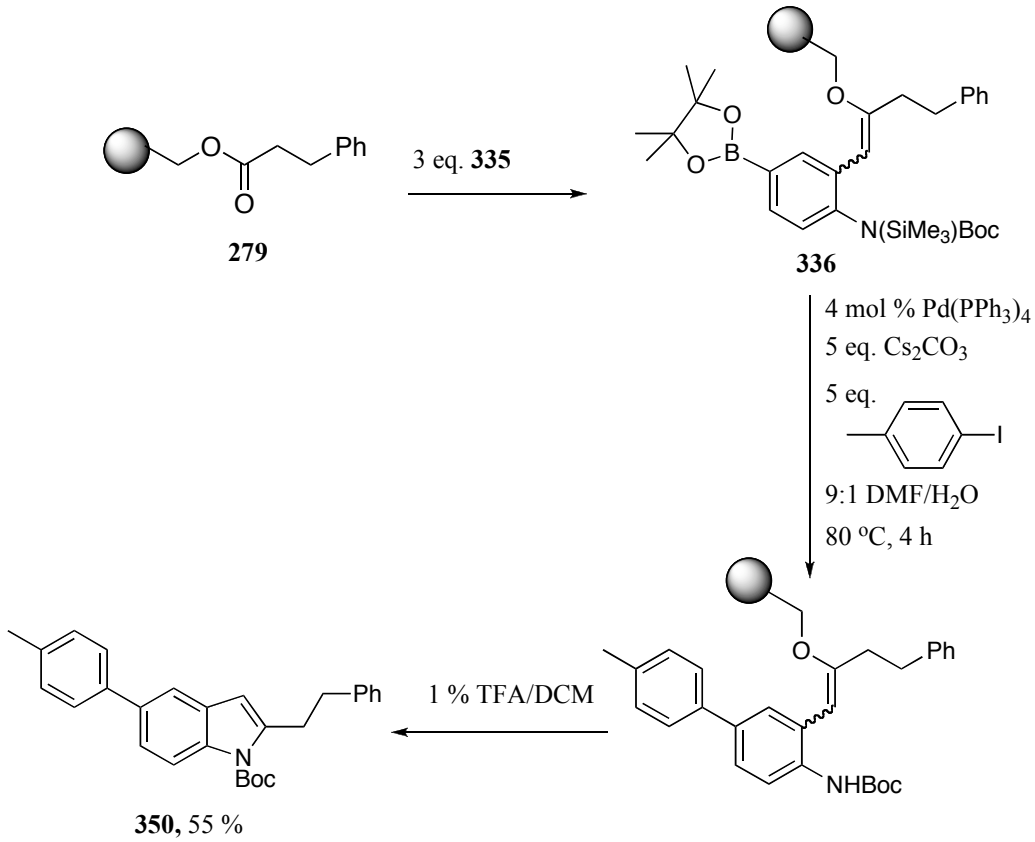
Time (h) at 80 °C	Number of equivalents of *para*-nitro-4-iodobenzene	Yields % (Combined)	Ratio **343**:**342**
24	5	64	4:1
6	1	54	5:1
5	2	61	4:1
4	***5***	***68***	***5:1***

Table 2

Reducing the number of equivalents of aryl iodide was expected to have favoured Suzuki cross-coupling. However the *N*-aryl product **342** was always present, due to *N*-arylation being favoured by the anion-stabilising nitro group, it was also noted that the overall yield was improved from 64 % to 68 % when the reaction time was lowered to 4 h. The question arose as to whether improved yields of Suzuki cross-coupled product could be obtained if a more electron-rich partner was employed with a 4 h reaction time.

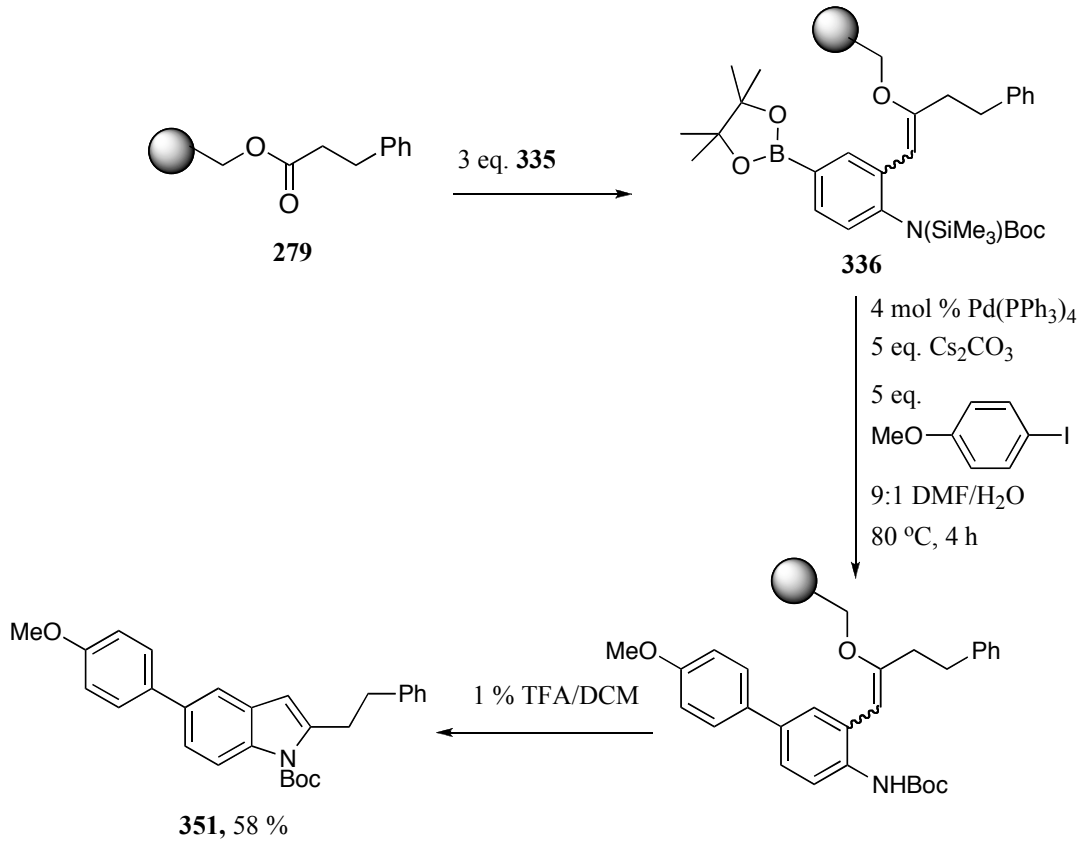
Reaction with *para*-iodo-toluene, followed by cleavage in acid, produced the target compound **350** in good yield without need for further purification or evidence of a Buchwald-Hartwig product (see Appendix A for spectra of crude indole) (Scheme 97).

With the emphasis now back on track to synthesising more examples of 2,5-disubstituted indoles using SPS, the possibility of further exploring conditions for selective Buchwald-Hartwig cross-couplings to give 1,2,5-trisubstituted indoles was put to one side.



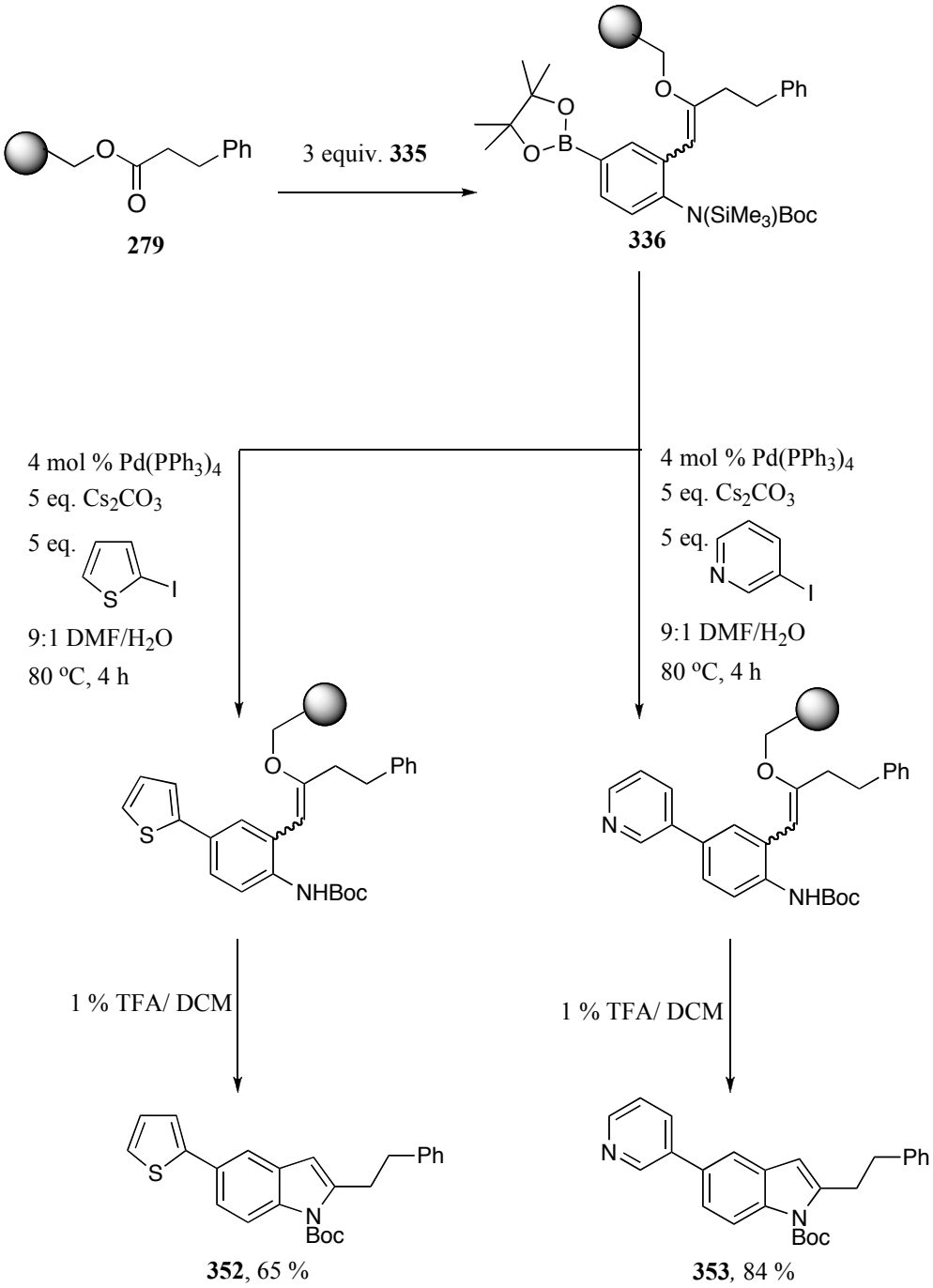
Scheme 97

An electron-rich coupling partner, *para*-iodo-methoxybenzene, was then treated to optimised conditions and underwent the sequence of reactions successfully to yield **351** (Scheme 98).



Scheme 98

In addition, simple heterocyclic ring systems, thiophene and pyridine, proved successful Suzuki cross-coupling partners, furnishing target compounds **352** and **353** in good yields and excellent purities (Scheme 99). Appendix A presents the NMR spectra of the unpurified materials as released from resin to show their purity.



Scheme 99

6.6 Conclusion

We had developed good conditions for the alkylidenation, cross-coupling and cleavage sequence to convert resin-bound esters into 2,5-disubstitued indoles using our boronate-bearing titanium benzylidene reagent **335**. Furthermore the route for preparing protected arylboronate **334**, the precursor to boronate-bearing benzylidene reagent **335**, in reasonable amounts was now robust.

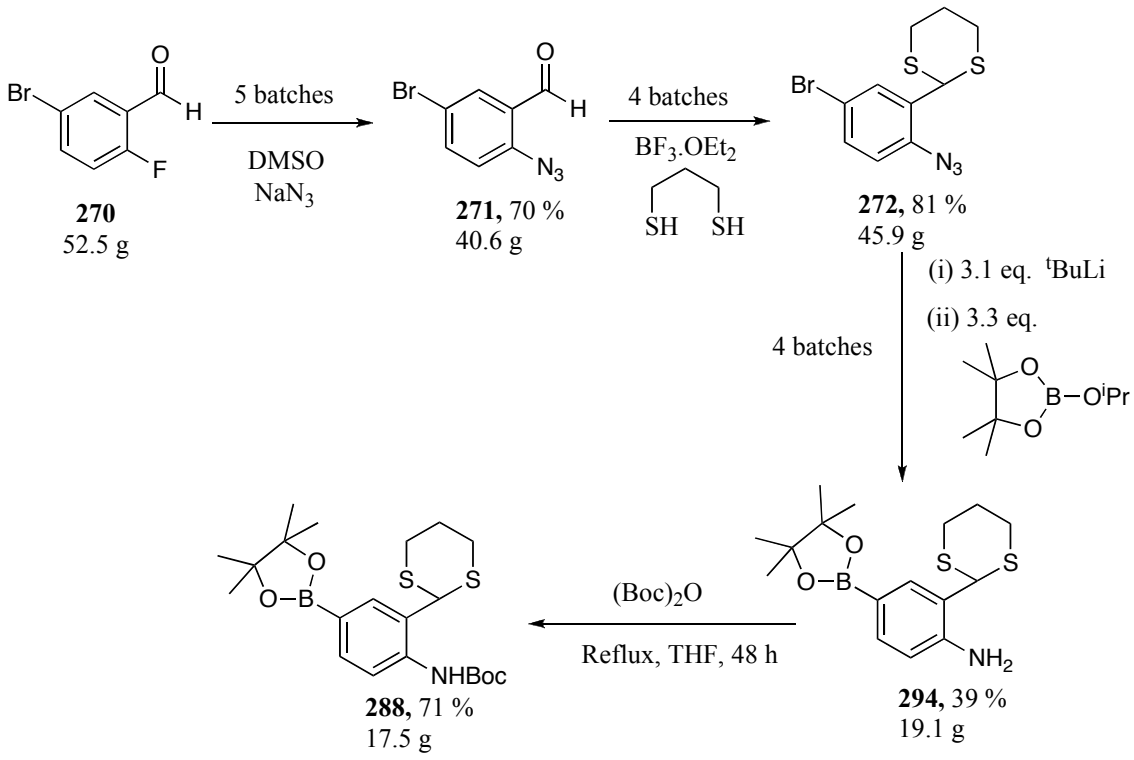
7.0 Combinatorial Synthesis of a 96-member Library

7.1 Scale Up

We were now ready to scale up the preparation of titanium benzylidene **335** so that a 96-member library of 2,5-disubtituted indoles could be prepared with a theoretical yield of 93 μmoles of each compound. We calculated that at least 12 g of dithiane **288** was needed based on previous yields.

Since both the silylated carbamate **334** and the boronate-bearing titanium benzylidene reagent **335**, were unstable and would have to be used immediately, we stopped the synthesis at the last stable compound in the route *i.e.* the Boc-protected derivative **288**.

Following our scheme (Scheme 100), the total amount of carbamate-protected arylboronate **288** (17 g) was achieved. The yields of each step are the average yield in each case.



Scheme 100

Significant amounts of material could be synthesised without problem, all steps up until the Boc-protection involved only recrystallisation for purification. The conversion of azide into amine by our one pot synthesis was achieved in batches (4 x 11.5 g), principally so as to operate in a controlled fashion when handling lithiated reagents. We were unable to find suitable recrystallising conditions to remove excess Boc anhydride after the final step, so we employed column chromatography. The material was purified in batches (2 x 10 g), although more time-consuming, this was certainly the more reassuring option. The carbamate-protected arylboronate **288** was only converted into silylcarbamate-protected substrate **334,** immediately before use in generation of boronate-bearing titanium benzylidene **335** for each alkylidenation reaction.

7.1.1 IRORI MiniKans™

GSK require in their initial hit generation step only 3-5 mg of final compound to be tested. Thus we used less resin in IRORI MiniKans™, which are smaller porous polypropylene reactors having an internal volume of only 660 μL as compared to the 2400 μL of the MacroKans™ used previously. 93 μeq. of resin was used per MiniKan™, employing Merrifield resin with a loading of 2.0 meq. g^{-1}.

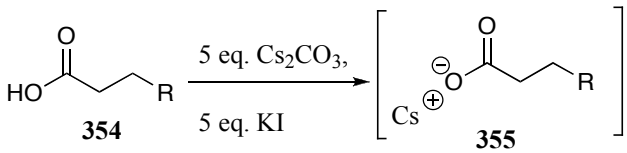
The first step was to carefully weigh 46 mg of Merrifield resin into 96 individual IRORI MiniKans™; this was achieved using the dry resin filler (Figure 25). Additionally as I had made a contingency of excess material it was an opportunity to prepare sacrificial MiniKans™. These were black polypropylene reactor vessels, in direct contrast to the 96 white MiniKans™ required for the library, thus easy to identify and isolate. The sacrificial MiniKans™, eight in total, were individually filled with Merrifield resin (46 mg). These would be used in monitoring the course of the reactions, thus fine tune and identify any potential issues before committing the entire 96 MiniKans™. Once weighed and prepared all the MiniKans™ were capped with a bar-coded lid to ensure no resin could escape (Figure 26). The barcode would store invaluable data, as each individual MiniKan™ would soon become a vessel for a potentially unique indole derivative.

Figure 25: Dry Resin Filler[200]

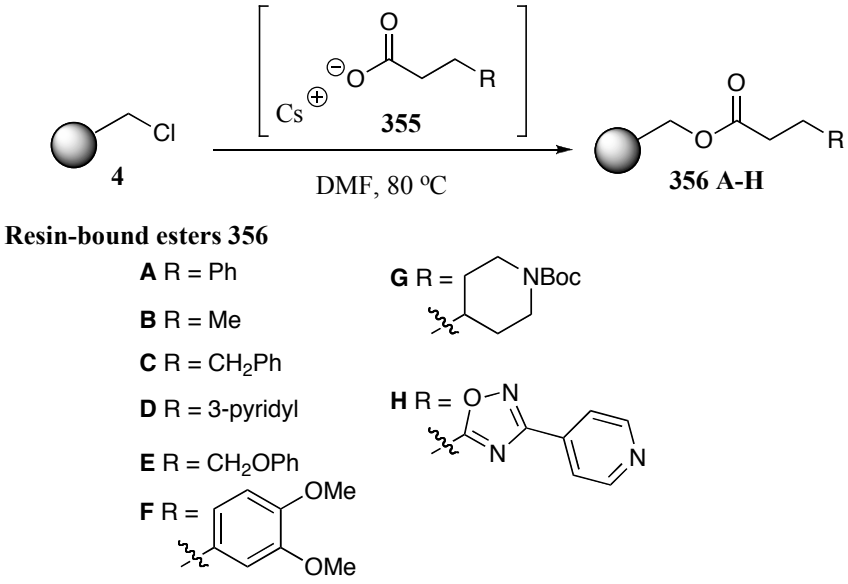
Figure 26: IRORI MiniKan™ with barcode lid[201]

7.1.2 Resin-Bound Esters

All the Merrifield resin-containing MiniKans™ were converted into one of eight resin-bound esters **356 A-H**, prepared using the same conditions we had employed previously (Schemes 83 and 84) from corresponding carboxylic acids **354** (Schemes 101 and 102). 13 MiniKans™ of each ester were prepared including the sacrificial MiniKans™. The choice of ester was centred on the idea of introducing maximum diversity to the final indole compound. The range covered from simple groups such alkyl chain derivative **B** to complex Boc-protected piperidine derivative **G**. The Boc-protected piperidine unit, if successfully introduced to the final indole compound would be a very interesting derivative because removal of the Boc-protecting groups would place a nitrogen atom in a similar position to that found in hydroxytriptamines (Chapter 5).[202]



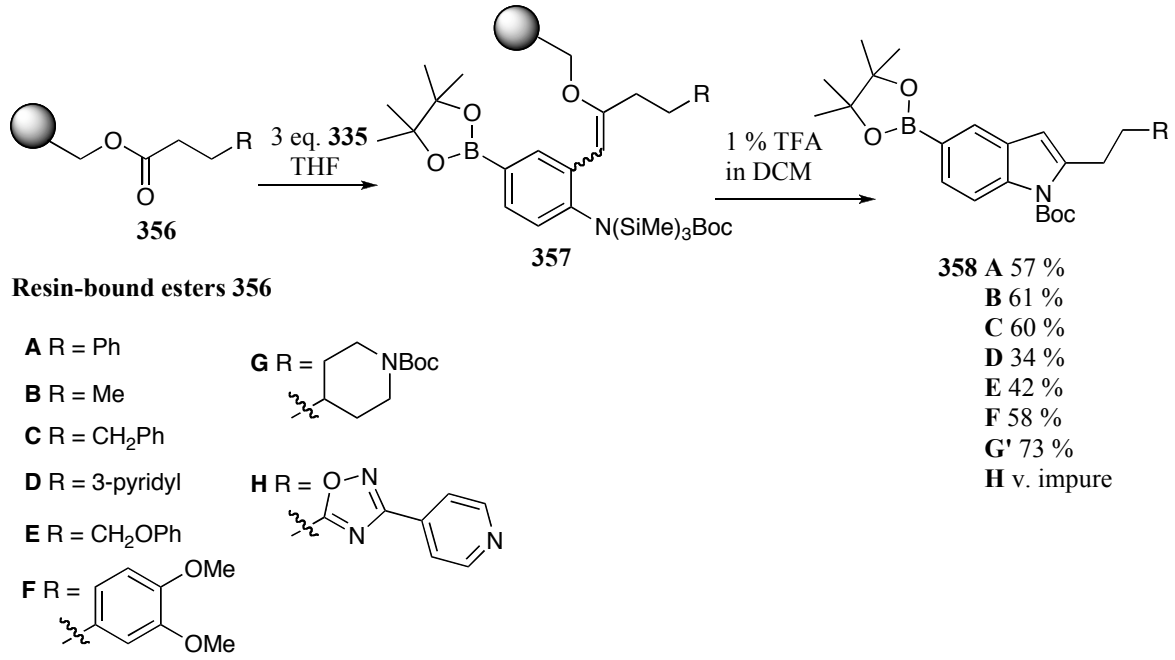
Scheme 101



Scheme 102

7.2 Alkylidenation and Cleavage

The sacrificial eight MiniKans^{TM} containing the resin-bound esters **356 A-H** were alkylidenated together to give enol ethers **357 A-H**. Each MiniKan^{TM} was then subjected to the cleavage conditions to give the boronate-bearing indole products **358 A-H** in good yield and purity, with the exception of **358 H**, which was very impure. The identity of the crude boronate products **358 A-H** from cleavage and evaporation of solvent was confirmed by ^{1}H NMR spectroscopy. Enol ether **357 G** contains two *N*-Boc groups, however after cleavage a mono-Boc compound **358 G'** was isolated. It is believed that the *N*-Boc on the indole is the Boc-group that is retained. This is based on the chemical shift of the *tert*-butyl group, and the obvious stability of the other *N*-Boc indoles **358**. It is noteworthy to observe the limitations of reagent **335**, indoles containing Lewis basic sites such as pyridine derivative **358 D** could be made, but it would appear that the 1,2,4-oxadiazole unit **356 H** has limited stability to the reaction conditions (Scheme 103).



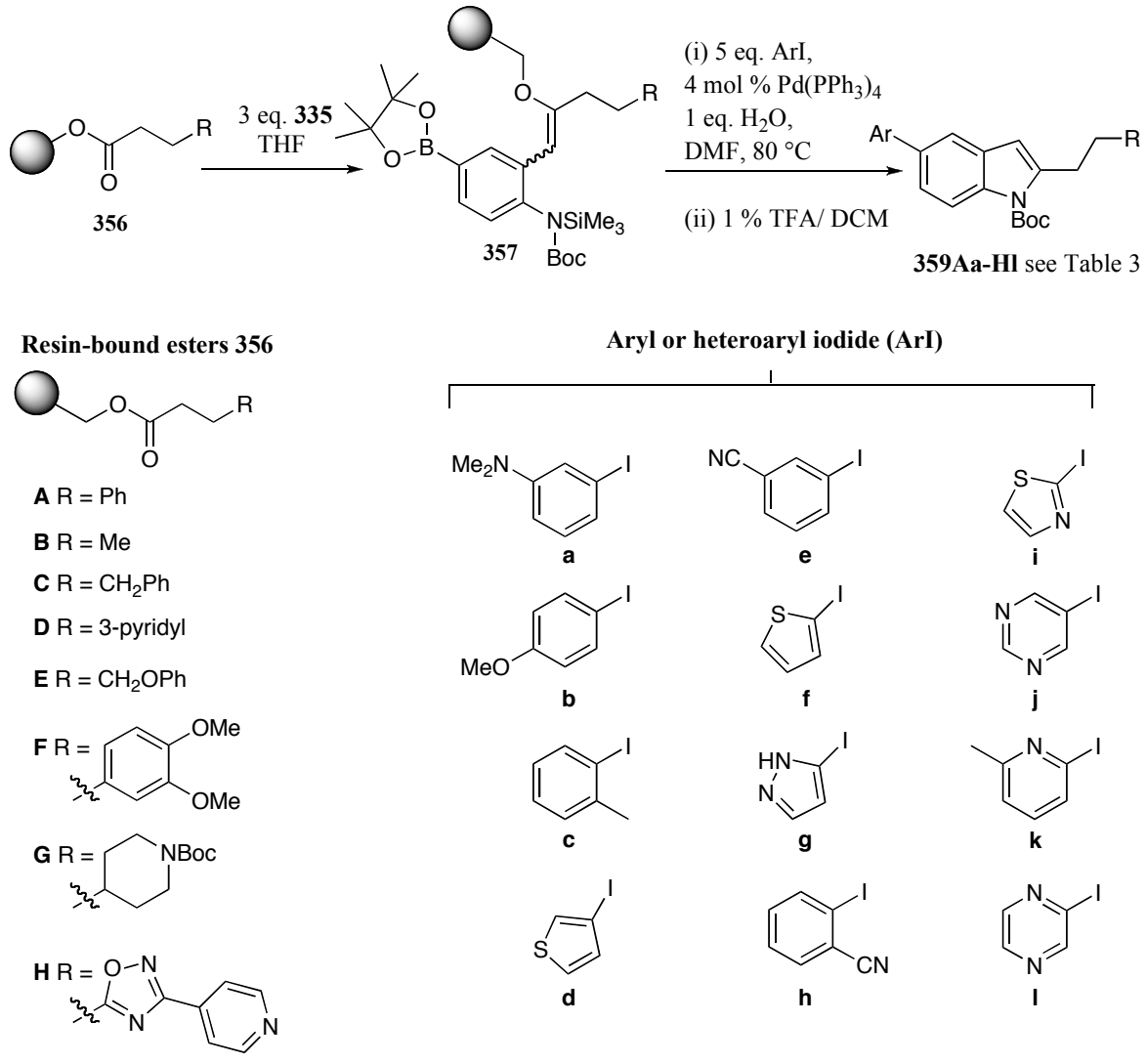
Scheme 103

7.2.1 Synthesis of 96-Member Library

With the confirmation that the sensitive alkylidenation conditions had been successful, the remaining 96 MiniKans^{TM}, arranged as 8 batches of 12, with each of the 12 Kans containing the same resin-bound esters **356 A-H** were alkylidenated in exact fashion to the 8 sacrificial Kans. The entire 96 MiniKans^{TM} were then washed (THF, DCM and methanol) and dried under high vacuum, to ensure the complete removal of residues/ reagents that could interfere with subsequent reaction conditions. The 96 MiniKans^{TM} were then arranged into 12 batches of the 8 different resin-bound enol ethers **357 A-H** and each batch was subjected to Suzuki cross-coupling with a different aryl or heteroaryl iodide. The entire process of sorting the MiniKans^{TM} into batches was automated by the X-Kan sorter (Figure 27) as a means of ensuring there were no miscounts or confusion as to which MiniKan^{TM} should go into which batch.

Figure 27, X-Kan sorter[203]

The choice of different aryl or heteroaryl iodide **a-l** was centred on the idea of introducing a wide range of diversity. Cross-coupling partners ranged from simple aromatics such as 2-iodotoluene **c**, to more interesting groups including heterocycles such as 2-iodothiophene **f** and 2-iodothiazole **i**, and included both electron-rich iodides **a-d** and electron poor iodides **i-l** (Scheme 104).



Scheme 104

After the Suzuki cross-coupling reactions had taken place the MiniKans™ were washed and placed in pre-assigned order *via* the X-Kan sorter into a 96 well plate (Figure 28). The MiniKan™ containing 96-well plate was then placed in the Clevap station (Figure 29) for the uniform exposure to mild acid (1 % TFA in DCM).

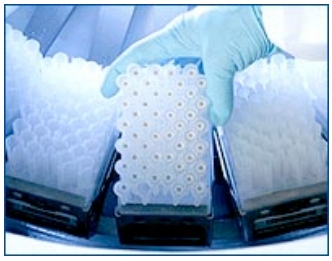


Figure 28, 96 Well plate[204]

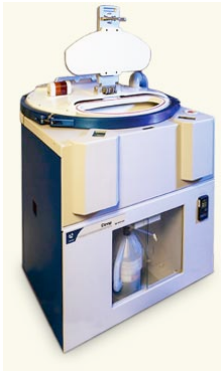


Figure 29, Clevap Station[205]

Addition of mild acid initiated cleavage from resin and the cyclisation. The MiniKans™ were exposed to these conditions for 1.5 h before transfer of each solution to a separate collection well, washing the Kans three times with DCM into the appropriate well. Evaporation of the solvent commenced to give the residue from each separate MiniKan™ vessel in each separate well. The process in the Clevap is illustrated in Figure 30.

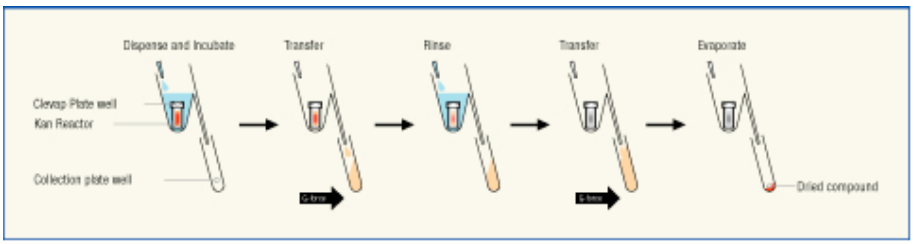


Figure 30, illustration of residue collection[206]

The residues from these individual wells were then analysed to reveal the identity and purity of each library member.

7.3 Results and Analysis

The crude yields and purities of each of the 96 library members are presented in Table 3. The library members were identified using reversed phase HPLC, with diode array UV detection (DAD-UV), evaporative light scattering detection (ELSD) and MS analysis. The molecular weight of each of the potential 96 indoles had previously been calculated and the information logged into the barcode lid of each MiniKan™. This ensured that, upon cleavage and evaporation, the MS analysis of each residue correctly ascertained whether the desired indole was present. The purity values for the library members were determined using summed diode array UV detection (DAD-UV) between the wavelengths of 210 nm

and 350 nm. In thirteen examples (highlighted in bold), the identity of the library members were further confirmed by ^{1}H NMR spectroscopy following purification by reversed phase HPLC. Even on occasions when the yield and purity were particularly low, as was the case for indole **359 Fh**, sufficient material could be obtained for identification in this way. This supported confidence that other compounds in the library were correctly identified by reversed phase HPLC/DAD-UV/ELSD/MS.

In 79 cases the desired indole was produced (82 % success). Surprisingly, di-Boc compounds **359 a-G** were produced with the exception of indoles **359 Gd** and **359 Gi**. The de-protection of the aliphatic amino group had dominated in the boronate-bearing indole example **358 G'** but in the instance of cross-coupling followed by cleavage this was not the case. As expected from the poor quality of boronate **358 H**, there were few indoles derived from 1,2,4-oxadiazole **356 H**. In the main, the enol ethers **357 A-H** had efficiently cross-coupled with a wide range of aryl and heteroaryl iodides including both electron-rich substrates **a-d** and electron-poor substrates **i-l**. It is not clear why some derivatives of 3-iodothiophene were not formed and that 3-iodopyrazole[39] **g** appears to be a poor substrate for Suzuki cross coupling. Indeed, there are no reports of palladium-catalysed cross couplings with this substrate in the literature.

Yields of indoles 359 synthesised (purities in parenthesis)								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
a	66 (89)	72 (97)	78 (81)	53 (70)	64 (88)	72 (94)	68 (71)	*
b	**62 (69)**	55 (77)	**35 (78)**	61 (84)	**67 (47)**	**74 (70)**	**59 (60)**	*
c	**53 (79)**	48 (80)	37 (83)	56 (69)	**57 (77)**	**37 (43)**	46 (16)	*
d	*	*	56 (54)	63 (44)	65 (50)	80 (46)	*	*
e	**60 (66)**	62 (91)	30 (73)	72 (87)	**64 (29)**	35 (32)	39 (24)	*
f	65 (41)	76 (8)	65 (39)	60 (64)	43 (27)	30 (35)	39 (18)	*
g	57 (36)	*	*	*	92 (33)	89 (21)	71 (20)	*
h	50 (70)	73 (64)	41 (59)	65(100)	**52 (48)**	**41 (13)**	57 (43)	39 (84)
i	58 (21)	49 (55)	48 (15)	62 (41)	59 (18)	40 (35)	*	18 (12)
j	85 (64)	69 (57)	41 (61)	57 (55)	60 (51)	38 (67)	34 (63)	*
k	81 (86)	62 (91)	78 (71)	90 (75)	89 (78)	68 (77)	67 (84)	*
l	45 (91)	74 (91)	51 (94)	76 (86)	**64 (64)**	48 (70)	42 (13)	*

* MW of product not detected

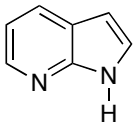
Table 3

7.4 Conclusion

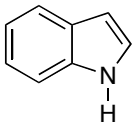
In summary, we have synthesised new boronate-bearing titanium carbenoid reagents, using a sequence that involved the novel reduction of an aryl azide with *tert*-butyllithium. We have demonstrated that this organotitanium reagent can be used for the SPS synthesis of 2,5-disubstituted indoles. Finally we exemplified the benzylidenation, Suzuki cross coupling, cleavage-cyclisation sequence for introducing diversity, by successfully preparing 79 members of a potential library of 96 indoles.

CHAPTER 8.0 – 7-Azaindoles

The success of the 2,5-disubstituted indole library gave rise to the idea of exploring a similar class of heterocycle i.e. 7-azaindoles (1*H*-pyrrolo[2,3-*b*]pyridine). 7-Azaindole can be considered to be two-nitrogen analogues of indole (Figure 31). Its derivatives are interesting, as substitution of a basic nitrogen atom at C-7 has been seen to modify the pharmacological properties of known indole pharmacophores.[207] For this reason, interest in the heterocyclic scaffold of 7-azaindoles has recently started to intensify and as such the number of syntheses to 7-azaindole derivatives, for a range of applications, has risen.[208]



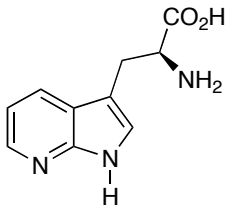
7-azaindole



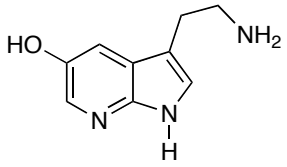
Indole

Figure 31

7-Azaindoles have a smaller HOMO-LUMO gap than indoles and this gives them useful fluorescence properties so that replacement of tryptophan with 7-azatryptophan **360** has been used widely in biology (Figure 32).[209] Furthermore, 7-azaserotonin **361**, which is an analogue of serotonin, has an unusual dual emission in some solvents (Figure 32). Additionally, numerous pharmaceutical uses of 7-azaindole derivatives as protein kinase inhibitors, H1 antagonists and PPAR agonists are currently being investigated.[210]



7-azatryptophan
360



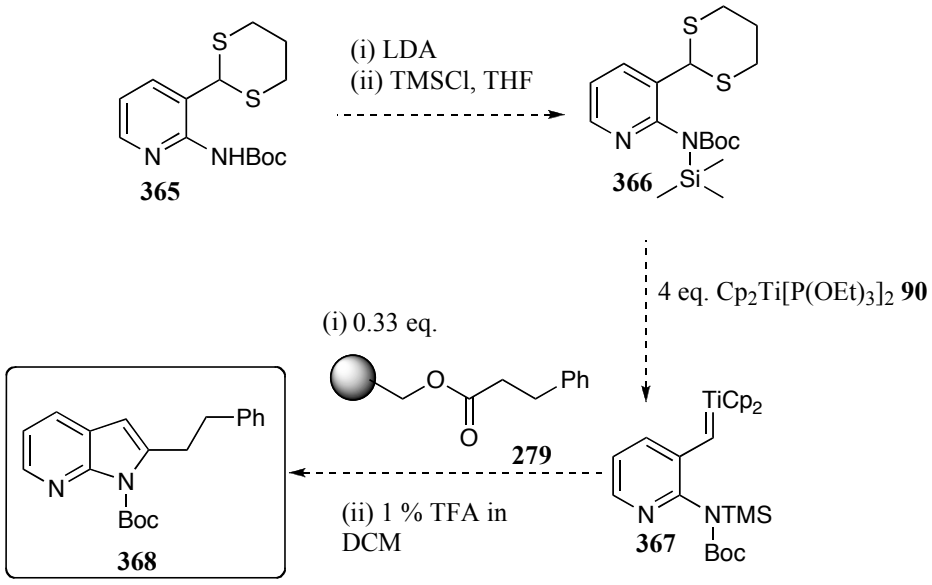
7-azaserotonin
361

Figure 32

The majority of routes to 7-azaindole derivatives have focused primarily on modified indole syntheses such as the Fischer and the Madelung syntheses.[211] Other popular routes include transition-metal catalysed cross-coupling/ heteroannulation of 2-amino-3-halo-pryidines with alkynes or ketones.[212] However, there is to date no literature precedent for the traceless SPS of 7-azaindole derivatives.

8.1 Proposed Route for the SPS of 7-Azaindoles

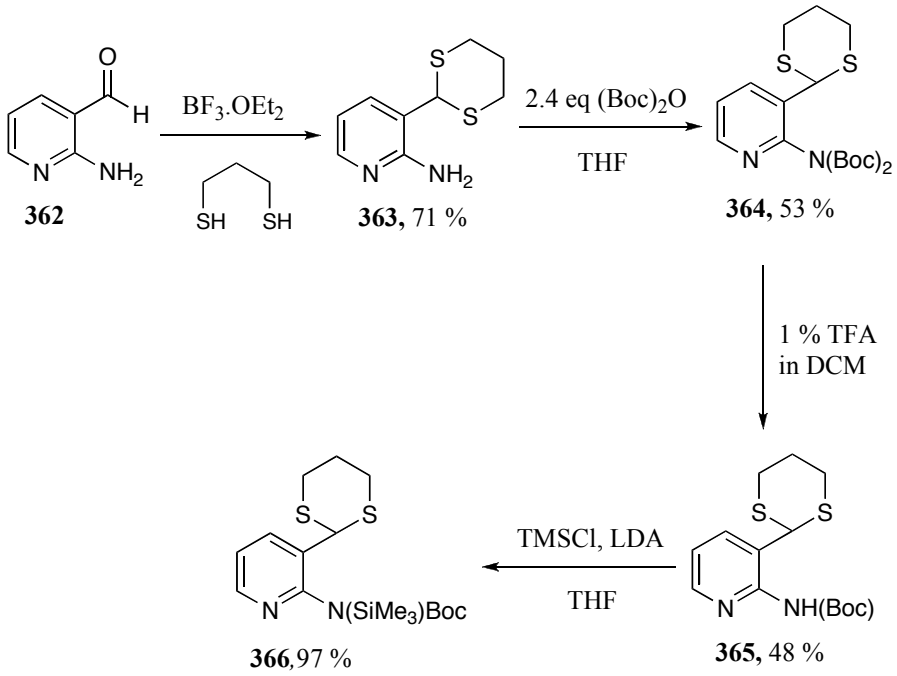
Considering all these reasons, the following synthetic pathway was envisaged to allow SPS of a library of 2-subsituted 7-azaindoles **368** (Scheme 105).



Scheme 105

8.1.1 Synthesis of *N*-Silylcarbamate Substrate

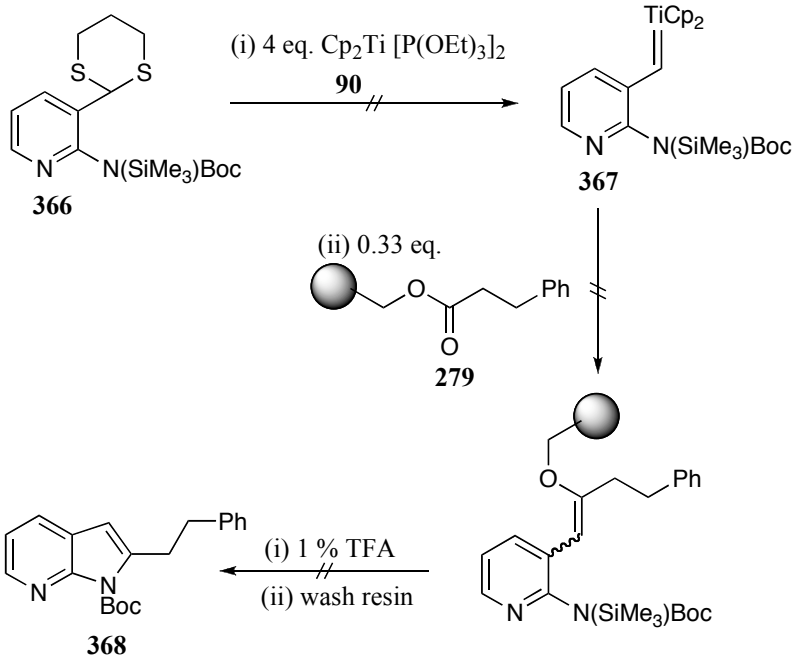
Commercially available 2-amino-3-pyridine carboxaldehyde **362** was converted into the dithiane derivative **363** in good yield. Carbamate protection of the amine group under standard Boc protection conditions[82] proved tedious, as a mixture of both mono and di-Boc derivatives were obtained. To resolve this, the amine was fully protected as the di-Boc derivative **364** then subsequently mono deprotected.[81] The resulting mixture of products was purified by column chromatography to give the desired mono-Boc compound **365**. Silyl protection then followed to furnish the *N*-silylcarbamate **366** without difficulty (Scheme 106).



Scheme 106

8.1.2 Attempted Alkylidenation of Resin-Bound Ester

Dithiane substrate **366** was added to low valent titanium species **90**, formed by the Takeda procedure, in an attempt to generate titanium benzylidene reagent **367**. The resulting mixture was used immediately in an attempt to benzylidenate resin-bound ester **279**. However, after cleavage in mild acid the resulting material did not contain the desired product **368** or indeed any trace of any possible derivative. The titanium probably co-ordinated the pyridine nitrogen atom during generation of the titanium benzylidene **367**, and this may have led to decomposition (Scheme 107).



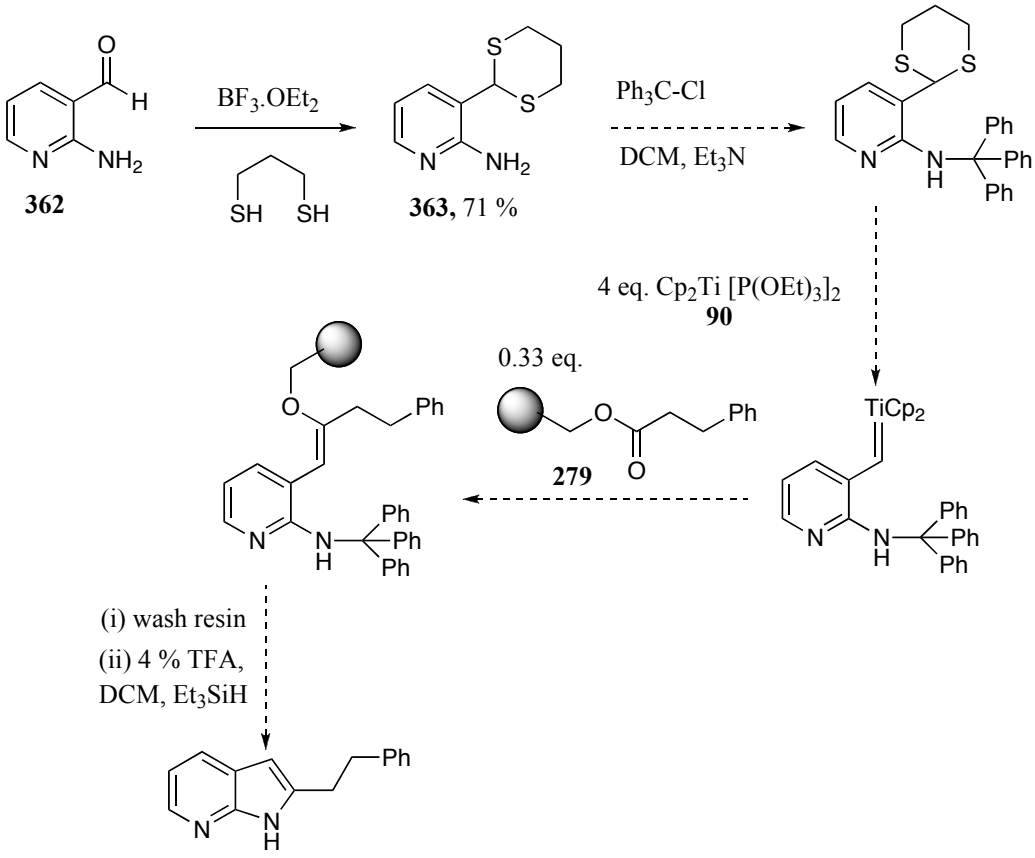
Scheme 107

8.2 Conclusion

We had been unsuccessful; however, trityl protection may prove to be rewarding. In Chapter 6, I showed that employing trityl protection in the SPS of an indole has proven successful. The bulky trityl group may prevent the pyridine nitrogen atom from co-ordinating with the titanium atom.

8.3 Future Work

It is my hope that the following route will be attempted, in order to verify the success of the chemistry. If indeed the synthetic scheme proves viable it could potentially be applied to an automated SPS of 2-substituted 7-azaindoles (Scheme 108).


O
H
N
NH2
362
BF3.OEt2
SH
SH
S
S
N
NH2
363, 71 %
Ph3C-Cl
DCM, Et3N
S
S
N
N
H
Ph
Ph
Ph
4 eq. Cp2Ti [P(OEt)3]2
90
0.33 eq.
O
O
Ph
279
TiCp2
(i) wash resin
(ii) 4 % TFA,
DCM, Et3SiH
Ph
N
H

Scheme 108

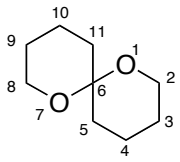
CHAPTER 9 – Solution Phase Synthesis of Spirocycles

Following the success of the previous titanium carbenoid chemistry in the SPS of an indole library, I turned my attention to the solution-phase synthesis of bicyclic nonaromatic heterocycles. This would, if successful, be an excellent demonstration of the versatility of the titanium alkylidene methodology developed within the group.

9.1 Spiroacetals

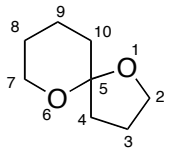
Spiroacetals are non-aromatic bicyclic substructures of naturally occurring metabolites from sources including: insects, microbes, plants, fungi and marine organisms.[213] Spiroacetals are key sub-units in a wide range of biologically active natural products and the pharmacological properties they posses has recently triggered a surge of interest in both their synthesis and chemical reactivity. The vast majority of chemistry in this area is focused on the generation of the spiroacetal ring systems **369**, **370** and **371** (Figure 33).[213] This is presumably because most spiroacetal-containing natural products fall into one of these structural categories. I shall refer to spiroacetals based on spiroacetals **369**, **370** and **371** as [5.5], [4.5] and [4.4] spiroacetals respectively.

a [5.5] spiroacetal



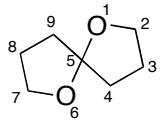
369

a [4.5] spiroacetal



370

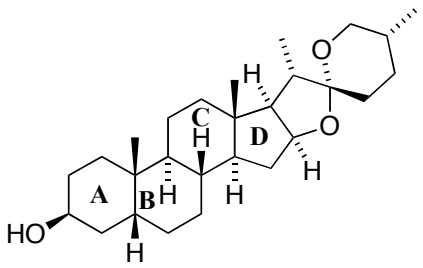
a [4.4] spiroacetal



371

Figure 33

The earliest examples of spiroacetal structures came from natural products extracted from plants found in the south west of the USA and in Mexico during the 1930's and 40's. The compounds were glycosides (saponins) in which the aglycone (sapogenin) consists of a steroid nucleus containing a spiroacetal assembly fused to the D-ring *e.g.* the aglycone smilagenin **372** (Figure 34),[214] new glycosides of which continue to be discovered.[215]

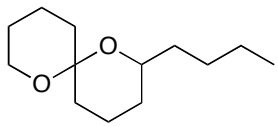


Smilagenin, **372**

Figure 34

Studies of the biological activity of these saponins revealed that they lower surface tension of plant cell walls and possess emulsifying properties. They also have haemolytic and antilipemic activities. They also displayed a capacity to lower serum cholesterol levels, and for this reason have been investigated as potential statins.[216]

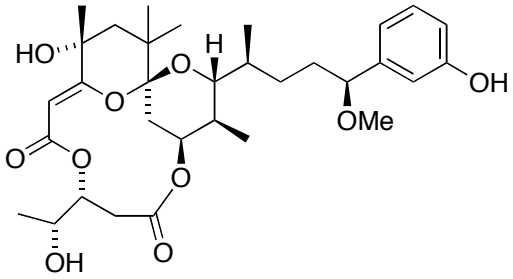
Many species of flying insect have been found to produce simple spiroacetals that exhibit pheromonal activity,[217] *e.g.* spiroacetal **373** (Figure 35), which was isolated from the Malaysian fruit fly *Dacus latifrons* (note the relative stereochemistry was not reported). The majority of these spiroacetals contain simple unbranched carbon chains. Due to their simple functionality, they played an important role in the early spiroacetal synthesis work, as they provided simple targets on which to test synthetic methodology (Figure 35). [213]



373

Figure 35

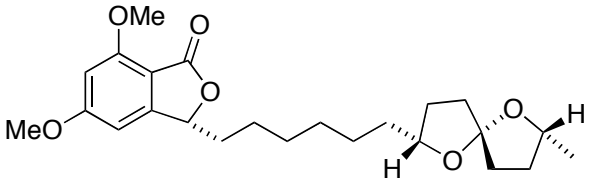
A number of spiroacetal-containing structures can also be found in marine sponges and some forms of algae. Blue-green algae contain several toxic metabolites that have been described to have spiroacetal substructures, *e.g.* oscillatoxin B **374** (Figure 36).[218] Their properties range from carcinogenic activity, including tumour-promoting properties to contact dermatitis (colloquially known as “swimmers itch”) that affects certain Pacific islands in the summer.



Oscillatoxin B **374**

Figure 36

A recent example of the biological significance of spiroacetals comes from Dekker *et al*.[219] who isolated several new 5,7-dimethoxyphthalide antibiotics with specific anti-*Helicobacter pylori* activity,[220] including CJ-12,954 **375** whose stereochemistry was assigned by Brimble and Bryant by synthesis (Figure 37). *Helicobacter pylori* (*H. pylori*), a Gram-negative bacterium, which resides in the gastric epithelium, can cause peptic ulcers and gastric cancer in humans. Thus spiroacetal-containing phthalide derivative **375** is providing promise as a new lead compound for the treatment of *H. pylori*-related diseases.



CJ-12,954 **375**

Figure 37

It should be noted that the term spiroketal is also used to describe spiroacetals, this is a popular term, spiroacetal, however is more correct by IUPAC standards.

9.1.1 Conformations of Naturally Occurring Spiroacetals

When work began on the synthesis of complex spiroacetals, it proceeded on the assumption that the configuration of the spiro carbon of the natural metabolites corresponded to the most thermodynamically stable form.[213] Therefore, acid-promoted spirocyclisation of a dihydroxyketone precursor would proceed to give the correct configuration at the spiro centre. This has generally been found to be a valid assumption, with early work in many systems focused on the assembly of fully functionalised precursors to natural products that were then cyclised in an acid-catalysed process under thermodynamic control to complete the synthesis. Thus, naturally occurring spiroacetals appear to reside in the most thermodynamically favoured conformation, in which steric effects are minimised and anomeric effects are maximised.[213]

The anomeric effect favours conformation A where a lone pair on the oxygen atom of the tetrahydropyran ring is antiperiplanar to the C-O bond of the other ring (Figure 38). This is because the lone pair interacts with the σ* orbital to form a molecular orbital of lower energy when orbital alignment is good as it is in conformation A but not in conformation B.[221] If the second ring is also a tetrahydropyran, then the C-O bonds of each will be axial to the other ring.

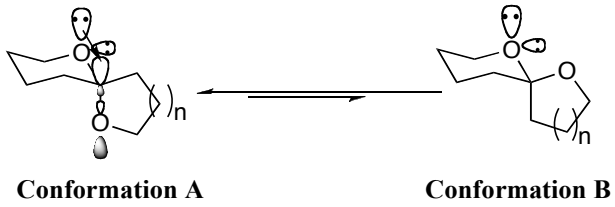
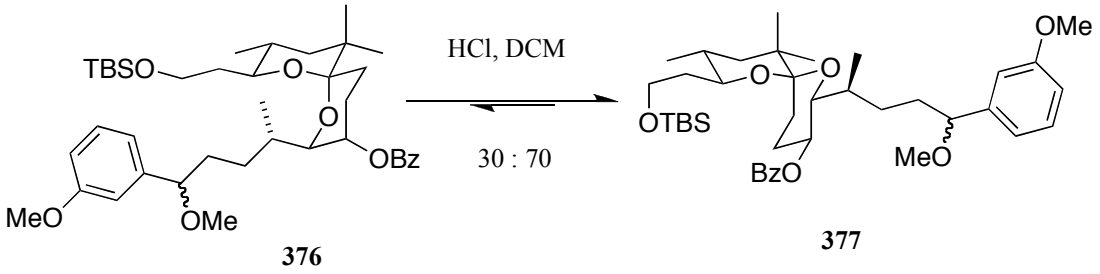


Figure 38 The anomeric effect

The preference for axial spiro C–O bonds in these ring systems is particularly evident from acid-catalysed spirocyclisations of dihydroxy ketones. Deslongchamps has studied this phenomenon intently and in doing so made important contributions to the understanding of the anomeric effect and its role in determining the configuration of simple and complex spiroacetals.[222]

The stabilizing influence of the anomeric effect can however be overpowered by severe steric interactions, this can be seen from Ireland's work on the equilibration of spiroacetals **376** and **377**. In this case the bis-axial C–O arrangement in isomer **376** was isomerised to the less anomerically favourable isomer **377**. In this example, the steric crowding in isomer **376** caused by the two axial groups outweighed the ground state stabilization of the anomeric effect (Scheme 109).[223]

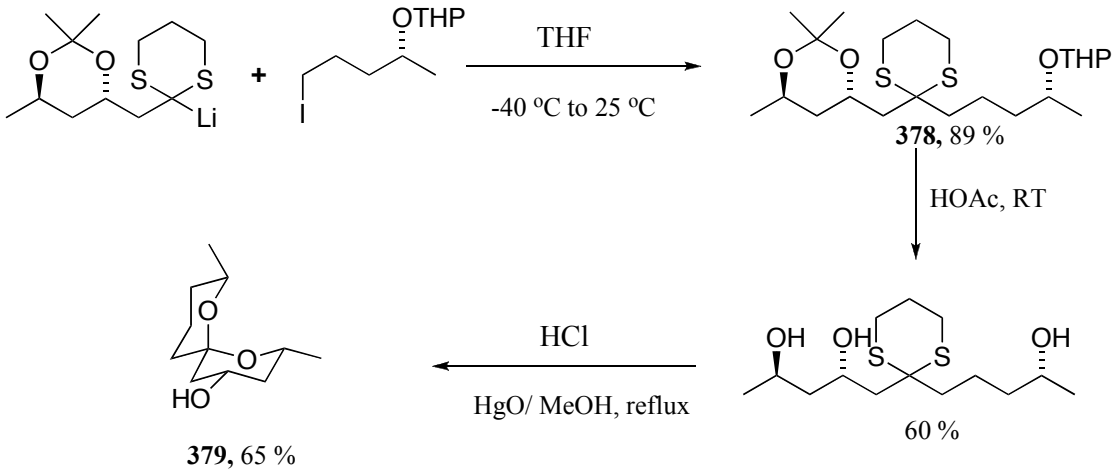


376 **377**

Scheme 109

9.1.2 Spiroacetal Synthesis

The predominant ring-forming process in spiroacetal synthesis is the acid-catalysed cyclisation of dihydroxy ketones or an equivalent thereof. With this as the staple, many methods reporting spiroacetal synthesis concentrate on the efficient assembly of dihydroxy ketone precursors.[213] Acyl anion equivalents such as 1,3-dithiane **378** are ideal precursors for connecting two hydroxyalkyl fragments to a pro-carbonyl group that will eventually become the spiro carbon of a spiroacetal *e.g.* alcohol **379**, which comes from the work of Evans *et al*. (Scheme 110).[224]



378, 89 %

60 %

379, 65 %

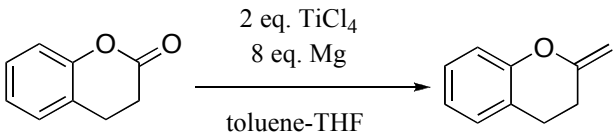
Scheme 110

9.1.3 Exocyclic Enol Ethers in The Preparation of Spiroacetals

Since so many methods exist for the formation of spiroacetals in this way and in related approaches, I will concentrate on routes to exocyclic enol ethers in the preparation of spiroacetals, as this is most relevant to our own approach. Exocyclic enol ethers have been used to prepare spiroacetals using cycloadditions[225,226,227,228,229] or acid-induced cyclisation of alcohols.[230,231,232,233] The starting enol ethers have been prepared by cyclisation of alcohols onto alkynes bearing an electron-withdrawing group,[232] by E2 elimination of hemiacetal derivatives[229,234] or β-alkoxyalkyl iodides,[226] by Ramberg-Baecklund rearrangement,[230] by Wittig reaction between exocyclic α-alkoxyphophorus ylides and aldehydes[231,233] and by methylenation of lactones[223,227,228] with the Tebbe reagent, the Petasis reagent or using Yan's adaptation of the Takai reagent.[235] These methods involving the methylenation of lactones are particularly relevant to our own work and the examples from the groups of Ireland,[223] Rizzacasa[228] and Xie and Li,[227] illustrate the use of cycloadditions in accessing spiroacetals.

9.1.4 Methylenation of Lactones Followed by Hetero-Diels-Alder Cycloaddition

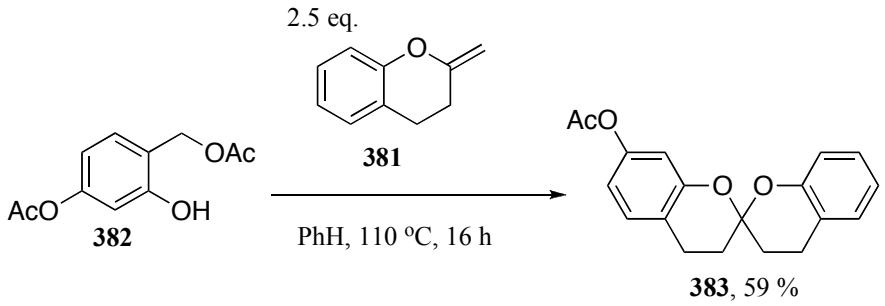
Recently the group of Xie and Li[227] employed Yan's adapted Takai reagent for the methylenation of aryl esters to give enol ethers *e.g.* lactone **380** gave enol ether **381** in excellent yield (Scheme 111).[235]



Scheme 111

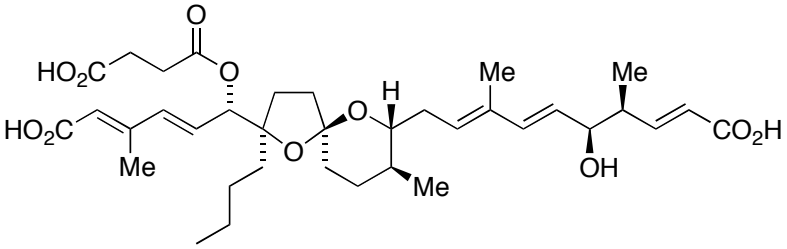
Yan *et al*. had investigated the generation of a titanium methylene complex capable of affecting the methylenation of esters without the need for expensive reagents and/ or the complicated procedures used in the Tebbe, Petasis and Takeda methylenations. They discovered that they could directly couple a CH_2Cl_2 unit to ester functionality using magnesium and $TiCl_4$. Additionally it was possible to tune the nucleophilicity of the organotitanium reagent by varying the amount of Mg used. The system was applied to a number of esters with great success and a high degree of chemoselectivity.[235]

Xie, Li and co-workers employed Yan's methodology to prepare enol ethers from lactones and then employed the hetero-Diels-Alder cycloaddition between *o*-quinone methides and enol ethers to give spiroacetals. For example the quinone methide, derived from phenol **382** reacted with enol ether **381** to give [5.5] spiroacetal **383** (Scheme 112). In total seven spiroacetals were successfully prepared in this fashion in modest to good yields.[227]



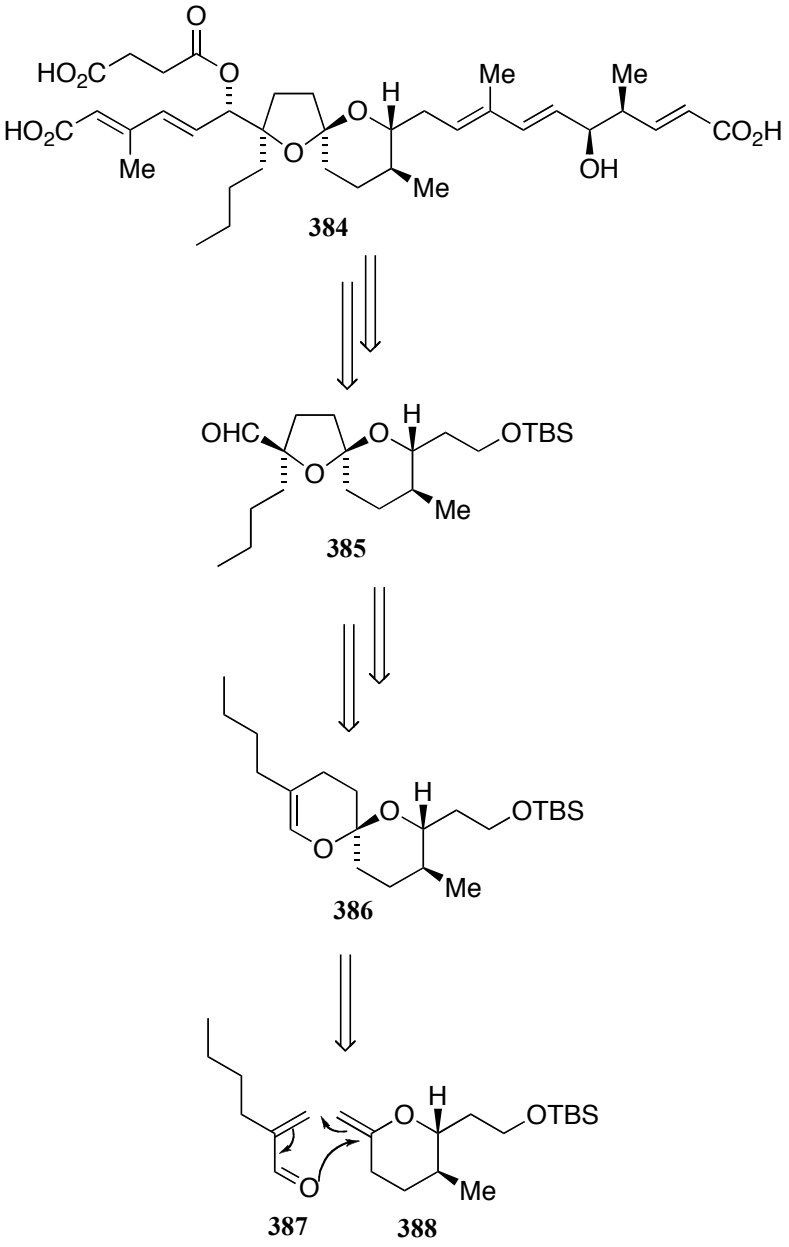
Scheme 112

The Rizzacasa group from their retro-synthesis of reveromycin B **384** (Figure 39, Scheme 113), an inhibitor of the mitogenic activity of epidermal growth factor EGF, identified that formation of spiroacetal **386** would be pivotal to the overall success of the total synthesis. They envisaged the formation of [5.5] spiroacetal **386** from a hetero-Diels-Alder reaction between diene **387** and dienophile **388** (Scheme 113).



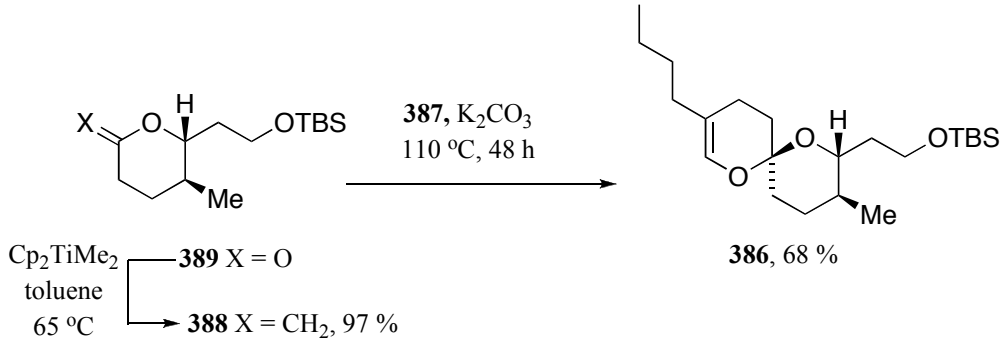
reveromycin B **384**

Figure 39



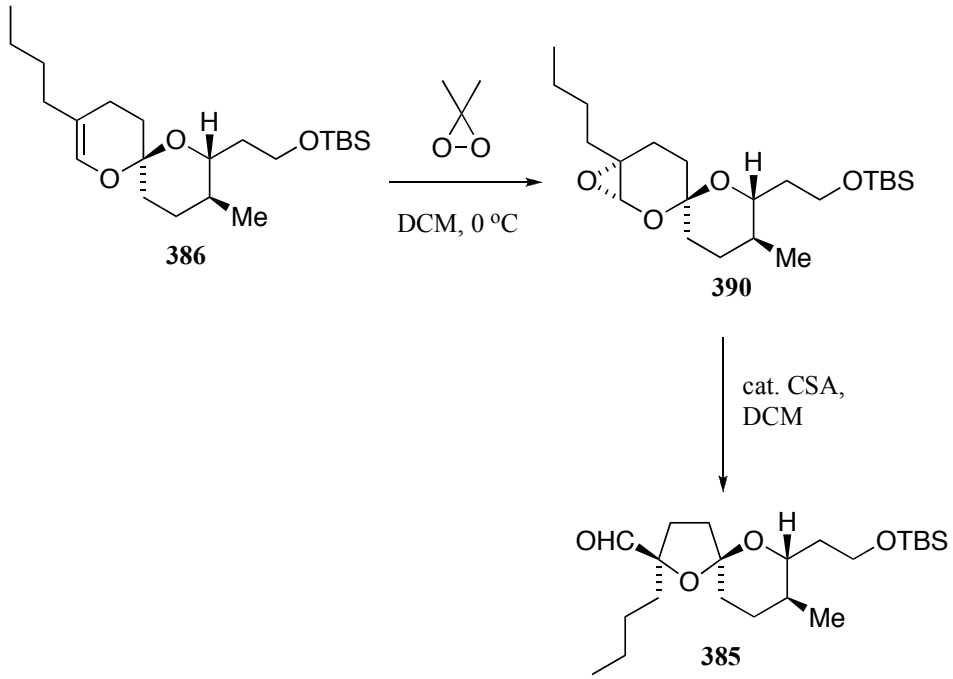
Scheme 113

Conversion of lactone **389** to required dienophile **388** was best achieved by Petasis methylenation (Scheme 114). Isomerisation of **388** to the *endo* isomer was avoided by purification on activity II-III basic alumina. The hetero-Diels-Alder reaction between **387** and **388** in the presence of K_2CO_3 proceeded smoothly, providing [5.5] spiroacetal **386** as one diastereomer in good yield (Scheme 114).[228]



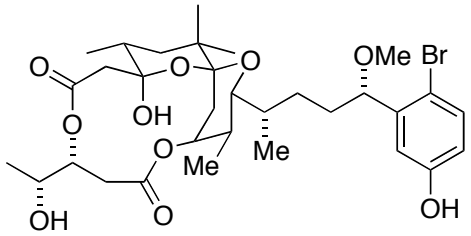
Scheme 114

From studies on related systems the group developed optimised conditions to perform ring contraction of [5.5] spiroacetal **386** to [4.5] spiroacetal **385**. Oxidation of the [5.5] spiroacetal **386** with anhydrous dimethyldioxirane gave corresponding epoxide **390** this was then rearranged by cat. (Camphor Sulfonic Acid) CSA resulting in synthesis of [4.5] spiroacetal **385,** the core scaffold towards reveromycin B (Scheme 115).[228]



Scheme 115

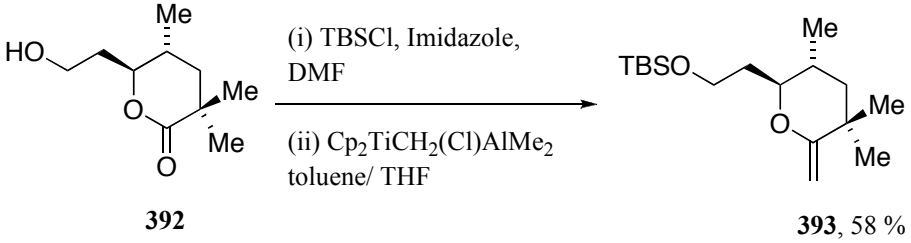
In the previous discussion of Ireland and co-workers' work, in which the anomeric effect was overpowered by allowing steric interaction to override the usual diaxial stereoelectronic bias (Scheme 109), it is important to note this achievement was key to the synthesis of spiroacetal **377**. The synthesis of spiroacetal **377** was an important intermediate in their approach toward the total synthesis of Aplysiatoxin **391** (Figure 40).[223]



391 Aplysiatoxin

Figure 40

Aplysiatoxin is a potent marine toxin isolated from the sea hare *Stylocheilus longicauda* as well as the blue green algae *Lyngba majusula*. Considered to belong to a class of powerful tumour promoters, Ireland and co-workers were keen to discover new synthetic methodologies in their approach to its construction.[223] They envisioned using the spiroacetal framework of spiroacetal **377** as the chassis for synthesising aplysiatoxin. They prepared spiroacetal **377** from spiroacetal enol ether **395**, as not only could they capitalise on overpowering the anomeric effect, in later steps in the formation of spiroacetal intermediate **377**, but as spiroacetal **395** could be convergently constructed *via* a hetero Diels-Alder cyclisation between enol ether **393** and diene **394** (Scheme 117). Enol ether **393** was afforded by protection of the hydroxyl group of lactone **392** as the *tert*-butyldimethylsilyl ether (TBS) and reaction of the lactone with the Tebbe reagent (Scheme 116).

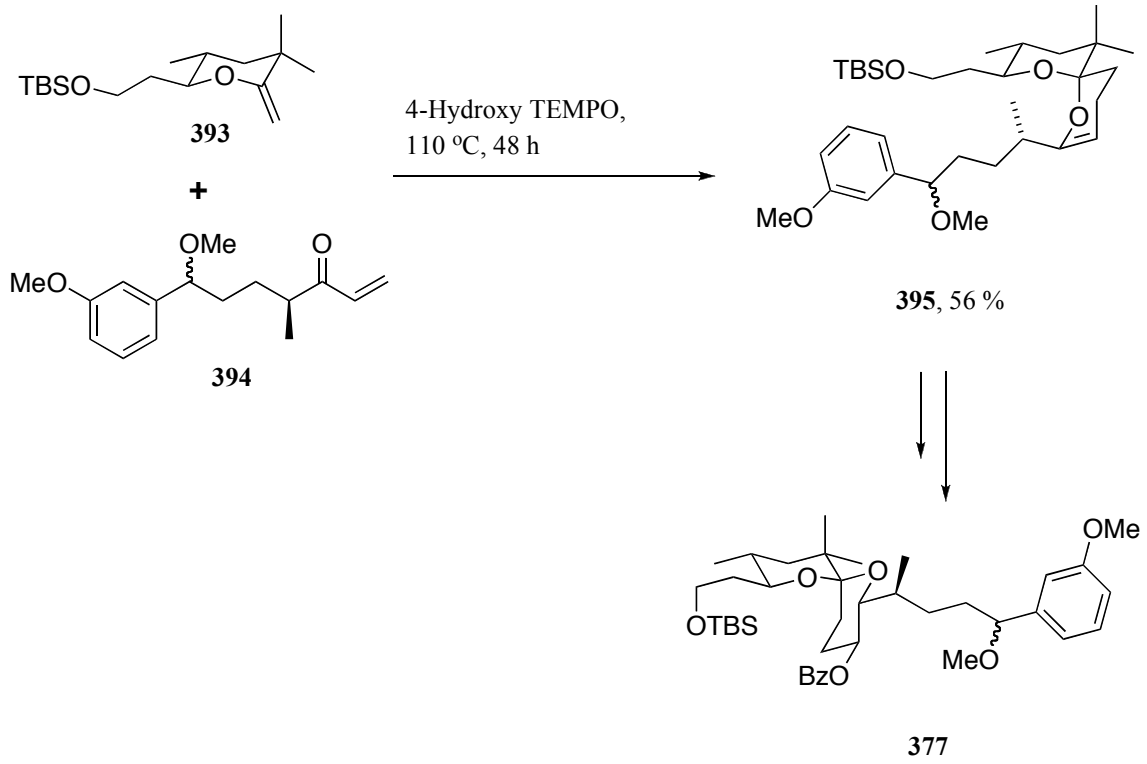


392

393, 58 %

Scheme 116

A mixture of diasteromeric dienes **394**, derived from (*S*)-citronellene, was added in a 50 % excess with respect to enol ether **393** and heated together for 48 h at 110 °C to afford spiroacetal **395** (Scheme 117).

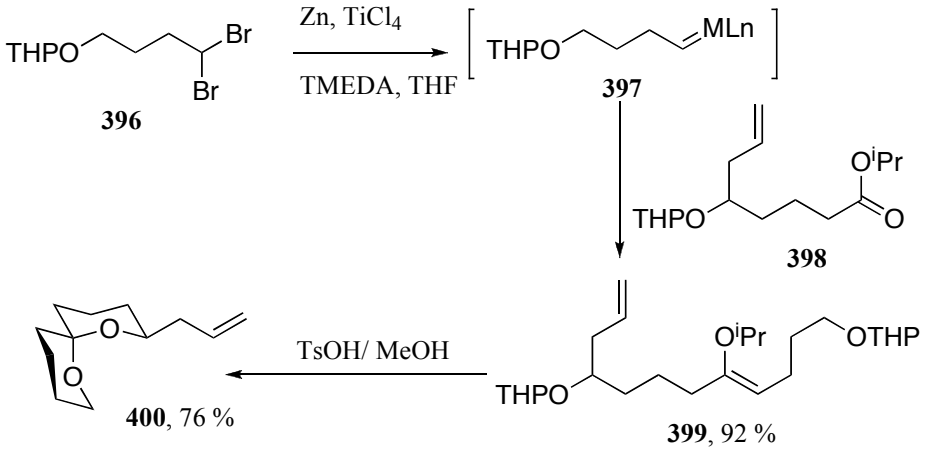


Scheme 117

It should be noted that the addition of 4-hydoxy-2,2,6,6-tetramethylpipridinyl oxy free radical (4-hydroxyTEMPO) greatly reduced the amount of enone-derived by-products, thus its contribution was reflected in isolating spiroacetal **395** in at least modest yield.[223]

9.1.5 Spiroacetals *via* Titanium-mediated Enol Ether Formation

The previous three methods used titanium carbenoids to introduce a methylene unit. A related method introduced by Mortimore and Kocienski is the only example of a procedure involving alkylidenation of esters with functionalised titanium carbenoids followed by acid-induced cyclisation to give spiroacetals. Acyclic esters were used, as the carbenoids derived under Takai conditions were ineffective for the alkylidenation of lactones. They discovered that metal carbenoid complex **397** generated from alkoxy-substituted 1,1-dibromoalkane **396** reacted with alkoxy-substituted ester **398** to give enol ether intermediate **399**. This intermediate then underwent acid-catalysed methanolysis of the THP groups, followed by cyclisation to give spiroacetal **400** (Scheme 118).[97]

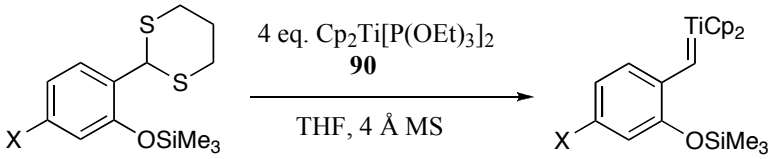


Scheme 118

The approach was based on Takai and co-workers' alkylidenation of esters using titanium carbenoids generated *in situ* by the reaction of 1,1-dibromoalkanes with $TiCl_4$ and Zn in THF-TMEDA. By utilising alkoxy-esters in the alkylidenation reaction, Mortimore and Kocienski synthesised enol ethers that were useful precursors to spiroacetals. In total six mono-substituted (4 x [5.5] and 2 x [4.5]) spiroacetals were synthesised in excellent yields (62 % to 90 %) and purities (95 % to 100 %).[97]

9.2 New Titanium Carbenoids Bearing Masked Oxygen Nucleophiles

Inspired by Mortimore and Kocienski's work we began our own investigation into a titanium-mediated synthesis of spiroacetals, with the aim of generating a 12-member library of diverse spiroacetal derivatives from lactones. Previously, we had shown that using Takeda's procedure a range of functionalized titanium carbenoids could be generated from easily prepared thioacetals. The group had used titanium carbenoids bearing masked oxygen nucleophiles, but exclusively for SPS (see chapter 4) and never to prepare spiroacetals. As in this earlier work, dithiane **105** was synthesized in two steps from 2-hydroxybenzaldehyde, and converted into a titanium carbenoid, presumably titanium benzylidene **133**, using low valent titanium reagent **90** (Scheme 119). Similarly, a new titanium benzylidene **402** was prepared from dithiane **401** (Scheme 119).

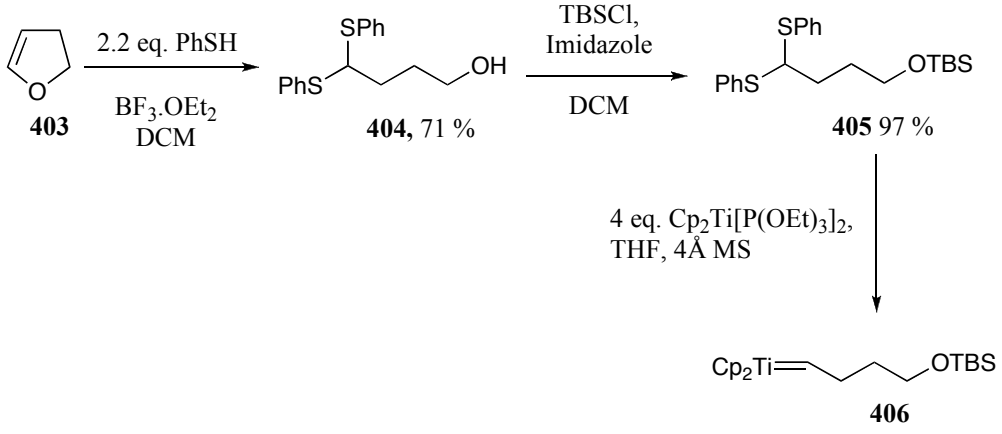


105 X = H
401 X = Cl

133 X = H
402 X = Cl

Scheme 119

Additionally, titanium alkylidene precursor **406** was prepared by the addition of thiophenol to dihydrofuran **403** to give thioacetal **404**.[236] The alcohol **404** was protected as the TBS-ether[237] in excellent yield after recrystallisation from 2-propanol. Subsequent treatment of TBS-ether **405** to Takeda conditions[82] formed titanium carbenoid reagent **406** (Scheme 120).



403

404, 71 %

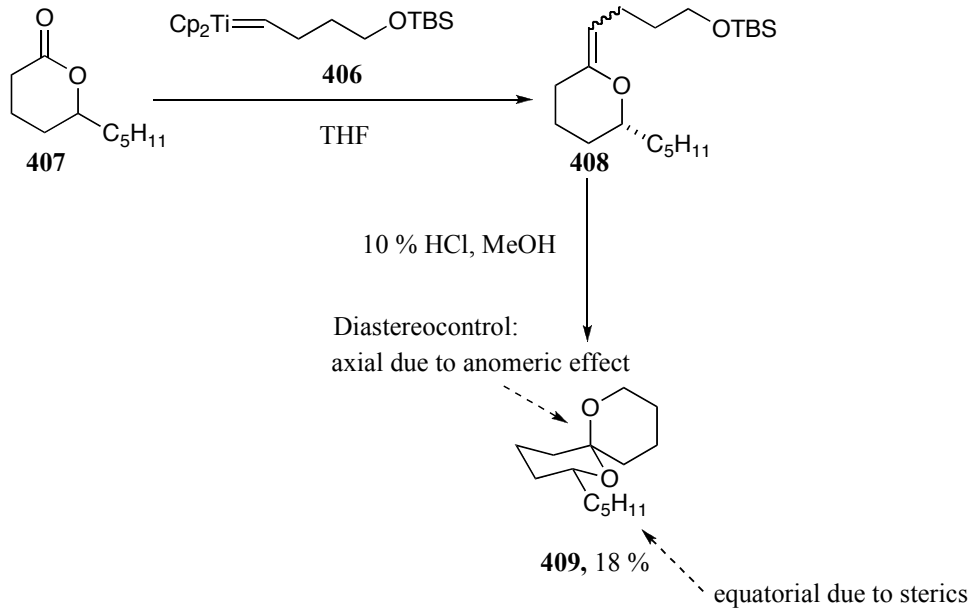
405 97 %

406

Scheme 120

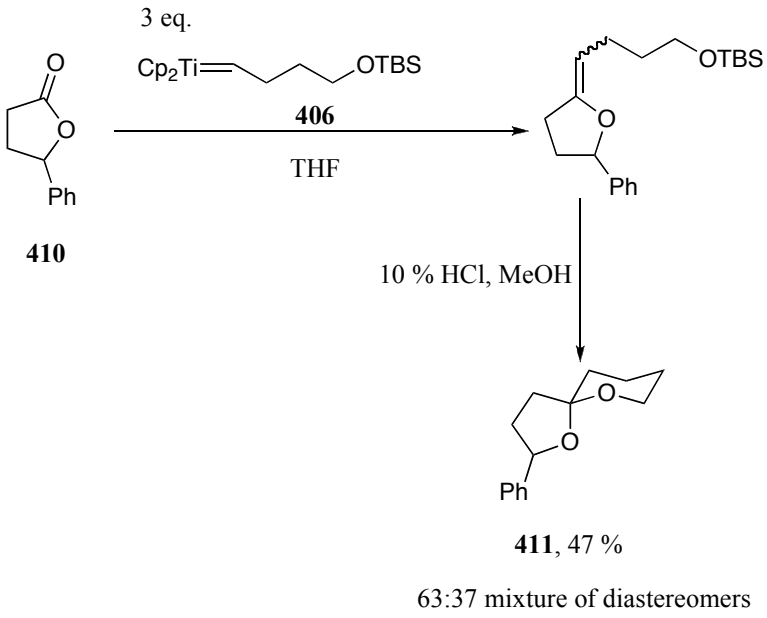
9.2.1 Synthesis of Spiroacetals from Titanium Alkylidene 406

Titanium carbenoid **406** was generated and used immediately with lactone **407** to give enol ether **408**. Addition of mild acid (10 % hydrochloric acid in methanol prepared by mixing conc. aqueous HCl and methanol in a 1:9 ratio) brought about intramolecular cyclisation to give, after column chromatography, spiroacetal derivative **409** (Scheme 121). Initial results proved a little disappointing, although spiroacetal **409** was isolated as a yellow oil, it was in low yield and purity. We concluded the low yield, may in part be due to spiroacetal **409** being highly volatile.[238] Despite efforts to purify spiroacetal **409** *via* column chromatography, the corresponding ^{13}C NMR spectrum still possessed unexplained peaks and for this reason we have not reported the compound in the experimental (Scheme 121).



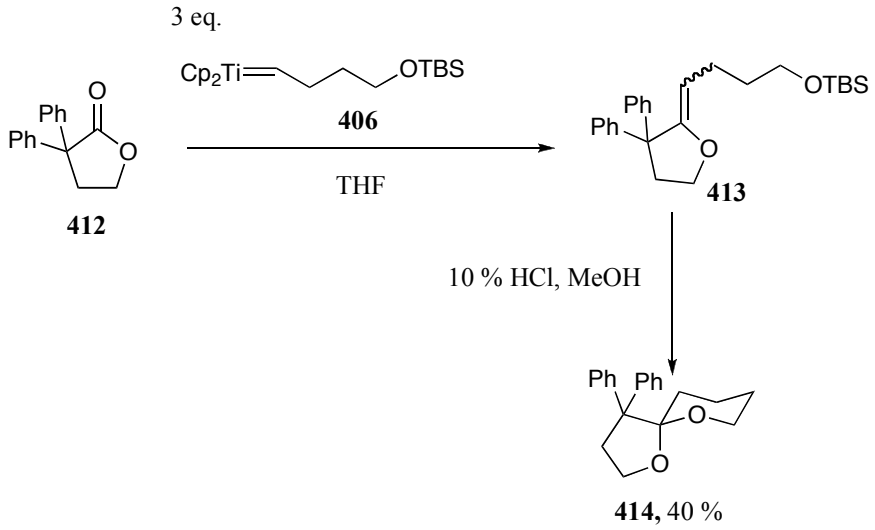
Scheme 121

With these early results to hand we repeated the generation of titanium carbenoid **406**, and then added a slightly heavier phenyl γ-lactone derivative **410**. This proved more rewarding, furnishing [4.5] spiroacetal **411** after column chromatography, in modest yield as a 63:37 mixture of diastereomers (Scheme 122).



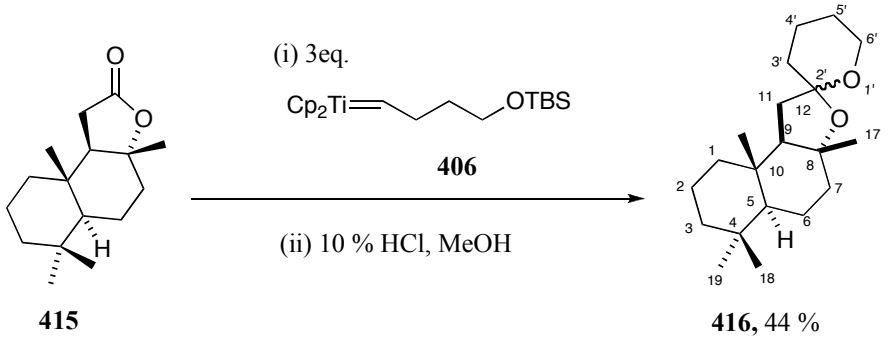
Scheme 122

In pursuit of synthesising further spiroacetals we investigated sterically hindered achiral lactone **412** as a substrate. Lactone **412** was added to the titanium carbenoid, most likely titanium alkylidene reagent **406**, generated under Takeda conditions. The resulting enol ether **413** was immediately treated with mildly acidic conditions, to induce deprotection and cyclisation. The two-step transformation appeared to tolerate sterics well, with the formation of [4.5] spiroacetal **414** in modest yield (Scheme 123).



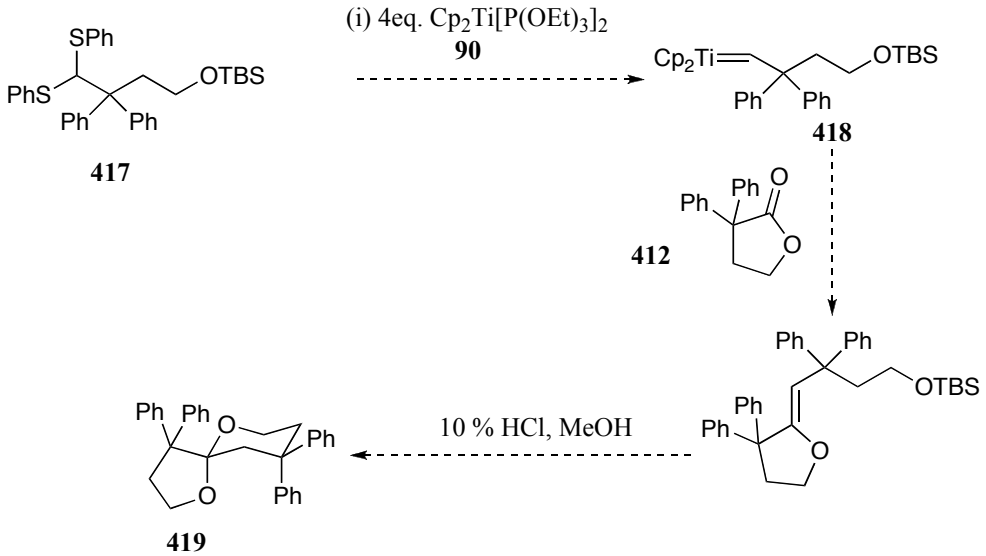
Scheme 123

We then decided to apply our spiroacetal-forming conditions to another γ-lactone, 3aR(+) sclareolide **415**. Lactone **415** was added to the titanium alkylidene **406**, generated from the dithiane **405** using low valent titanium species, $Cp_2Ti[P(OEt)_3]_2$ **90**. Acid-induced cyclisation under standard conditions gave spiroacetal **416** as a single epimer, following recrystallisation from methanol (Scheme 124). The crude mixture appeared also to contain the other epimer. Comparison of the integration for the signal (6') O–CH_2 in spiroacetal **416** at 3.85-3.91 ppm with that for the same proton in its epimer at 3.73-3.78 ppm allowed a dr of 73:27 to be calculated.



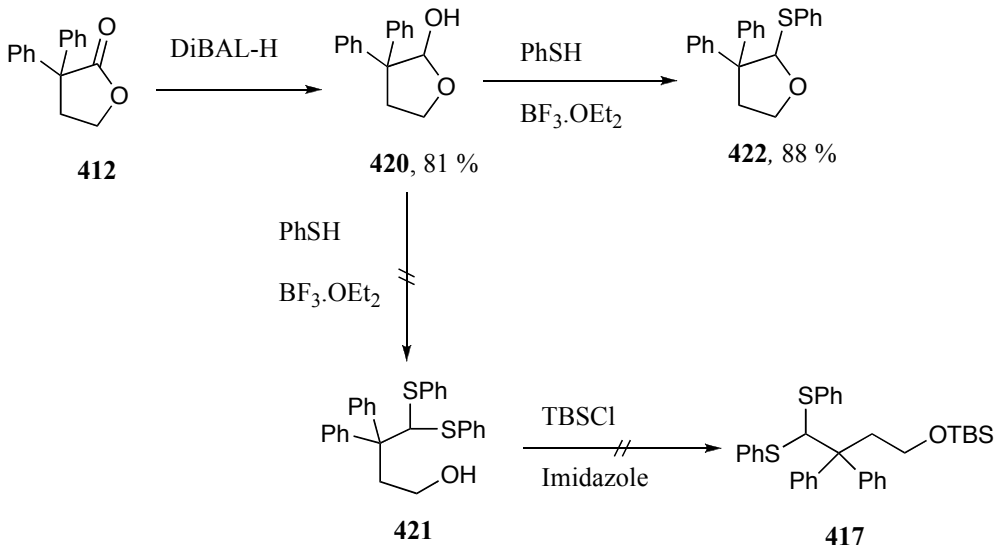
Scheme 124

The synthesis of spiroacetals utilising our new conditions had been rewarding, at this stage we thought it interesting to introduce functionality *via* the titanium carbenoid reagent **418**. This would also hopefully bring about conformational rigidity in spiroacetal **419** as well as introduce further functionality (Scheme 125).



Scheme 125

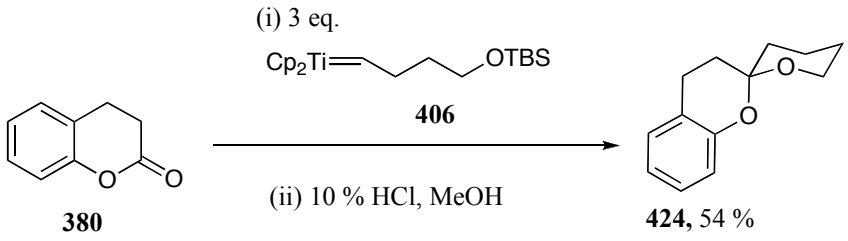
In order to generate titanium alkylidene **418** we first required thioacetal **417**. Attempts to make thioacetal derivative **417**, proceeded by conversion of α,α -diphenyl-γ-butyrolactone **412** to the corresponding lactol[239] **420**. Addition of hemiacetal **420** to thiophenol was hoped to generate thioacetal **421**, however the mono-substituted adduct **422** was isolated (Scheme 126).



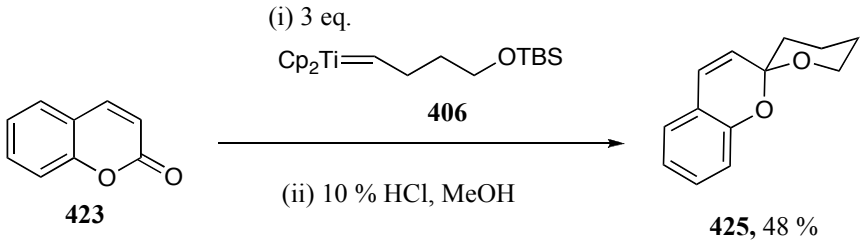
Scheme 126

With time pressing on, we returned to our original route with the aim of including more diversity in our library. This prompted investigation into the conversion of simple lactone-containing natural products into [5.5] spiroacetals. Dihydrocoumarin **380** and coumarin **423** are both natural products that possess lactone functionality. Coumarin is a toxin found in many plants with higher concentrations in tonka beans, woodruff and bison grass.[240] The sweet scent of coumarin is instantly recognisable as the smell of newly-morn hay and has been used in perfumes since the 1800's. Its clinical value is most notably as a precursor to anticoagulants such as warfarin.[241] The structurally similar dihydrocoumarin, found in sweet clover, is most commonly added to food, as a widespread flouring agent and it is also used in cosmetics.[242]

Alkylidenation of dihydrocoumarin **380** and coumarin **423** with titanium alkylidene reagent **406** proceeded smoothly and the crude products were subjected to the standard cyclisation conditions followed by column chromatography to give spiroacetal **424** (Scheme 127) and spiroacetal **425** (Scheme 128) respectively in good yields. The observation that coumarin **423** had proceeded to yield the [5.5] spiroacetal **425** was encouraging as this demonstrated that an α,β-unsaturated system was tolerated under our conditions.



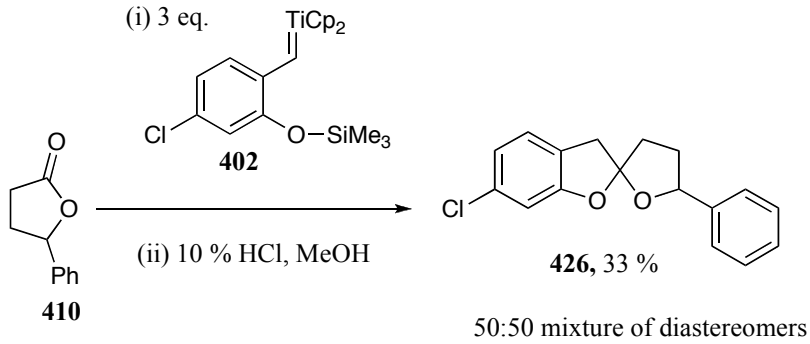
Scheme 127



Scheme 128

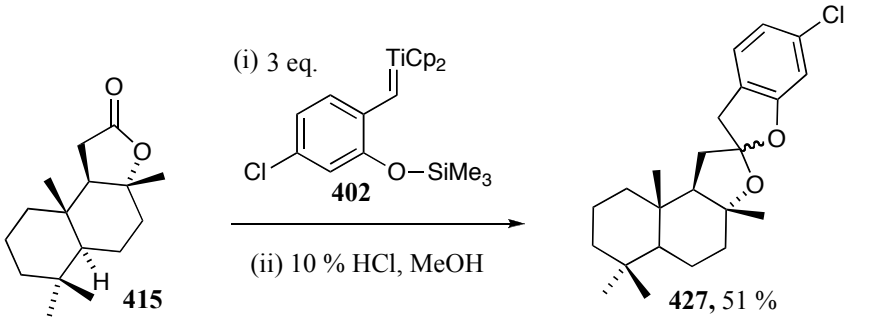
9.2.2 Synthesis of Spiroacetals from Titanium Benzylidene 402

We considered titanium reagent **402** to have potential in our new solution-phase synthesis of spiroacetals, based on the fact that related reagents had been used to alkylidenate carbonyl functionality during SPS of benzofurans.[83] Therefore, it was used to generate a [4.4] benzo-fused spiroacetal **426** from lactone **410** (Scheme 129).

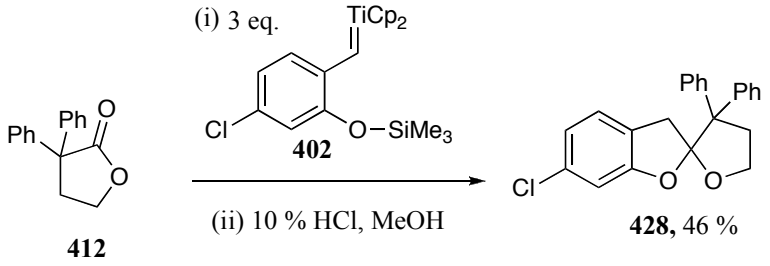


Scheme 129

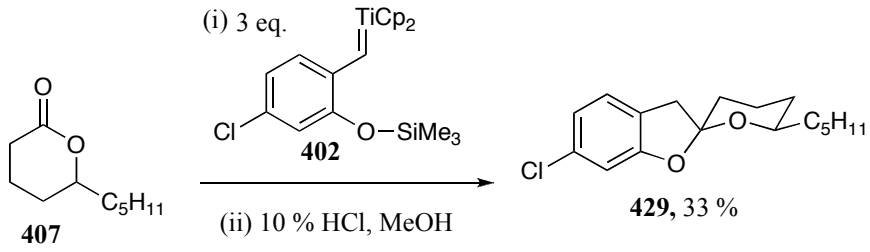
Benzofused spiroacetal **426** was isolated as a 50:50 mixture of diastereomers in modest yield after column chromatography. Following this success, the sequence was repeated using titanium benzylidene **402** with γ-lactones **415** (Scheme 130)**, 412** (Scheme 131) and with δ-lactone **407** (Scheme 132), to give spiroacetals **427**, **428** and **429** respectively in moderate yields.



Scheme 130



Scheme 131



Scheme 132

A 50:50 mixture of epimeric [4.4] spiroacetals **427** was produced, but recrystallisation improved the ratio to 60:40. Although, spiroacetal **429** was isolated as a single diastereomer by chromatography, the spectrum of the crude material appeared to contain the other diastereomer, with a signal for the CH-O at 3.63-3.69 ppm. Comparison of the integration for this signal and that for the CH-O of diastereomer **429** at 3.91-3.99 ppm, revealed a *dr* of 70:30 with the isolated diastereomer **429** dominating. The relative

stereochemistry of diastereomer **429** is assumed to be that shown, as this minimises steric interaction in the conformation shown, which also benefits from the anomeric effect.

It should be noted, the transformations that generated spiroacetals **427** (Scheme 130) and **428** (Scheme 131) tolerated sterics well, with quaternary centres both α to the carbonyl group and α to the endocyclic oxygen atom accommodated without apparent difficulty. Additionally, the low diastereoselectivites observed in the formation of spiroacetals **426** and **427**, under thermodynamic control, are consistent with those reported for similar compounds in the literature.[243] The moderate diastereoselectivity of spiroacetal **429** is also in agreement with those in the literature for [4.5]-spiroacetals[229] produced in acid.

9.2.3 Application of Chloro-Substituted Thioacetals

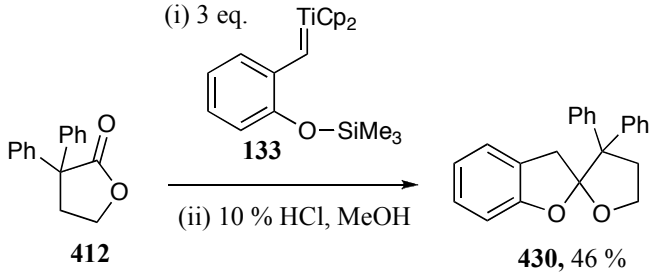
An area of some discussion within the Hartley team has been the tolerance of aryl-chlorides by the low valent titanium species, $Cp_2Ti[P(OEt)_3]_2$, used in the Takeda reaction.[81] Emma Guthrie, who worked on the titanium benzylidene mediated SPS of 2-substitued benzofuran derivatives, demonstrated successful isolation of a chloro-benzofuran derivative from the corresponding chloro-substituted thioacetal precursor.[101] Some years later Gordon McKiernan in his work on 2,5-disubstiuted benzofurans argued, from his findings of poor yields and the presence of the dechlorinated derivative, that titanium insertion into the C-Cl bond was occurring under the conditions used to generate the titanium benzylidene.[81] Additionally, Calum McLeod also experienced similar problems during his work on the SPS of 2-substitued indoles from titanium benzylidenes.[81]

The Hartley team's titanium alkylidenation approach to the synthesis of heterocycles will hopefully continue to be utilised to explore chemical space. In doing so, the development of conditions that consistently tolerate a chloro-substituent in the thioacetal substrate will also continue. In my own experience in applying titanium benzylidene **402** to the synthesis of spiroacetals, the chloro-substituent was always tolerated. This is evident from the formation of the chloro-substituted spirocycles **426** to **429** with no evidence of the dechlorinated products detected.

I would like to conclude that there is sufficient data to suggest on occasion, due perhaps to the individual experimentalist's method of preparing the Takeda reagent, there are times when aryl chlorides are tolerated. The exact reason for this phenomenon remains unclear, but it should not exclude the use of chloro-substituted thioacetals as substrates for forming novel titanium benzylidene reagents.

9.2.4 Synthesis of Spiroacetals from Titanium Benzylidene 113

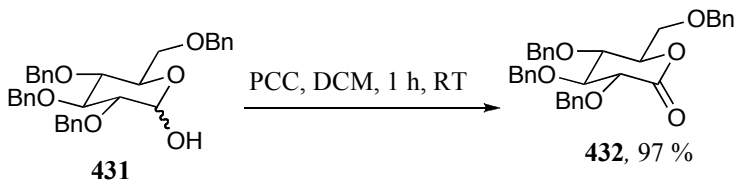
A definitive sample of the analogue **430** lacking the chloro-substituent was prepared using titanium benzylidene **133** generated from 2-phenyl-1,3-dithiane **105** (Figure 8, chapter 3.2.3).[101] Benzylidenation of achiral lactone **412**, followed by acid-induced cyclisation gave benzo-fused spiroacetal **430** in similar yield to the chlorinated benzo-fused spiroacetal **428** (Scheme 133).



412 **430,** 46 %

Scheme 133

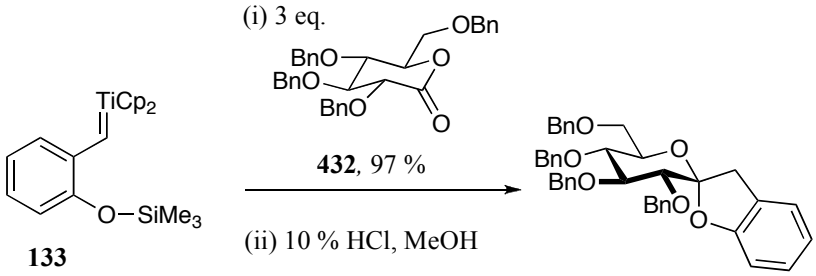
In the hope of adding further diversity to our spiroacetal collection we attempted to incorporate a sugar unit. Conversion of commercially available tetrabenzyl-protected glucose **431** into the corresponding lactone derivative **432** was accomplished quickly *via* a known literature procedure with pyridinium chlorochromate (PCC)[244] (Scheme 134).



431 **432**, 97 %

Scheme 134

Titanium benzylidene **133** was then reacted with lactone derivative **432** and the product treated with acid in the hope of producing sugar-derived spiroacetal **433** (Scheme 135).



133

433, 32 %

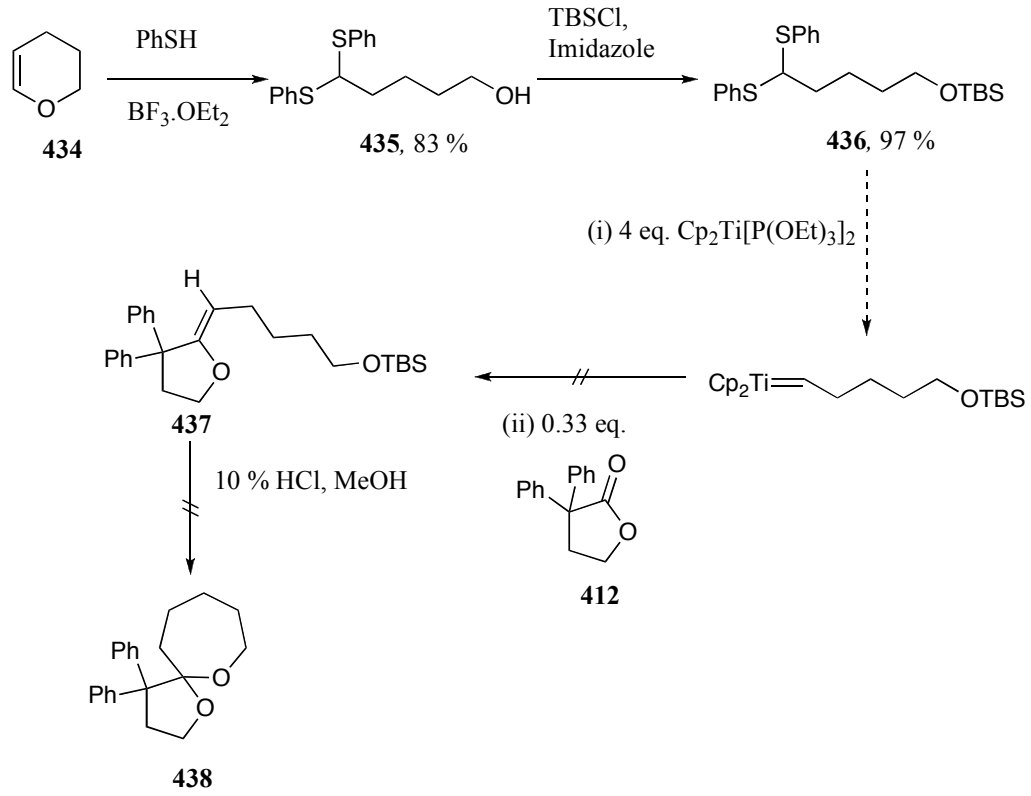
60:40 mixture of diastereomers

Scheme 135

The overall synthesis was successful although purification proved rather difficult. Column chromatography gave spiroacetal **433** as a 60:40 mixture of diastereomers in modest yield. The low diastereoselectivity is consistent with those in the literature for similar glucose-derived spiroacetals.[230] Attempted hydrogenation using PtO_2 as catalyst[245] removed the benzyl protecting groups to give the unprotected tetrahydroxy spiroacetals, but purification of these polar compounds by chromatography proved to be too difficult and the deprotected sugar-containing spiroacetal was not isolated.

9.2.5 Attempted Synthesis of [5.6] Spiroacetals

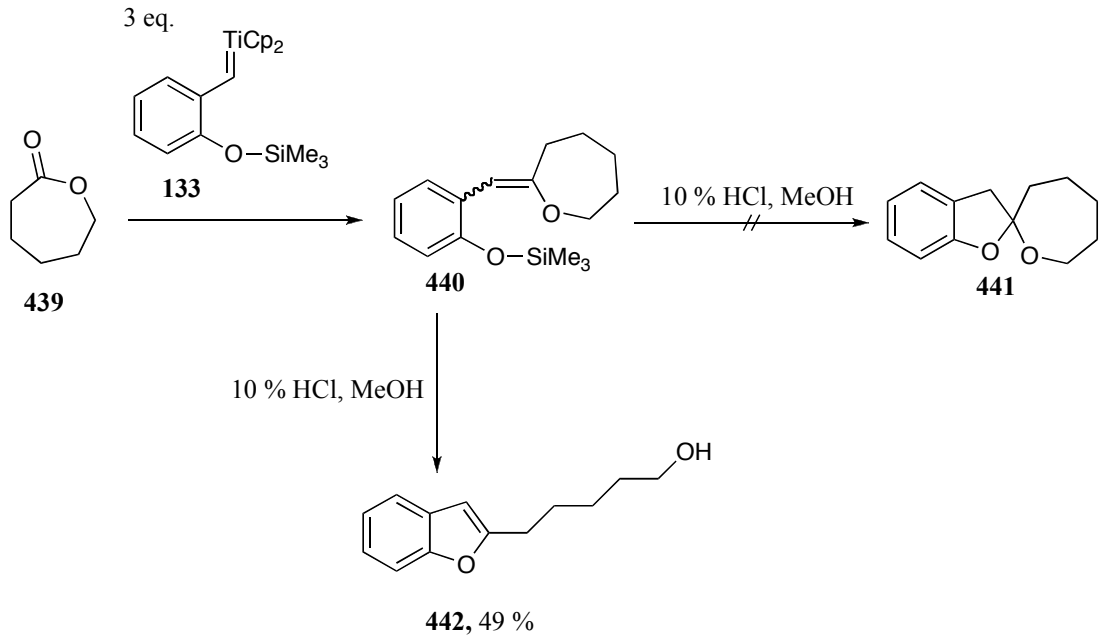
The success of forming [4.4], [4.5] and [5.5] spiroacetals gave us the idea to extend the route to the synthesis of [5.6] spiroacetals *via* the following scheme (Scheme 136).



Scheme 136

Formation of TBS-protected thioacetal **436** from pyran **434** was straightforward and presented few problems.[236] Addition of thioacetal **436** to $Cp_2Ti[P(OEt_3)]_2$ followed by the lactone **412** and then cyclisation conditions did not prove encouraging. The ^{1}H NMR spectrum of the crude product showed no sign of spiroacetal **438**. The reaction was repeated and stopped before cyclisation was preformed. This was to establish whether the enol ether **437** was actually synthesised and if so whether the cyclisation conditions needed to be optimised. Identification of enol ether **437** was very difficult due to the presence of triethyl phosphite from the Takeda reaction. Attempts were made to purify enol ether **437** by column chromatography but only a mixture of decomposition products was isolated. However, there was no evidence of the starting lactone **412** from the column chromatography, indicating successful consumption in the alkylidenation reaction. The result was ambiguous, but it was clear that we had not found the conditions for the preparation of spiroacetal **438** from lactone **412**.

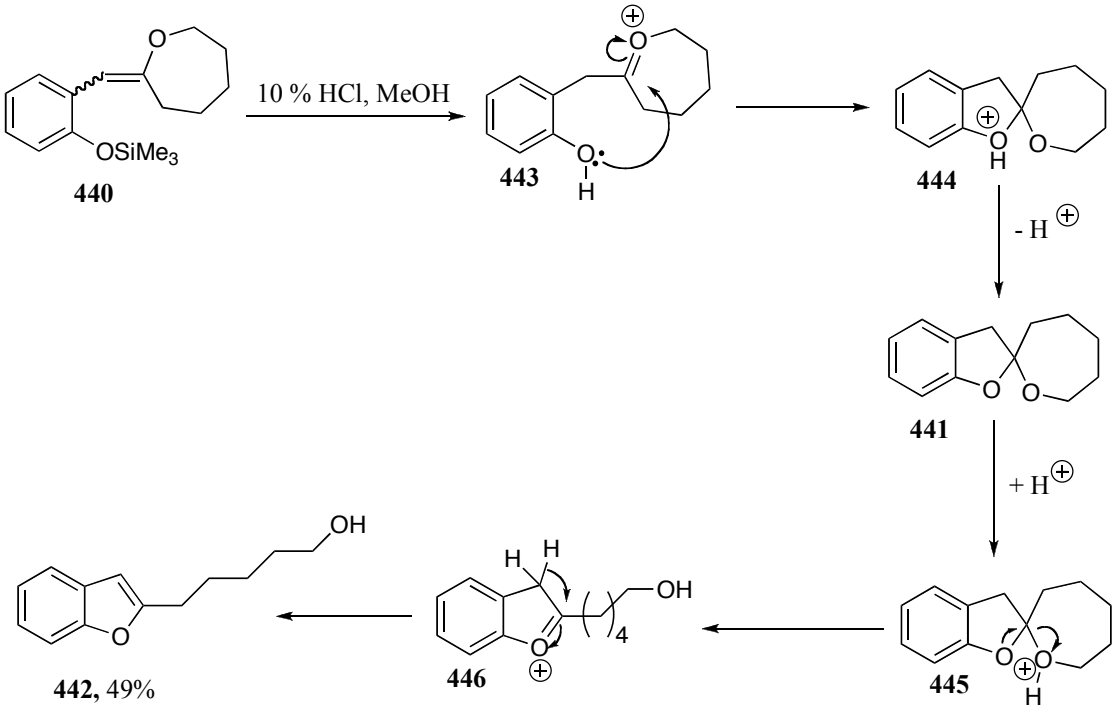
We decided to investigate the formation of a [5.6] spiroacetal from a different approach instead of forming the 7-membered ring by acid-induced cyclisation it would be introduced with a lactone. ε-Caprolactone **439** is a simple 7-membered lactone and addition to titanium benzylidene reagent **133** should give the enol ether **440**, which upon treatment with the cyclisation conditions was expected to give the [5.6] spiroacetal **441** (Scheme 137).



Scheme 137

However, instead of isolating the target spiroacetal **441**, from column chromatography, 2-substituted benzofuran derivative **442** was isolated. It would appear that the spiroacetal **441** might have been an intermediate but the strong driving force of aromatisation resulted in the formation of the benzofuran **442** (Scheme 138).

Cyclisation of enol ether **440** to give spiroacetal **444** would involve a 5-*exo-trig* cyclisation of the intermediate oxonium ion **443**, which is favoured by Baldwin's rules.[246] Loss of a proton would give spiroacetal **441**, but protonation followed by opening of the spiroacetal **445** to give oxonium ion **446**, finally loss of a proton gives benzofuran **442** by an E1 process (Scheme 138).



Scheme 138

Although the formation of 2-substituted benzofuran **442** was not intentional, it did highlight a novel route to the synthesis of such privileged structures.

9.2.6 Re-synthesis of Spiroacetals and Completion of 12 Compound Library

In total we had synthesised 12 structurally diverse spiroacetals (Figure 41) from alkylidenation-cyclisation of the corresponding lactones (Figure 42). In the hope of improving on our yields, we repeated the syntheses, with an increased number of equivalents of thioacetal substrate (1.2 equivalents to 3.0 equivalents). The larger quantity of triethyl phosphite, now 12 equivalents with respect to the lactone, hampered purification by column chromatography. However, we found that washing the crude spiroacetals with excess saturated aqueous iron(III) chloride prior to chromatography removed the triethyl phosphite and expedited purification. The results from this re-synthesis are presented in Table 4 along with the results from the previous work. The ratios of diastereomers shown in Figure 41 are those determined in the crude mixture or when the diastereomers are isolated together by chromatography and appear as a single spot on TLC. Where these ratios are different from those in the isolated products there is a footnote to the table.

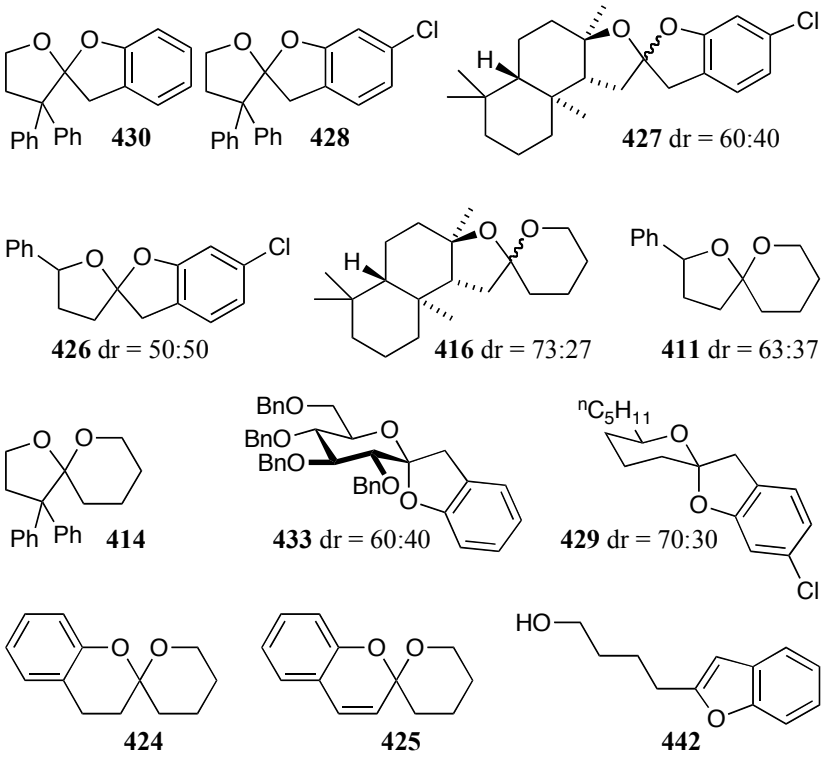


Figure 41

Entry	Lactone	Titanium reagent	Spiroacetal	% Isolated yield using 1.2 eq. of titanium reagent	% Isolated yield using 3 eq. of titanium reagent
1	**412**	**133**	**430**	46	53
2	**412**	**402**	**428**	46	54
3	**415**	**402**	**427**	51†	62†
4	**410**	**402**	**426**	33	44
5	**415**	**406**	**416**	44*	52*
6	**410**	**406**	**411**	47	58
7	**412**	**406**	**414**	40	51
8	**431**	**133**	**433**	32	48
9	**407**	**402**	**429**	33*	44*
10	**380**	**406**	**424**	54	65
11	**423**	**406**	**425**	48	57
12	**439**	**133**	**442**	49	61

*Isolated yield of major diastereomer.

†Isolated mixture of diastereomers differs from that in crude mixture as discussed previously.

Table 4

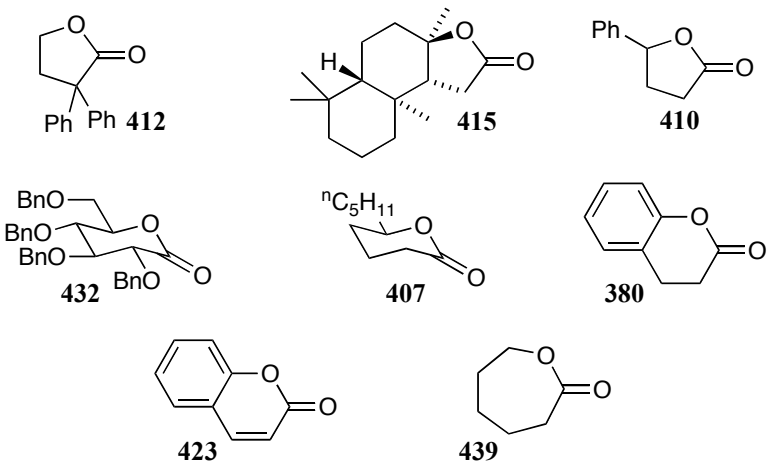
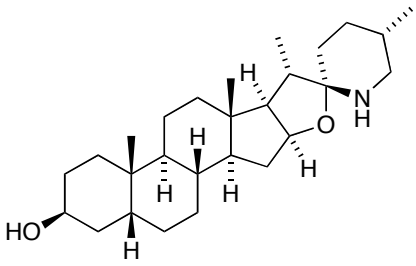


Figure 42

9.3 Spiroaminals

Based on the success of our 12-member spiroacetal library we turned our attention to the analogous route for the preparation of the nitrogen-containing analogues of spiroacetals: spiroaminals. The earliest examples of spiroaminals came roughly at the same time as the isolation of spiroacetals. Tomatidine **447** was isolated from tomato leaves and belongs to the saponin family with the related spiroacetal smilagenin (Figure 43).[247]

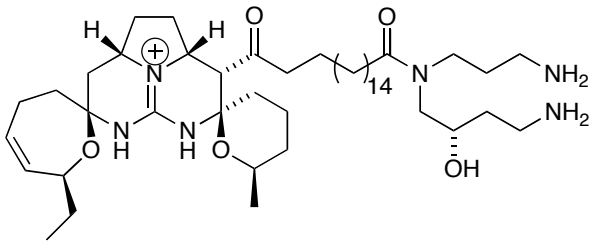


Tomatidine, **447**

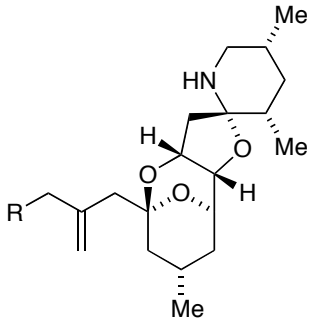
Figure 43

In vitro studies with tomatidine **447** have shown limited inhibition of a number of bacteria, plant-pathogenic and animal-pathogenic fungi. When compared to other antibiotics (*e.g.* penicillin and streptomycin) inhibition is weak and non-specific. In addition, the efficacy of tomatidine *in vivo* was reported to be very limited.[247]

There are relatively few reports in the literature of the synthesis of spiroaminals; indeed the natural abundance of spiroaminals is less in comparison to spiroacetals.[248] Most of the literature concentrates on synthetic routes to the formation of spiroaminal units as part of total syntheses of marine alkaloids. Some of the most recent targets are crambescidin alkaloids **448** found in marine sponges[249] and azaspiracid-1, isolated from mussels the spiroaminal domain **449**, of which is shown[250] (Figure 44).



Crambescidin, **448**



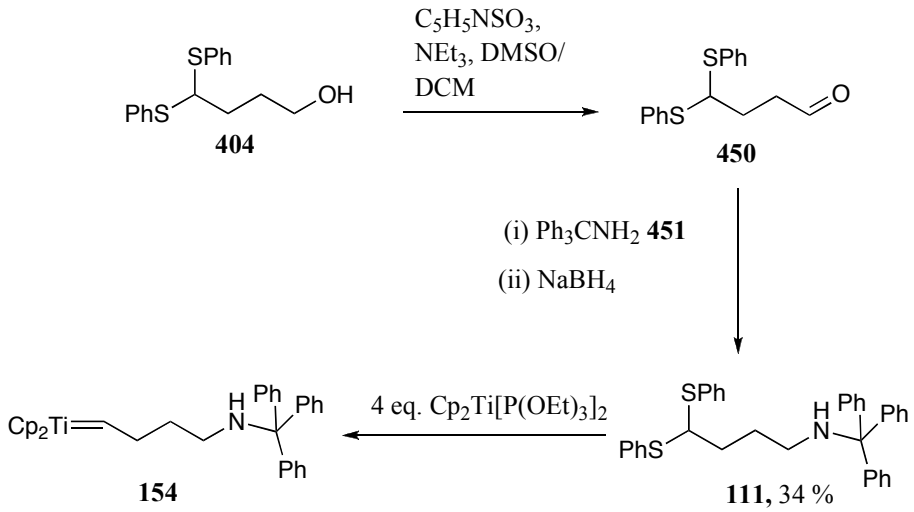
Azaspiracid; common spiroaminal containing domain, **449**

Figure 44

Diverse biological activities have been reported for crambescidin alkaloids including cytotoxicity, antifungal activity and antiviral activity towards, amongst others, human immuno deficiency virus (HIV).[249] Additionally, spiroaminal-containing azaspiracid-1 is the causative agent of a recently defined class of human poisoning resulting from the consumption of tainted shellfish.[251]

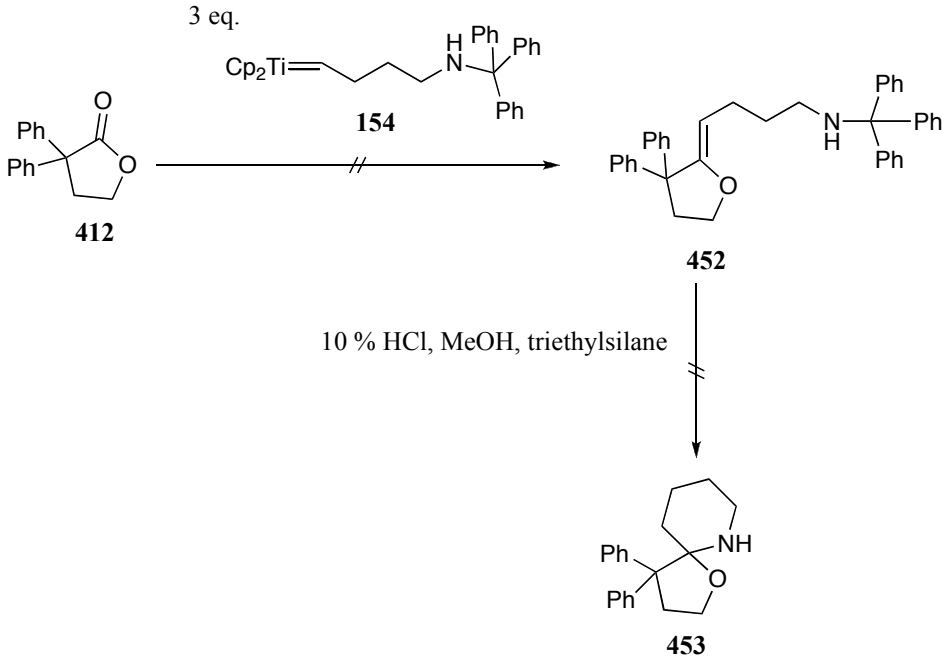
9.3.1 Proposed Route to Spiroaminals and Preliminary Studies

Titanium alkylidene **154** bearing an *N*-trityl protected amine had been used by Carolyn Austin, in the Hartley group, to make imines[86] (Chapter 4). We considered using this reagent to prepare spiroaminal **453** from lactone **412** (Scheme 140). Thioacetal **111** was prepared by Carolyn Austin's procedure[86] and then converted into the corresponding titanium carbenoid **154** under our standard conditions (Scheme 139).



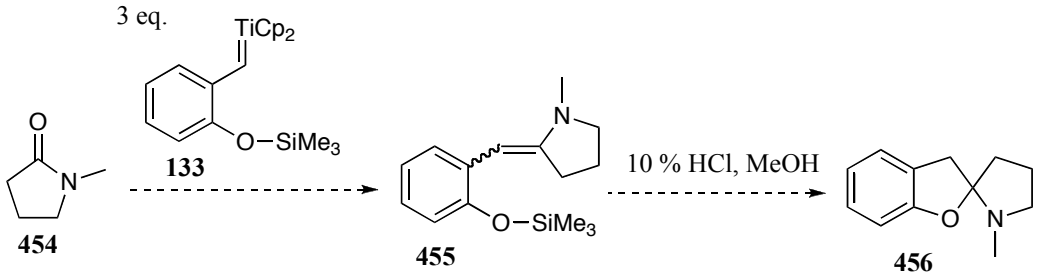
Scheme 139

Unfortunately, studies into the alkylidenation of α,α-diphenyl-γ-butyrolactone **412** proved disappointing (Scheme 140). The reaction was repeated a number of times but isolation of either the spiroaminal **453** or the enol ether **452** was hampered, as in prior cases, by the presence of triethyl phosphite. Column chromatography of the crude product of alkylidenation did not permit the isolation of the enol ether **452**, but large amounts of the starting lactone **412** were isolated signalling unsuccessful alkylidenation.



Scheme 140

An alternative route to spiroaminals investigated the addition of an *N*-substituted lactam **454** to titanium benzylidene **133**, followed by treatment of enol ether **455** with acid in order to form target spiroaminal **456** (Scheme 141).



Scheme 141

The crude ^{1}H NMR spectrum of the final compound appeared to contain a geminal CH_2 signal at 3.44 ppm perhaps belonging to spiroaminal **456**, however during column chromatography the compound was lost. It is possible the compound became attached to the silica due the polar nature of the nitrogen group. Unfortunately, not enough material remained to repeat the reaction and crucially there was not enough time to make more. It is my hope that this reaction will be repeated and perhaps the column chromatography may prove rewarding.

9.4 Conclusion

In conclusion, we had developed a concise two-step method for the solution phase synthesis of spiroacetals from commercially available lactones. The route employs novel titanium carbenoids, generated from corresponding dithianes and thioacetals, that alkylidenate lactones to give enol ethers that can be then cyclised to give spiroacetals in modest to good yields. Some early attempts to make spiroaminals in a similar way have been made, but this needs further study.

CHAPTER 10 – Experimental

Where general procedures are given for transformations, the exact quantities used in each preparation are listed under the compound name, together with reaction times where these vary. Unless otherwise stated, all reactions were carried out using oven dried or flame-dried glassware.

Tetrahydrofuran and diethyl ether were dried over sodium and benzophenone, and dichloromethane was dried over calcium hydride. DCM, $P(OEt)_3$ and toluene were distilled from calcium hydride prior to use. DMF and $BF_3.Et_2O$ were distilled from calcium hydride under reduced pressure and stored under inert gas and over molecular sieves.

Reagents were obtained from commercial suppliers and used without further purification unless stated otherwise. Cp_2TiCp_2 (Titanocene Dichloride) was purchased from STREM Fine Chemicals. $Pd(PPh_3)_4$ was prepared by the procedure of Malpass *et al*.[252] The solid-phase syntheses were carried out using resin derived from commercially available Merrifield resin with the loadings described in the general procedures below and contained in IRORI MacroKans^{TM} (porous polypropylene reactors with an internal volume 2.4 mL, and a pore size of 74 μm) and IRORI MiniKans^{TM} (porous polypropylene reactors with an internal volume 660 μL, and a pore size of 74 μm).

Purification was carried out on silica gel, 70-230 mesh, or neutral alumina (Brockmann grade III), as stationary phase. TLC was carried out using Merck silica gel foil-backed plates (0.25 mm layer thickness), the plates were visualised by illumination with UV light, permanganate or iodine stains.

^1H and ^{13}C NMR spectra were obtained on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively. Chemical shifts are given in ppm relative to tetramethylsilane. Chemical shifts ^{13}C NMR spectra are given in ppm relative to $CDCl_3$ as internal standard (77.0 ppm). All coupling constants are measured in Hz and are uncorrected. DEPT was used to assign the signals in the ^{13}C NMR spectra as C, CH, CH_2 or CH_3. Mass spectra (MS) were recorded on a Jeol JMS700 (MStation) spectrometer. In the special case of the Indole library, analysis of the library was by reversed phase HPLC/DAD-UV/ELSD/MS using a Waters Analytical 4-way MUX QC System with an Agilent Zorbax SB C8, 21.2 x 250 mm column and eluting with 0.1 % trifluoroacetic acid in MeCN:H_2O (4:1), Flow = 25 mL/min.

Infra-red (IR) spectra were obtained on a Perkin-Elmer 983 spectrophotometer. A Golden Gate™ attachment that uses a type IIa diamond as a single reflection element was used so that the IR spectrum of each compound (solid or liquid) could be directly detected without any sample preparation.

10.1 General Experimental Procedures

10.1.1 Merrifield Resin-Bound Esters 279

Cesium carboxylate (3.01 g, 9.2 mmol), potassium iodide (0.262 g, 1.6 mmol) and 3-phenylpropionic acid (0.931 g, 6.2 mmol) were added to IRORI MacroKans™ (x 10) containing Merrifield Resin [0.311 meq. Prepared from 170 mg per IRORI MacroKans™, with a loading of 2.01 meq. (chloride) g^{-1}], in distilled DMF (80 mL) stirring at RT. The reaction mixture was then heated to 80 °C and left overnight. The following day, reaction mixture was decanted and the IRORI MacroKans™ washed: 9:1 DMF/H_2O (3 x 100 mL), THF (2 x 100 mL), alternately MeOH and DCM (2 x 100 mL), MeOH (100 mL) and finally diethyl ether (100 mL). IRORI MacroKans™ were then dried under vacuum.

10.1.2 Resin–Bound Enol Ether 323 *via* Trityl Protected Dithiane 319

Titanocene dichloride (0.901 g, 3.6 mmol, 12.0 eq.), magnesium turnings (0.102 g, 3.9 mmol, 13 eq., pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.203 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (8 mL) was followed by dry $P(OEt)_3$ (1.2 mL, 7.2 mmol, 24 eq.). After stirring for 3 h at RT, a solution of dithiane **319** (0.423 g, 0.93 mmol, 3 eq.) in dry THF (4 mL) was added to the mixture and stirring continued for 15 min. The solution was added to a flask containing resin-bound ester (as per the general method) pre-swollen in THF (6 mL) under argon. After 17 h the reactor was removed from the flask and washed with THF (5 ×) then alternately with MeOH and DCM (5 ×) and finally MeOH then Et_2O. The reactor containing the resin-bound enol ether **323** was then dried under vacuum.

10.1.3 Resin–Bound Enol Ether 336 *via* Silylcarbamate Protected Dithiane 334

Titanocene dichloride (0.901 g, 3.6 mmol, 12.0 eq.), magnesium turnings (0.102 g, 3.9 mmol, 13 eq., pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.203 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (8 mL) was followed by dry $P(OEt)_3$ (1.2 mL, 7.2 mmol, 24 eq.). After stirring for 3 h at RT, a solution of dithiane **334** (0.473 g, 0.93 mmol, 3 eq.) in dry THF (4 mL) was added to the mixture and stirring continued for 15 min. The solution was added to a flask containing resin-bound ester (as per the general method) pre-swollen in THF (6 mL) under argon. After 17 h the reactor was removed from the flask and washed with THF (5 ×) then alternately with MeOH and DCM (5 ×) and finally MeOH then Et_2O. The reactor containing the resin-bound enol ether **336** was then dried under vacuum.

10.1.4 Solid-Phase Suzuki Cross-Coupling Reaction

$Pd(PPh_3)_4$ (15 mg, 4 mol %) was added to a stirring suspension of resin-bound enol ether **336** (0.311 meq) contained in an IRORI MacroKan^{TM}, Cs_2CO_3 (0.510 g, 1.5 mmol, 5.3 eq.) and aryl iodide (0.39 g, 1.55 mmol, 5.1 eq.), in degassed DMF (10 mL) with H_2O (5.6 μL, 1 eq.) under argon. The suspension was stirred at 80 °C for 17 h. The mixture was allowed to cool and the MacroKan^{TM} was separated from the reaction mixture and washed with 9:1 DMF-H_2O (3 ×), alternately with MeOH and DCM (3 ×), and finally with MeOH and Et_2O. The MacroKan^{TM} containing resin bound ester was then dried under vacuum before being cleaved with 1 % TFA in a solution of DCM (5 mL) and shaken for 2 h. The MacroKan^{TM} was washed with DCM (3 × 5 mL) and the organic washings were combined and then concentrated.

10.2 LIBRARY SYNTHESIS – GSK

10.2.1 Merrifield Resin-Bound Esters 356 A-H

Cesium carboxylate (1.823 g, 5.6 mmol), potassium iodide (1.110 g, 6.7 mmol) and carboxylic acids **356 A-H** (4.8 mmol, 4.0 eq) were added to IRORI MiniKans^{TM} (x 13 containing Merrifield Resin, 46.5 mg per IRORI MiniKan^{TM}), in distilled DMF (40 mL) shaken at RT. The reaction mixture was then heated to 80 °C and left overnight. The following day, reaction mixture was decanted and the MiniKans^{TM} washed: 9:1 DMF/H_2O (3 × 100 mL), THF (2 × 100 mL), alternately MeOH and DCM (2 × 100 mL), MeOH (100 mL) and finally diethyl ether (100 mL). The IRORI MiniKans^{TM} were then dried under vacuum. Loading ~ 2.0 meq/ IRORI MiniKan^{TM}.

10.2.2 Resin-Bound Enol Ethers 357 A-H

Cp_2TiCl_2 (3.623 g, 14.5 mmol, 12 eq.), magnesium turnings (0.391 g, 15.9 mmol, 13 eq., predried at 250 °C overnight) and freshly activated 4 Å molecular sieves (703 mg) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (20 mL) was added followed by dry $P(OEt)_3$ (5.2 mL, 29 mmol, 24 eq.). After stirring for 3 h at RT, a solution of the dithiane **334** (1.85 g, 3.6 mmol, 3 eq.) in dry THF (20 mL) was added to the mixture and stirring continued for 15 min. After this time, 13 MiniKans^{TM}, each containing one of the resin-bound esters **356 A-H** [93 μeq. /MiniKan^{TM} prepared from 46.5 mg of Merrifield resin with a loading of 2.0 meq. (chloride) g^{-1}], that had been purged with argon were added. After 17 h the MiniKans^{TM} were removed from the flask and washed with THF (5 ×) then alternately with MeOH and DCM (5 ×), and finally with MeOH then Et_2O. The 13 MiniKans^{TM} containing one of the resin-bound enol ethers **357 A-H** were then dried under vacuum. The same procedure was employed for all 8 resin-bound esters **356 A-H**, using 104 MiniKans^{TM} in total.

10.2.3 Solid-Phase Suzuki Cross-Coupling

$Pd(PPh_3)_4$ (15 mg, 4 mol %) was added to a flask containing 8 MiniKans^{TM} each containing a different resin-bound enol ether **357A-H** (93 μeq./MiniKan^{TM}), stirring with Cs_2CO_3 (1.21 g, 3.7 mmol), one of the aryl iodides **a-h** (3.7 mmol), and water (13.3 μL, 0.74 mmol) in degassed DMF (30 mL) under argon. The suspension was shaken at 80 °C for 6 h. The mixture was allowed to cool and the MiniKans^{TM} were separated from the reaction mixture and washed with 9:1 DMF-H_2O (3 ×), alternately with MeOH and DCM (3 ×), and finally with MeOH and Et_2O. The MiniKans^{TM} containing resin were then dried under vacuum. This procedure was used for each of the 12 different aryl iodides **a-h** and the resulting 96 MiniKans^{TM}, each containing a different resin-bound enol ether, were placed in an IRORI Clevap^{TM} (automatic cleavage and evaporation) station, so that each MiniKan^{TM} was treated separately with trifluoroacetic acid (1 %) in DCM for 1.5 h, then with DCM-MeOH (4:1) for 0.5 h and the combined organics from each MiniKan^{TM} were collected separately and evaporated.

10.3 SPIROACETALS

10.3.1 Synthesis of Spiroacetals from *tert*-butyl-dimethylsilyl Protected Thioacetal 405

Method 1

Cp_2TiCl_2 (1.84 g, 7.4 mmol, 4.0 eq), magnesium turnings (0.21 g, 8.8 mmol, pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.5 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (2.5 mL, 14.8 mmol). After stirring for 3 h at RT, a solution of thioacetal **405** (2.2 mmol, 1.2 eq.) in dry THF (2 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with THF (2 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (40 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3), removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After

this time, the mixture was added to 1M HCl and extracted with DCM (100 mL). The organics were then combined, dried ($MgSO_4$) and concentrated under reduced pressure.

Method 2

Cp_2TiCl_2 (5.53 g, 22.2 mmol, 12.0 eq), magnesium turnings (0.59 g, 24.2 mmol, pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (1.2 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (10 mL) was added followed by dry $P(OEt)_3$ (7.6 mL, 44.4 mmol). After stirring for 3 h at RT, a solution of thioacetal **405** (5.5 mmol, 3.0 eq.) in dry THF (5 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with THF (5 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (60 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3) removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After this time, the mixture was added to 1M HCl and extracted with DCM (200 mL). The organics were then combined and concentrated under reduced pressure. The resulting residual oil was then treated with a solution of $FeCl_{3\ (aq)}$ and allowed to stir for 2 h at RT, to remove excess $P(OEt)_3$. The solution was then washed with DCM (100 mL) and the layers separated, the organics were then dried ($MgSO_4$) and concentrated under *vacuo*.

10.3.2 Synthesis of Spiroacetals from *tert*-methylsilyl Protected Dithiane 401

Method 1

Cp_2TiCl_2 (1.84 g, 7.4 mmol, 4.0 eq.), magnesium turnings (0.21 g, 8.8 mmol., pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.5 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (2.5 mL, 14.8 mmol). After stirring for 3 h at RT, a solution of dithiane **401** (2.2 mmol, 1.2 eq.) in dry THF (2 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with

THF (2 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (40 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3), removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After this time, the mixture was added to 1M HCl and extracted with DCM (100 mL). The organics were then combined, dried ($MgSO_4$) and concentrated under reduced pressure.

Method 2

Cp_2TiCl_2 (5.53 g, 22.2 mmol, 12.0 eq), magnesium turnings (0.59 g, 24.2 mmol, pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (1.2 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (10 mL) was added followed by dry $P(OEt)_3$ (7.6 mL, 44.4 mmol). After stirring for 3 h at RT, a solution of dithiane **401** (5.5 mmol, 3.0 eq.) in dry THF (5 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with THF (5 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (60 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3) removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After this time, the mixture was added to 1M HCl and extracted with DCM (200 mL). The organics were then combined and concentrated under reduced pressure. The resulting residual oil was then treated with a solution of $FeCl_{3\ (aq)}$ and allowed to stir for 2 h at RT, to remove excess $P(OEt)_3$. The solution was then washed with DCM (100 mL) and the layers separated, the organics were then dried ($MgSO_4$) and concentrated under *vacuo*.

10.3.3 Synthesis of Spiroacetals from *tert*-methylsilyl Protected Dithiane 105

Method 1

Cp_2TiCl_2 (1.84 g, 7.4 mmol, 4.0 eq.), magnesium turnings (0.21 g, 8.8 mmol., pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.5 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (2.5 mL, 14.8 mmol). After stirring for 3 h at RT, a solution of dithiane **105** (2.2 mmol, 1.2 eq.) in dry THF (2 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with THF (2 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (40 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3), removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After this time, the mixture was added to 1M HCl and extracted with DCM (100 mL). The organics were then combined, dried ($MgSO_4$) and concentrated under reduced pressure.

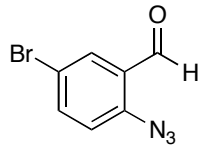
Method 2

Cp_2TiCl_2 (5.53 g, 22.2 mmol, 12.0 eq), magnesium turnings (0.59 g, 24.2 mmol, pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (1.2 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (10 mL) was added followed by dry $P(OEt)_3$ (7.6 mL, 44.4 mmol). After stirring for 3 h at RT, a solution of dithiane **105** (5.5 mmol, 3.0 eq.) in dry THF (5 mL) was added to the mixture and stirring continued for 15 min. During this time, a flask containing lactone (1.8 mmol, 1eq.) was purged with dry argon. The contents were then made into solution with THF (5 mL) and quickly added to the reaction mixture. The resulting solution was stirred vigorously, under argon, overnight at RT. After this time, the reaction was quenched upon addition of 1M NaOH (60 mL) and the resulting insoluble materials filtered off through Celite®. The filtrate was extracted with diethyl ether and dried (K_2CO_3) removal of solvent in *vacuo* gave the crude enol ether derivative. The crude oil was then added to 10 % HCl-MeOH solution and stirred for 1.5 h – 2 h, under argon. After this time, the mixture was added to 1M HCl and extracted with DCM (200 mL). The

organics were then combined and concentrated under reduced pressure. The resulting residual oil was then treated with a solution of $FeCl_{3\ (aq)}$ and allowed to stir for 2 h at RT, to remove excess $P(OEt)_3$. The solution was then washed with DCM (100 mL) and the layers separated, the organics were then dried ($MgSO_4$) and concentrated under *vacuo*.

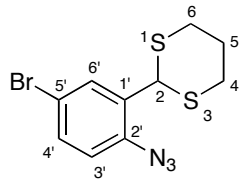
10.4 Experimental Data

2-Azido-5-bromobenzaldehyde 271



Sodium azide (6.71 g, 103 mmol, 2 eq.) was added to a stirring solution of 5-bromo-2-flourobenzaldehyde (10.5 g, 51.6 mmol, 1 eq.) in DMSO (100 mL) under argon. Reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was then poured into ice water, acidified with concentrated HCl. It was then extracted with DCM (2 ×), washed with water (2 ×), dried ($MgSO_4$) and concentrated to give 2-azido 5-bromobenzaldehyde **271** as a yellow solid (10.1 g, 44.8 mmol, 87 %); mp: 87-90 °C (yellow needles from ^{i}PrOH). R_f[SiO_2, hexane-DCM (2:1)]: 0.58. υ_{max}(Golden Gate)/cm^{-1}: 1670 (CHO), 2129 (N_3), 2759 (CH stretch), 2877 (CH stretch). δ_H (400 MHz, $CDCl_3$): 7.17 (1H, d, *J* 8.6 Hz, H-3), 7.71 (1H, dd, *J* 2.4 and 8.6 Hz, H-4), 7.98 (1H, d, *J* 2.4 Hz, H-6), 10.28 (1H, s, CHO). δ_C (100 MHz, $CDCl_3$): 118.25 (C), 120.75 (CH), 127.94 (C), 131.62 (CH), 137.98 (CH), 141.85 (C), 187.07 (CH). m/z (EI): 227 [$M^{+\bullet}$(^{81}Br), 6 %], 225 [$M^{+\bullet}$(^{79}Br), 6], 199 [$M^{+\bullet}$(^{81}Br) – N_2, 27], 197 [$M^{+\bullet}$(^{79}Br) – N_2, 27], 83 (100). HRMS: 226.9513 and 224.9541. $C_7H_4{}^{81}BrN_3O$ requires 226.9518, [$M^{+\bullet}$(^{79}Br)], and $C_7H_4{}^{79}BrN_3O$ requires 224.9538.

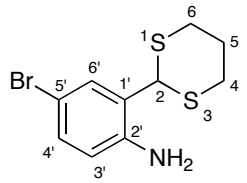
2-(2'-Azido-5'-bromophenyl)-1,3-dithiane 272.



1,3-Propanedithiol (6.0 mL, 51 mmol, 1.2 eq.) was added to a solution of 2-azido-5-bromo-benzaldehyde **271** (10.0 g, 44.5 mmol, 1 eq.) and BF_3.OEt_2 (7.0 mL, 55 mmol, 1.2 eq.) in dry toluene (100 mL) under an atmosphere of argon. The reaction mixture was stirred for 2 h. The reaction was then quenched by adding water and was extracted into DCM (2 ×). Combined organics were washed with 1 M NaOH (2 ×), water (2 ×), dried ($MgSO_4$) and concentrated to give 2-(2'-azido-5'-bromophenyl)-1,3-dithiane **272** (12.8 g, 40.3 mmol, 91 %). A small sample was recrystallised from isopropanol to give dithiane

272 as yellow needles; mp 162-164 ºC. R_f[SiO_2, hexane-DCM (2:1)]: 0.74. υ_{max}(Golden Gate)/cm^{-1}: 2093 cm^{-1} (N_3), 2135 (N_3), 2898 (CH stretch). δ_H (400 MHz, $CDCl_3$): 1.86-1.97 (1H, m, H_{ax}-5), 2.14-2.21 (1H, m, H_{eq}-5), 2.91 (2H, dt, *J* 13.7 and 4.1 Hz, H_{eq}-4 and H_{eq}-6), 3.09 (2H, dt, *J* 2.4 and 13.5 Hz, H_{ax}-4 and H_{ax}-6), 5.43 (1H, s, H-2), 7.00 (1H, d, *J* 8.5 Hz, H-3'), 7.43 (1H, dd, *J* 2.3 and 8.5 Hz, H-4'), 7.74 (1H, d, *J* 2.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 24.95 (CH_2), 32.13 (CH_2), 44.29 (CH), 118.18 (C), 119.25 (CH), 132.08 (C), 132.48 (CH), 132.63 (CH), 135.99 (C). m/z (EI): 317 [$M^{+\bullet}$(^{81}Br), 20 %], 315 [$M^{+\bullet}$(^{79}Br), 20], 215 [$M^{+\bullet}$(^{81}Br) – N_2 and CH_2CHCH_2SH, 30], 213 [$M^{+\bullet}$(^{79}Br) – N_2 and CH_2CHCH_2SH, 30], 83 (100). HRMS: 316.9484 and 314.9503. $C_{10}H_{10}{}^{81}BrN_3S_2$ requires 316.9478, and $C_{10}H_{10}{}^{79}BrN_3S_2$ requires 314.9500. Microanalysis: C, 38.05; H, 3.13; N, 13.08 %. $C_{10}H_{10}BrN_3S_2$ requires C, 37.98; H, 3.19; N, 13.29 %.

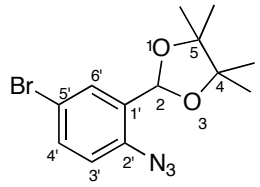
2-(2'Amino-5'-bromophenyl)-1,3-dithiane 295



tert-Butyllithium (1.00 mL, 1.6 M, 1.6 mmol) was added drop-wise over a period of 40 min to a cooled (–80 °C to –89 °C), stirred solution of 2-(2'azido-5'-bromophenyl)-1,3-dithiane **272** (0.049 g, 1.6 mmol), dissolved in THF (20 mL) ensuring the temp did not exceed –80 °C. Reaction mixture was allowed to stir for 1 h at –80 °C. Addition of $B(O^iPr)_3$ (0.73 mL, 3.2 mmol) proceeded drop-wise over 10 min at –80 °C and resulting mixture stirred for 1 h at this temperature. After this time, the reaction mixture was allowed to warm to 0 °C and allowed to stir for 1 h. Pinacol (0.37 g, 3.2 mmol) and AcOH (0.18 mL, 3.2 mmol) were then added and the reaction stirred overnight at RT. The reaction mixture was then quenched upon addition of water, extracted with DCM (2 × 100 mL), combined organics washed with brine (2 × 100 mL) and dried ($MgSO_4$). Removal of solvent in *vacuo* gave dark brown oil. Column chromatography, (DCM), gave aniline **295** as a yellow solid (0.143 g, 26 %). R_f [SiO_2, DCM]: 0.71. υ_{max}(Golden Gate)/cm^{-1}: 1618 (NH_2 bend), 2898 (CH stretch), 2931 (CH stretch), 3353 (NH stretch), 3443 (NH stretch). δ_H (400 MHz, $CDCl_3$): 1.72-1.84 (1H, m, H_{ax}-5), 2.01-2.08 (1H, m, H_{eq}-5), 2.80 (2H, dt, *J* 13.7 and 4.0 Hz, H_{eq}-4 and H_{eq}-6), 2.94 (2H, dt, *J* 2.4 and 13.5 Hz, H_{ax}-4 and H_{ax}-6), 4.09 (2H, s, NH_2), 5.11 (1H, s, H-2), 6.45 (1H, d, *J* 8.5 Hz, H-3'), 7.09 (1H, dd, *J* 2.3 and 8.5

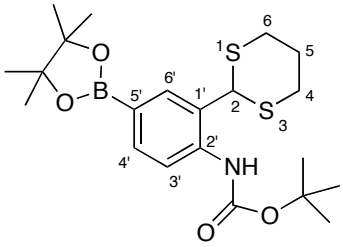
Hz, H-4'), 7.34 (1H, d, *J* 2.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 24.60 (CH_2), 31.05 (CH_2), 46.81 (CH), 109.34 (C), 117.48 (CH), 123.91 (C), 130.06 (CH), 130.87 (CH), 142.54 (C). m/z (EI): 291 [$M^{+\bullet}$(^{81}Br), 45 %], 289 [$M^{+\bullet}$(^{79}Br), 45], 216 [$M^{+\bullet}$(^{81}Br) – $^{\bullet}CH_2CH_2CH_2SH$, 57], 214 [$M^{+\bullet}$(^{79}Br) – $^{\bullet}CH_2CH_2CH_2SH$, 57], 83 (100). HRMS: 290.9570 and 288.9598. $C_{10}H_{12}{}^{81}BrNS_2$ requires 290.9573, and $C_{10}H_{12}{}^{79}BrNS_2$ requires 288.9595. Microanalysis: C, 41.32; H: 4.11; N, 4.70 %. $C_{10}H_{12}BrNS_2$ requires C, 41.38; H, 4.17; N, 4.83 %.

2-[2'-Azido-5'-bromophenyl]-4,4,4,5-tetramethyl-1,3-dioxolane 283



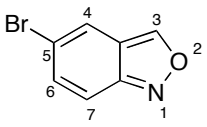
A solution of 2-azido-5-bromobenzaldehyde **271** (5.08 g, 22.1 mmol), p-toluene sulfonic acid monohydrate (24 mg, 0.22 mmol) and pinacol (5.21 g, 44.2 mmol) in toluene (60 mL) was refluxed for 9 h, with Dean Stark apparatus. The solution was allowed to cool to RT whilst stirring. The reaction mixture was then added to aqueous $NaHCO_3$ (200 mL), the organic phase separated and washed with water (2 × 100 mL). Removal of solvent in *vacuo* gave orange solid. Column chromatography, (10:1 hexane/ ethyl acetate) gave azide **283** as an orange solid (1.63 g, 22 %); mp: 80–82 °C. R_f[SiO_2; hexane: EtOAc (10:1)]: 0.69. υ_{max}(Golden Gate)/cm^{-1}: 1145 (C-O), 2074 (N_3). δ_H (400 MHz, $CDCl_3$): 1.19 (6H, s, CH_3), 1.23 (6H, s, CH_3), 5.99 (1H, s, H-2), 6.93 (1H, d, *J* 8.3 Hz, H-3'), 7.39 (1H, dd, *J* 2.2 Hz and 8.3 Hz, H-4'), 7.18 (1H, d, *J* 2.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 22.19 (CH_3), 24.28 (CH_3), 83.02 (C), 94.95 (CH), 117.82 (C), 119.85 (CH), 130.25 (CH), 132.48 (C), 132.74 (CH), 137.57 (C). m/z (EI): 327 [$M^{+\bullet}$ (^{81}Br), 9 %], 325 [$M^{+\bullet}$(^{79}Br) 9], 197 (100)]. HRMS 327.0410 and 325.0424. $C_{13}H_{16}{}^{81}BrN_3O_2$ requires 327.0415, [$M^{+\bullet}$(^{79}Br)], and $C_{13}H_{16}{}^{79}BrN_3O_2$ requires 325.0422.

2-[2'-*tert*-Butoxycarboxyamino-5'-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl]-1,3-dithiane 288.



A solution of amine **294** (5.81 g, 17.2 mmol) in dry THF (150 mL) and $(Boc)_2O$ (7.89 g, 36.2 mmol) was heated under reflux for 12 h under argon. After this time an additional equivalent of $(Boc)_2O$ (3.75 g) was added and the reaction mixture stirred at reflux for a further 24 h. The reaction mixture was then allowed to cool to RT and quenched with water. The mixture was extracted with DCM (2 ×) and the combined organics washed with water (2 ×) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow solid. Column chromatography eluting with hexane-EtOAc (4:1) gave carbamate **288** as a pale yellow solid (5.41 g, 71 %). Mp 99 – 101 °C. R_f [SiO_2, hexane-EtOAc (4:1)]: 0.45. υ_{max}(Golden Gate)/cm^{-1}: 1366 (B-O), 1478 (Ar), 1682 (C=O). δ_H (400 MHz, $CDCl_3$): 1.32 (12H, s, CH_3), 1.54 (9H, s, ^{t}Bu), 1.91 (1H, ttd, 3.0, 12.5 and 14.1 Hz, H_{ax}-5), 2.17 (1H, ttd, *J* 2.3, 3.9 and 14.2 Hz, H_{eq}-5), 2.93 (2H, ddd, J 3.3 , 3.9 and 14.4 Hz, H_{eq}-4 and H_{eq}-6), 3.06 (2H, ddd, *J* 2.3, 12.5 and 14.4 Hz, H_{ax}-4 and H_{ax}-6), 5.34 (1H, s, H-2), 7.69 (1H, broad s, NH), 7.71 (1H, dd, *J* 1.4 and 8.3 Hz, H-4'), 7.78 (1H, d, *J* 1.4 Hz, H-6'), 7.96 (1H, d, *J* 8.3 Hz, H-3'). δ_C (100 MHz, $CDCl_3$): 24.86 (CH_3), 25.17 (CH_2), 28.40 (CH_3), 31.93 (CH_2), 49.52 (CH), 80.59 (C), 83.73 (C), 85.17 (CH), 135.61 (CH), 135.91 (CH), 139.62 (C), 146.75 (C), 152.75 (C). m/z (EI): 437 ($M^{+\bullet}$, 6 %), 380 (71), 274 ($M^{+\bullet}$, $-^{\bullet}C(CH_3)_3$ and $HSCH{=}CHCH_2SH$, 100). HRMS: 437.1866. $C_{21}H_{32}BNO_4S_2$ requires 437.1867.

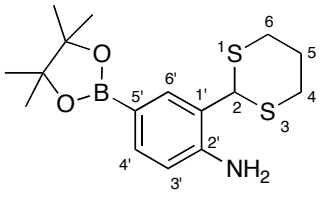
5-Bromoanthranil 290



A stirred solution of 2-azido-5-bromobenzaldehyde **271** (0.512 g, 2.2 mmol) and p-toluenesulfonic acid monohydrate (4 mg, 0.02 mmol) in toluene (6 ml) was refluxed for 9

h in a Dean–Stark apparatus under argon. The solution was allowed to cool to room temperature with stirring. The reaction mixture was then added to aqueous sodium bicarbonate (5 ml), the organic phase separated and washed with water (2 × 10 ml). Removal of the solvent in vacuo, followed by recrystallisation from hexane, gave 5-bromoanthranil **290** as colourless needles (yield 0.451 g, 92 %). mp: 81–82 °C. R_f[SiO_2; hexane: EtOAc (10:1)]: 0.23. δ_{max}(Golden Gate)/cm^{-1}: 1633 (Ar), 2363 (C=N). δ_H (400 MHz, $CDCl_3$): 7.28 (1H, dd, *J* 2.2 Hz and 8.2 Hz, H-5), 7.47 (1H, d, *J* 2.2 Hz, H-6), 7.70 (1H, d, *J* 7.7 Hz, H-4), 9.02 (1H, s, H-3). δ_C (100 MHz, $CDCl_3$): 116.84 (CH), 118.17 (C), 119.27 (C), 121.47 (CH), 134.89 (CH), 153.95 (CH), 154.55 (C). m/z (EI): 199 [$M^{+\bullet}$ (^{81}Br), 59 %], 197 [$M^{+\bullet}$(^{79}Br) 60 %], 83 (100)]. HRMS 198.9456 and 196.9476. $C_7H_4{}^{81}BrNO$ requires 198.9460, [$M^{+\bullet}$(^{79}Br)], and $C_7H_4{}^{79}BrNO$ requires 196.9478.

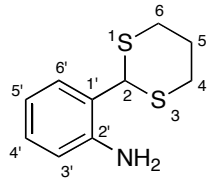
2-[2'-Amino-5'-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl]-1,3-dithiane 294



tert-Butyllithium (69.5 mL, 1.7 M, 118 mmol) was added drop-wise over a period of 1 h 45 min to a cooled (–80 °C to –89 °C) to a stirred solution of aryl azide **272** (12.1 g, 38.1 mmol) in dry THF (120 mL) under argon ensuring the temperature did not exceed –80 °C. The reaction mixture was stirred for 15 min at –80 °C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **297** (25.6 mL, 126 mmol) was added drop-wise over 45 min and the resulting mixture was stirred for 1 h 30 min before being allowed to warm to RT and stirred overnight. Water buffered to pH 7 was added, and the mixture extracted with DCM (3 ×). The combined organics were washed with water and then brine (3 ×) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a dark brown oil. Crystallisation from pentane and ethyl acetate gave the boronate **294** as a brown solid (4.97 g, 39 %). Mp 190 – 193 °C. R_f [SiO_2, DCM/Hexane]: 0.70. υ_{max}(Golden Gate)/cm^{-1}: 1607 (Ar), 3402 (NH_2). δ_H (400 MHz, $CDCl_3$): 1.23 (12H, s, CH_3), 1.82-1.99 (1H, m, H_{ax}-5), 2.09-2.21 (1H, m, H_{eq}-5), 2.83 (2H, td, *J* 4.0 and 13.0 Hz, H_{eq}-4 and H_{eq}-6), 3.01 (2H, dt, *J* 2.0 and 13.0 Hz, H_{ax}-4 and H_{ax}-6), 4.40 (2H, broad s, NH_2), 5.26 (1H, s, H-2), 6.57 (1H, d, *J* 8.1 Hz, H-3'), 7.48 (1H, dd, *J* 1.4 and 8.1 Hz, H-4'), 7.63 (1H, d, *J* 1.3 Hz, H-6'). δ_C (100

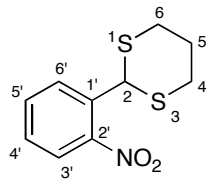
MHz, $CDCl_3$): 24.89 (CH_3), 25.29 (CH_2), 32.00 (CH_2), 49.97 (CH), 83.40 (C), 116.16 (CH), 121.50 (C), 136.21 (CH), 136.29 (CH), 147.82 (C). m/z (EI): 337 ($M^{+\bullet}$, 79 %), 262 (100), HRMS: 337.1338. $C_{16}H_{24}BNO_2S_2$ requires 337.1341. Microanalysis: C, 57.02; H: 7.17; N: 4.22 %. $C_{16}H_{24}BNO_2S_2$ requires C, 56.97; H, 7.17; N, 4.15 %.

2-(2'-Aminophenyl)-1,3-dithiane 296[82]



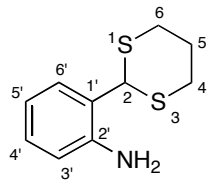
tert-Butyllithium (1.00 mL, 1.6 M, 1.6 mmol) was added drop-wise over a period of 40 min to a cooled (–80 °C to –89 °C), stirred solution of 2-(2'azido-5'-bromophenyl)-1,3-dithiane **272** (0.051 g, 1.6 mmol), dissolved in THF (20 mL) ensuring the temp did not exceed –80 °C. The reaction mixture was allowed to stir for 1 h at –80 °C. Addition of $B(O^iPr)_3$ (0.73 mL, 3.2 mmol) proceeded drop-wise over 10 min at –80 °C and the resulting mixture stirred for 1 h at this temperature. After this time the reaction mixture was allowed to warm to 0 °C and allowed to stir for 1 h. Pinacol (0.37 g, 3.2 mmol) and AcOH (0.18 mL, 3.2 mmol) were then added and the reaction mixture stirred overnight at RT. The reaction was then quenched upon addition of water, extracted with DCM (2 × 100 mL), combined organics washed with brine (2 × 100 mL) and dried ($MgSO_4$). Removal of solvent in *vacuo* gave dark brown oil. Column chromatography, (DCM), gave compound **296** as a yellow solid (370 mg, 8 %). R_f [SiO_2, DCM]: 0.51. δ_H (400 MHz, $CDCl_3$): 1.85-1.91 (1H, m, H_{ax}-5), 2.16-2.19 (1H, m, H_{eq}-5), 2.94 (2H, td, *J* 4.0 Hz and 13.2 Hz, H_{eq}-4 and H_{eq}-6), 3.11 (2H, dt, *J* 2.2 Hz and 13.2 Hz, H_{ax}-4 and H_{ax}-6), 3.99 (2H, broad s, NH_2), 5.29 (1H, s, H-2), 6.70 (1H, dd, *J* 1.0 Hz and 7.9 Hz, H-3'), 6.76 (1H, dt, *J* 1.1 Hz and 7.8 Hz, H-5'), 7.11 (1H, dt, *J* 1.5 Hz and 7.8 Hz, H-4'), 7.31 (1H, dd, *J* 1.6 Hz and 7.9 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 25.31 (CH_2), 32.05 (CH_2), 48.62 (CH), 117.39 (CH), 119.59 (CH), 123.55 (C), 128.61 (CH), 129.34 (CH), 143.71 (C). m/z (EI^+): 211 ($M^{+\bullet}$, 56 %), 136 [($M^{+\bullet}$ – $^{\bullet}C_3H_7S$, 100)]. HRMS: 211.0487. $C_{10}H_{13}NS_2$ requires 211.0485.

2-(2'-Nitrophenyl)-1, 3-dithiane 316[82]



1,3-Propanedithiol (1.19 mL, 11.9 mmol) was added to a stirred solution of 2-nitrobenzaldehyde **315** (1.52 g, 9.9 mmol) and boron trifluoride diethyletherate (1.48 mL, 11.9 mmol) in toluene (10 mL), under argon and stirred for 16 h at RT. After this time, the reaction was quenched by addition of water (15 mL) and then extracted into DCM (2 × 20 mL). The combined organics were washed with 1M NaOH aq. (2 × 20 mL), water (2 × 50 mL) and dried ($MgSO_4$). Removal of solvent in *vacuo* gave a yellow solid. Recrystallisation from propan-2-ol gave 2–(2'nitrophenyl)–1,3–dithiane **316** as yellow needles (2.20 g, 89 %). δ_H (400 MHz, $CDCl_3$): 1.97-2.01 (1H, m, H_{ax}-5), 2.18-2.21 (1H, m, H_{eq}-5), 2.94 (2H, dt, *J* 3.7 Hz and 14.1 Hz, H_{eq}-4 and H_{eq}-6), 3.16 (2H, dt, *J* 2.2 Hz and 12.7 Hz, H_{ax}-4 and H_{ax}-6), 5.90 (1H, s, H-2), 7.45 (1H, dt, *J* 1.4 Hz and 8.3 Hz, H-4'), 7.62 (1H, dt, *J* 1.4 Hz and 7.6 Hz, H-5'), 7.89 (2H, m, H-3' and H-6'). δ_C (100 MHz, $CDCl_3$): 25.01 (CH_2), 32.27 (CH_2), 45.96 (CH), 124.75 (CH), 129.09 (CH), 130.74 (CH), 133.44 (C), 133.50 (CH), 147.71 (C). m/z (EI^+): 241 ($M^{+\bullet}$, 15 %), 224 [($M^{+\bullet}$– $^{\bullet}OH$, 53)], 106 [($M^{+\bullet}$– $^{\bullet}C_4H_7S_2O$, 100)], HRMS: 241.0230. $C_{10}H_{11}NS_2O_2$ requires 241.0229.

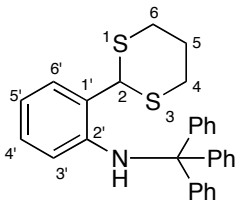
2-(2'-Aminophenyl)-1,3-dithiane 317[82]



Iron powder (1.51 g, 27.0 mmol) was added to a stirred solution of 2-(2'-nitrophenyl)-1,3-dithiane **316** (2.16 g, 9.0 mmol) in ethanol (40 mL) and water (20 mL) and heated under reflux for 4 h, under an inert atmosphere of argon. After allowing the reaction mixture to cool, it was filtered through Celite© washing with ethanol, the resulting pale yellow solution was then concentrated *in vacuo*. The slurry residue was then partitioned between ethyl acetate (50 mL) and brine (60 mL). The organics separated, washed with water (2 × 60 mL) and then dried ($MgSO_4$). Removal of solvent *in vacuo* gave the target aniline **317**

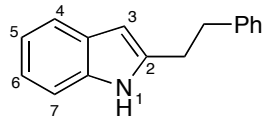
as yellow solid (1.44 g, 76 %). δ_H (400 MHz, $CDCl_3$): 1.87-1.89 (1H, m, H_{ax}-5), 2.14-2.19 (1H, m, H_{eq}-5), 2.94 (2H, td, *J* 4.0 Hz and 13.2 Hz, H_{eq}-4 and H_{eq}-6), 3.11 (2H, dt, *J* 2.2 Hz and 13.2 Hz, H_{ax}-4 and H_{ax}-6), 3.99 (2H, broad s, NH_2), 5.29 (1H, s, H-2), 6.70 (1H, dd, *J* 1.0 Hz and 7.9 Hz, H-3'), 6.76 (1H, dt, *J* 1.1 Hz and 7.8 Hz, H-5'), 7.11 (1H, dt, *J* 1.5 Hz and 7.8 Hz, H-4'), 7.31 (1H, dd, *J* 1.6 Hz and 7.9 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 25.31 (CH_2), 32.05 (CH_2), 48.62 (CH), 117.39 (CH), 119.59 (CH), 123.55 (C), 128.61 (CH), 129.34 (CH), 143.71 (C). m/z (EI^+): 211 ($M^{+\bullet}$, 56 %), 136 ($M^{+\bullet}$ – $^{\bullet}C_3H_7S$, 100). HRMS: 211.0487. $C_{10}H_{13}NS_2$ requires 211.0485.

2-(2'-Aminotrityl)-1,3-dithiane 319



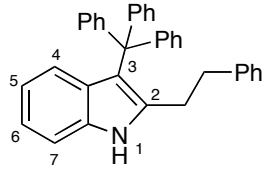
2-(2'-Aminophenyl)-1,3-dithiane **317** (513 mg, 2.4 mmol) and chlorotriphenylmethane (731 mg, 2.6 mmol) in a solution of pyridine (8 mL) was stirred for 20 h at RT, under an inert atmosphere of argon. After this time, the reaction mixture was diluted with ethyl acetate (20 mL), the resulting mixture was washed with $CuSO_4$ aq. (0.5 M, 2 × 20 mL) and brine (20 mL). This solution was then dried ($MgSO_4$) and concentrated under reduced pressure to give yellow foam. Recrystallisation from hexane-chloroform (10:1), yielded target dithiane **319** as golden flakes (662 mg, 61 %). υ_{max}(Golden Gate)/cm^{-1}: 1439 (Ar), 1488 (Ar), 2846 (CH). δ_H (400 MHz, $CDCl_3$): 1.61-1.72 (1H, m, H_{ax}-5), 2.14-2.21 (1H, m, H_{eq}-5), 2.91 (2H, td, *J* 4.1 Hz and 13.2 Hz, H_{eq}-4 and H_{eq}-6), 3.04 (2H, dt, *J* 2.1 Hz and 13.1 Hz, H_{ax}-4 and H_{ax}-6), 5.42 (1H, s, H-2), 6.07 (1H, dd, *J* 1.4 Hz and J 7.9 Hz, H-3'), 6.50 (1H, dt, *J* 1.2 Hz and 7.9 Hz, H-5'), 6.54 (1H, broad s, NH), 6.69 (1H, dt, *J* 2.1 Hz and 7.9 Hz, H-4'), 7.16-7.25 (4H, m, H-6' & Ar-H), 7.27-7.39 (6H, m, Ar-H), 7.41-7.52 (6H, m, Ar-H). δ_C (100 MHz, $CDCl_3$): 25.32 (CH_2), 31.91 (CH_2), 50.88 (CH), 71.39 (C), 116.51 (CH), 116.58 (CH), 122.36 (C), 126.70 (CH), 127.88 (CH), 128.15 (CH), 128.58 (CH), 129.69 (CH), 144.18 (C), 145.53 (C). m/z (EI^+): 453 ($M^{+\bullet}$, 2 %), 210 [($M^{+\bullet}$ – $^{\bullet}C(Ph)_3$, 100)]. HRMS: 453.1585. $C_{29}H_{27}NS_2$ requires 453.1583.

2-(2'-Phenylethyl)indole 324[253]



A MacroKan^{TM} containing the resin-bound enol ether **323** (0.311 meq.) was shaken with trifluoroacetic acid (4 %) and triethylsilane (0.05 mL) in DCM (5 mL) for 1.5 h. The solution was removed and the reactor was washed with DCM (3 ×). Combined organics were concentrated under reduced pressure to yield a dark purple solid. The solid was then washed with cold hexane, to remove triphenyl methane, producing indole **324** as a purple solid (33 mg, 48 %). mp: 110-113 ºC. υ_{max}(Golden Gate)/cm^{-1}: 2926 (CH), 2856 (CH), 1452 (Ar). δ_H (400 MHz, $CDCl_3$): 2.99-3.10 (4H, m, C$\underline{H_2}$C$\underline{H_2}$), 6.27 (1H, s, H-3), 7.03-7.12 (2H, m, Ar-H), 7.20-7.33 (6H, m, Ar-H), 7.52 (1H, dd, *J* 1.2 Hz and 7.6 Hz, H-4), 7.72 (1H, s, NH). δ_C (100 MHz, $CDCl_3$): 30.19 (CH_2), 35.66 (CH_2), 99.85 (CH), 110.38 (CH), 119.67 (CH), 119.90 (CH), 121.14 (CH), 126.33 (CH), 128.46 (CH), 128.68 (C), 129.50 (CH), 135.82 (C), 139.06 (C), 141.23 (C). m/z (EI$^+$): 221 ($M^{+\bullet}$, 23 %), 130 ($M^{+\bullet}$– $^{\bullet}CH_2Ph$, 75), 91 ($M^{+\bullet}$– $^{\bullet}CH_2C_8H_6N$, 100), HRMS: 221.1204. $C_{16}H_{15}N$ requires 221.1202.

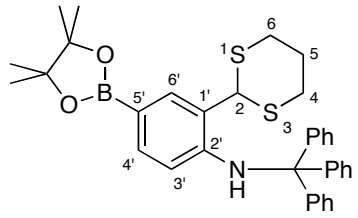
2-(2'-Phenylethyl)-3-tritylindole 325



A MacroKan^{TM} containing the resin-bound enol ether **323** (0.311 meq.) was shaken with trifluoroacetic acid (4 %) in DCM (5 mL) for 1.5 h. The solution was removed and the reactor was washed with DCM (3 ×). Combined organics were concentrated under reduced pressure to yield a dark yellow solid. Column chromatography eluting with DCM-hexane (6:4), gave indole **325** as a grey solid (18 mg, 12 %). mp: 162 ºC. R_f[SiO_2; DCM-hexane (6:1)]: 0.81. υ_{max}(Golden Gate)/cm^{-1}: 1446 (Ar), 1490 (Ar), 2849 (CH), 2918 (CH). δ_H (400 MHz, $CDCl_3$): 2.28 (2H, t, *J* 8.4 Hz, C$\underline{H_2}$$CH_2$), 2.40 (2H, t, *J* 8.4 Hz, CH_2C$\underline{H_2}$), 6.24 (1H, broad. d, *J* 8.0 Hz, H-4), 6.63 (1H, dt, *J* 1.2 Hz and J 7.8 Hz, H-5), 6.82 (1H, dd, *J* 1.2 Hz and 7.8 Hz, H-7), 6.92 (1H, dt, *J* 2.0 Hz and 7.9 Hz, H-6), 7.06-7.22 (15H, m, CPh_3), 7.32-7.39 (5H, m, ArH), 7.60 (1H, bs, NH). δ_C (100 MHz, $CDCl_3$): 28.68 (CH_2), 33.95

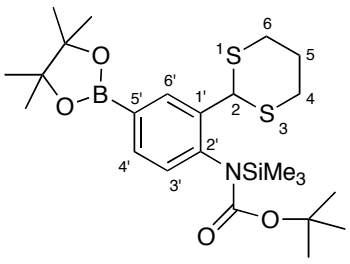
(CH_2), 59.07 (C), 108.84 (CH), 117.19 (C), 117.64 (CH), 119.64 (CH), 121.44 (CH), 124.74 (CH), 125.13 (CH), 126.07 (C), 126.39 (CH), 127.21 (CH), 127.39 (CH), 128.80 (CH), 134.31 (C), 135.57 (C), 140.06 (C), 145.88 (C). m/z (EI^+): 463 ($M^{+\bullet}$, 95 %), 386 ($M^{+\bullet}$ – $^{\bullet}$Ph, 100), HRMS: 463.2300. $C_{35}H_{29}N$ requires 463.2301.

2-(2'-Aminotrityl)-5'-(4'',5''-tetramethyl-1'',3'',2''-dioxaborolan-2''-yl]-1,3-dithiane 331.



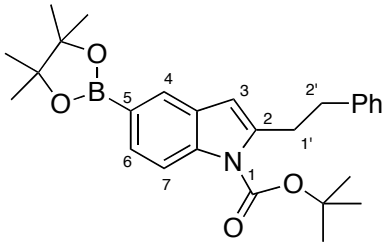
Amine **294** (3.319 g, 9.84 mmol) was added to a stirred solution of DMAP (48 mg, 0.39 mmol), triethyl amine (2.74 mL, 19.68 mmol) and chlorotriphenyl methane (3.09 g, 10.82 mmol) in DCM (20 mL). The resulting reaction mixture was then stirred overnight at RT, in an inert atmosphere of argon. After this time, the reaction mixture was diluted with ethyl acetate (30 mL) and water (40 mL). The organic layer was extracted with EtOAc (2 × 15 mL), the organics combined, washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give rusty brown solid. Recrystallisation from hexane/ methanol 10:1, yielded target dithiane **331** as yellow solid (2.84 g, 51 %). mp 103-104 ºC. υ_{max}(Golden Gate)/cm^{-1}: 1446 (Ar), 1490 (Ar), 2897 (CH), 2932 (CH). δ_H (400 MHz, $CDCl_3$): 1.19 (12H, s, CH_3), 1.61-1.72 (1H, m, H_{ax}-5), 1.98-2.05 (1H, m, H_{eq}-5), 2.78 (2H, td, *J* 4.1 Hz and 13.2 Hz, H_{eq}-4 and H_{eq}-6), 2.91 (2H, dt, *J* 2.1 Hz and 13.1 Hz, H_{ax}-4 and H_{ax}-6), 5.42 (1H, s, H-2), 5.97 (1H, d, *J* 7.9 Hz, H-3'), 6.94 (1H, broad s, NH), 7.04 (1H, dd, *J* 2.3 Hz and 7.9 Hz, H-4'), 7.16-7.21 (10H m, Ar-H), 7.29-7.38 (5H, m, Ar-H), 7.51 (1H, d, *J* 2.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 24.82 (CH_3), 31.15 (CH_2), 31.74 (CH_2), 51.73 (CH), 115.51 (CH), 121.22 (C), 126.54 (CH), 126.72 (CH), 127.81 (CH), 127.87 (CH), 127.90 (CH), 128.15 (CH), 128.27 (C), 128.87 (CH), 128.90 (C), 129.21 (CH), 129.54 (CH), 130.06 (C), 135.19 (CH), 136.08 (CH), 144.82 (C), 146.83 (C), 147.16 (C). m/z (EI^+): 579 ($M^{+\bullet}$, 3 %), 336 [($M^{+\bullet}$ – $^{\bullet}C(Ph)_3$, 100)]. HRMS: 579.2437. $C_{35}H_{38}BNO_2S_2$ requires 579.2439.

2-[2'-Aminosilylcarbamate-5'-(4", 5"-tetramethyl-1", 3", 2"-dioxaborolan-2"-yl]-1,3-dithiane 334.



A solution of lithium diisopropylamide (1.80 mL, 2.0 M, 3.4 mmol) was added drop-wise to a cooled stirred solution of carbamate **288** (1.22 g, 2.8 mmol) and TMSCl (0.42 mL, 3.4 mmol) in THF (30 mL) at –78 °C under an inert atmosphere of argon. The reaction mixture was then allowed to warm to RT over 45 min and was allowed to stir for a further 1 h at RT. After this time, the solvent was removed in *vacuo* and ether (30 mL) was added. The resulting white solid was filtered off and the ethereal solution concentrated to furnish target *N*-silylcarbamate **334** as an off-white solid (1.40 g, 98 %). δ_H (400 MHz, $CDCl_3$): 0.24 (9H, s, Si-CH_3), 1.33 (12H, s, CH_3), 1.54 (9H, s, ^{t}Bu), 1.92-2.05 (1H, m, H_{ax}-5), 2.14-2.22 (1H, m, H_{eq}-5), 2.88-3.07 (4H, m, H_{eq}-4, H_{eq}-6, H_{ax}-4 and H_{ax}-6), 5.21 (1H, s, H-2), 6.94 (1H, d, *J* 7.7 Hz, H-3'), 7.65 (1H, dd, *J* 1.3 and 7.7 Hz, H-4'), 8.06 (1H, d, *J* 1.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 0.60 (CH_3), 23.52 (CH_3), 23.82 (CH_2), 27.05 (CH_3), 30.59 (CH_2), 48.18 (CH), 79.26 (C), 82.39 (C), 119.35 (C), 126.95 (C), 134.27 (CH), 134.58 (CH), 138.28 (C), 151.41 (C). m/z (EI): 509 ($M^{+\bullet}$, 3 %), 452 [($M^{+\bullet}$ – $^{\bullet}C(CH_3)_3$ 55)], 408 [($M^{+\bullet}$ – $^{\bullet}C(CH_3)_3$ and CO_2 60)], 346 ($M^{+\bullet}$, – $^{\bullet}C(CH_3)_3$ and $HSCH{=}CHCH_2SH$, 100). HRMS: 509.2263. $C_{24}H_{40}BNS_2SiO_4$ requires 509.2261.

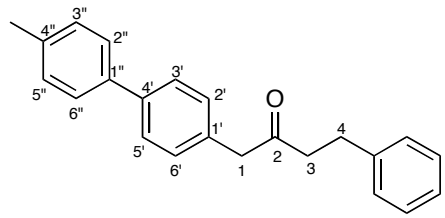
***N*-Boc-2-phenylethyl-5-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl]-indole 338**.



A MacroKan^{TM} containing the resin-bound enol ether **336** (0.311 meq.) was shaken with trifluoroacetic acid (1 %) in DCM (5 mL) for 1.5 h. The solution was removed and the

reactor was washed with DCM (3 ×). Combined organics were concentrated under reduced pressure gave indole **338** as a purple solid (81 mg, 57 %). Mp 101-104 ˚C. R_f [SiO_2, DCM]: 0.76. υ_{max}(Golden Gate)/cm^{-1}: 1734 (C=O), 2976 (CH). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.68 (9H, s, ^{t}Bu), 3.01 (2H, t, *J* 8.4 Hz, H-2'), 3.32 (2H, t, *J* 8.4 Hz, H-1'), 6.33 (1H, s, H-3), 7.18-7.29 (5H, m, Ar-H), 7.69 (1H, dd, *J* 0.9 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 0.9 Hz, H-4), 8.04 (1H, d, *J* 8.4 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 24.93 (CH_3), 28.27 (CH_3), 31.76 (CH_2), 35.20 (CH_2), 83.65 (C), 83.95 (C), 107.64 (CH), 114.94 (CH), 126.00 (CH), 127.06 (CH), 128.38 (CH), 128.43 (CH) 128.90 (C), 129.74 (CH), 138.69 (C), 141.47 (C), 141.59 (C), 150.52 (C). m/z (EI): 447 ($M^{+\bullet}$, 19 %), 391 ($M^{+\bullet}$ – CH_2=C(CH_3)$_2$, 44), 300 (82), 83 (100). HRMS: 447.2577. $C_{27}H_{34}BNO_4$ requires 447.2571.

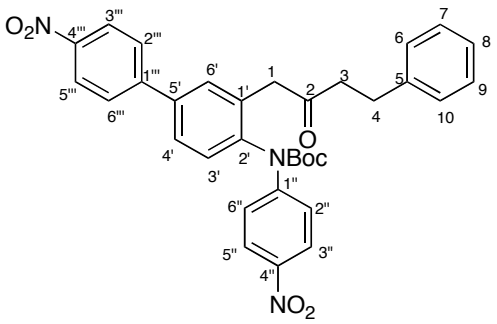
1-[4'-(4"-Methylphenyl)phenyl]-4-phenylbutan-2-one 341[83]

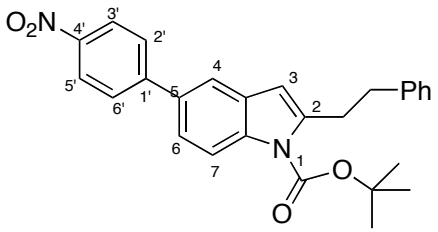


Titanocene dichloride (0.901 g, 3.6 mmol, 12.0 eq.), magnesium turnings (0.102 g, 3.9 mmol, 13 eq., pre-dried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.203 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (8 mL) was followed by dry $P(OEt)_3$(1.2 mL, 7.2 mmol, 24 eq.). After stirring for 3 h at RT, a solution of dithiane **339** (0.473 g, 0.93 mmol, 3 eq.) in dry THF (4 mL) was added to the mixture and stirring continued for 15 min. The solution was added to a flask containing resin-bound ester (as per the general method) pre-swollen in THF (6 mL) under argon. After 17 h the reactor was removed from the flask and washed with THF (5 ×) then alternately with MeOH and DCM (5 ×) and finally MeOH then Et_2O. The reactor containing the resin-bound enol ether **340** was then dried under vacuum. Reaction procedure was as per the general method for solid-phase Suzuki cross-coupling, resin-bound enol ether **340** (0.311 meq.) and 4-iodotoluene (338 mg, 1.55 mmol, 4.8 eq.) yielded a dark brown solid **341**. (74 mg, 75 %). δ_H (400 MHz, $CDCl_3$): 2.39 (3H, s, Ar$C\underline{H}_3$), 2.74–2.87 (4H, m, H-3 and H-4), 3.69 (2H, s, H-1), 7.13 (2H, d, *J* 7.0 Hz, Ar-H), 7.15–7.27 (7H, m, Ar-H), 7.47 (2H, d, *J* 8.1 Hz, Ar-H), 7.51 (2H, d, *J* 8.1 Hz, Ar-H) δ_C (100 MHz, $CDCl_3$): 21.50 (CH_3), 30.16 (CH_2), 43.19 (CH_2), 50.37 (CH_2), 126.49 (CH),

127.25 (CH), 127.65 (CH), 128.72 (CH), 128.86 (CH), 129.88 (CH), 130.16 (CH), 133.12 (C), 137.47 (C), 138.20 (C), 140.25 (C), 141.29 (C), 207.91.

1-[2'-(*N*-Boc- 4"-nitrophenylamino)-5'-(4"'-nitrophenyl)phenyl]-4-phenylbutan-2-one 342 and *N*-Boc-5-(4"-nitrophenyl)-2-(2'-phenylethyl)indole 343.

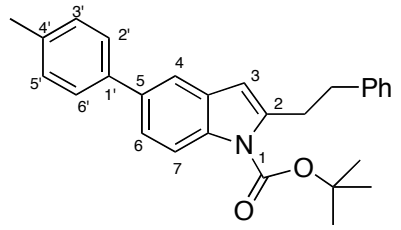




As per the general method for solid-phase Suzuki cross-coupling, resin-bound enol ether **336** (0.311 meq.) using 1-iodo-4-nitrobenzene (391 mg) and heating at 80 °C for only 2 h in the Suzuki cross-coupling, gave a 5:1 mixture of indole **343** and ketone **342** (97 mg, 68 %) after cleavage. Pure samples of each compound were obtained by chromatography (DCM). Indole **343** was isolated as a yellow solid (71 mg). R_f [SiO_2, DCM]: 0.85. υ_{max}(Golden Gate)/cm^{-1}: 1341 (NO_2), 1516 (NO_2), 1595 (Ar), 1734 (C=O), 2926 (CH), 2968 (CH). δ_H (400 MHz, $CDCl_3$): 1.63 (9H, s, CH_3), 2.97 (2H, t, *J* 7.9 Hz, C*H*$_2$Ph), 3.28 (2H, t, *J* 7.9 Hz, C*H*$_2$CH$_2$Ph), 6.33 (1H, s, H-3), 7.13-7.22 (5H, m, Ar-H), 7.41 (1H, dd, *J* 1.9 and 8.7 Hz, H-6), 7.61 (1H, d, *J* 1.7 Hz, H-4), 7.67 (2H, d, *J* 8.8 Hz, H-2" and 6"), 8.09 (1H, d, *J* 8.7 Hz, H-7), 8.19 (2H, d, *J* 8.8 Hz, H-3" and 5"). δ_C (100 MHz, $CDCl_3$): δ 28.30 (CH_3), 31.77 (CH_2), 35.16 (CH_2), 84.39 (C), 107.50 (CH), 116.57 (CH), 119.43 (CH), 122.73 (CH), 124.10 (CH), 126.14 (CH), 128.38 (CH), 127.71 (CH), 128.42 (CH), 130.03 (C), 133.26 (C), 136.93 (C), 141.29 (C), 143.04 (C), 146.67 (C), 148.24 (C), 150.34 (C). m/z (EI): 442 ($M^{+\bullet}$, 16 %), 386 ($M^{+\bullet}$ – CH_2=C(CH_3)$_2$, 63), 295 (86), 57 (100), HRMS: 442.1893. $C_{27}H_{26}N_2O_4$ requires 442.1893. Ketone **342** was isolated as an orange solid (13 mg). R_f [SiO_2, DCM]: 0.48. υ_{max}(Golden Gate)/cm^{-1}: 1342 (NO_2), 1517 (NO_2), 1592 (Ar), 1717 (C=O), 2924 (CH). δ_H (400 MHz, $CDCl_3$): δ 1.38 (9H, s, CH_3), 2.71 (4H, m, C*H*$_2$C*H*$_2$Ph), 3.46 (1H, d, *J* 15.7 Hz), 3.54 (1H, d, *J* 15.7 Hz), 7.03-7.21 (5H, m, Ar-H), 7.25 (1H, d, *J* 8.2 Hz, H-3'), 7.29 (2H, d, 9.3 Hz, H-2" and H-6"), 7.41 (1H, d, *J* 2.2 Hz, H-6'), 7.55 (1H, dd, *J* 2.2 and 8.2 Hz, H-4'), 7.67 (2H, d, *J* 8.8 Hz, H-2"' and H-6"'), 8.04 (2H, d, *J* 9.3 Hz, H-3" and H-5"), 8.25 (2H, d, *J* 8.8 Hz, H-3"' and H-5"'). δ_C (100 MHz, $CDCl_3$): 28.09 (CH_3), 29.60 (CH_2), 45.18 (CH_2), 83.28 (C), 123.48 (CH), 124.21 (CH),

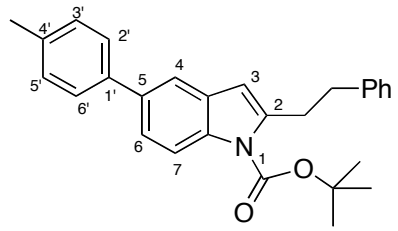
124.31 (CH), 126.31 (CH), 127.54 (CH), 127.99 (CH), 128.28 (CH), 128.56 (CH), 130.59 (CH), 131.27 (CH), 133.50 (C), 138.96 (C), 140.48 (C), 140.59 (C), 143.70 (C), 146.03 (C), 147.45 (C), 147.64 (C), 152.65 (C), 205.36 (C). m/z (FAB^+): 582 ($M + H^+$, 22 %), 526 [$(M + H)^+ - CH_2=C(CH_3)_2$, 40], 482 (58), 481 (32), 59 (100), HRMS: 582.2240. $C_{33}H_{32}N_3O_7$ requires $M + H^+$, 582.2240.

_N_-Boc-5-(4'-methylphenyl)-2-(2"phenylethyl)indole 350.



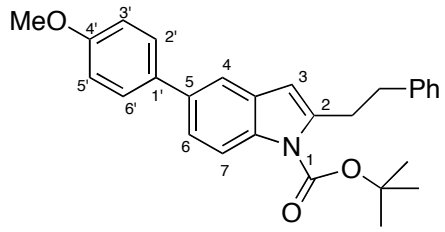
As per the general method for solid-phase Suzuki cross-coupling, resin-bound enol ether **336** (0.311 meq.) and 4-iodotoluene (338 mg, 1.55 mmol, 4.8 eq.) yielded a dark brown solid. Column chromatography, (DCM), gave indole **350** as brown solid (21 mg, 37 %). Mp 75-78 ˚C. R_f [SiO_2, DCM]: 0.76. υ_{max}(Golden Gate)/cm^{-1}: 1468 (Ar), 1731 (C=O), 2929 (CH), 2077 (CH), 3025 (Ar-H). δ_H (400 MHz, $CDCl_3$): 1.63 (9H, s, ^{t}Bu), 2.33 (3H, s, CH_3), 2.97 (2H, t, *J* 8.4 Hz, CH_2Ph), 3.28 (2H, t, *J* 8.4 Hz, CH_2CH_2Ph), 6.32 (1H, s, H-3), 7.14-7.27 (5H, m, Ar-H), 7.22 (2H, d, *J* 8.8 Hz, Ar-H), 7.40 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.47 (2H, d, *J* 8.8 Hz, Ar-H), 7.56 (1H, d, *J* 2.0 Hz, H-4), 8.03 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 21.12 (CH_3), 28.32 (CH_3), 32.52 (CH_2), 35.25 (CH_2), 83.93 (C), 107.57 (CH), 115.80 (CH), 118.06 (CH), 122.71 (CH), 126.07 (CH), 127.14 (CH), 128.45 (CH), 128.47 (CH), 129.78 (CH), 129.87 (C), 135.85 (C), 135.91 (C), 136.49 (C), 138.84 (C), 141.52 (C), 142.31 (C), 150.62 (C). m/z (EI): 411 ($M^{+\bullet}$, 34 %), 355 ($M^{+\bullet} - CH_2=C(CH_3)_2$, 56), 264 (95), 290 (100). HRMS: 411.2199. $C_{28}H_{29}NO_2$ requires 411.2198.

_N_-Boc-5-(4'-methylphenyl)-2-(2"-phenylethyl)indole 350



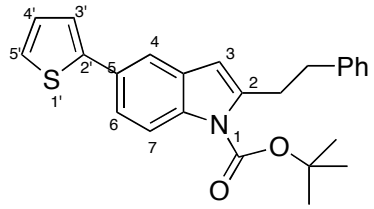
In the same way, but using 4-iodotoluene (338 mg) and heating at 80 °C for 5 h in the Suzuki cross-coupling, followed by cleavage in the same way gave indole **350** as a brown solid (74.1 mg, 53 %). Mp 75-78 ˚C. R_f [SiO_2, DCM]: 0.76. Analytical data as reported for previous indole **350** above.

_N_-Boc-5-(4'-methoxyphenyl)-2-(2"-phenylethyl)indole 351.



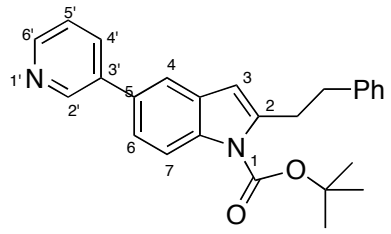
In the same way, but using 4-iodoanisole (365 mg) as the aryl iodide in the Suzuki cross coupling gave indole **351** as a dark brown solid (74.3 mg, 54 %). Mp 80-83 ˚C. υ_{max}(Golden gate)/cm^{-1}: 1468 (Ar), 1731 (C=O), 2929 (CH). δ_H (400 MHz, $CDCl_3$): δ 1.61 (9H, s, ^{t}Bu), 2.95 (2H, t, *J* 7.8 Hz, CH_2Ph), 3.26 (2H, t, *J* 7.8 Hz, CH_2CH_2Ph), 3.76 (3H, s, OCH_3), 6.29 (1H, s, H-3), 6.89 (2H, d, *J* 2.0 Hz, H-3' and H-5'), 7.09-7.25 (5H, m, Ph) 7.34 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.48 (2H, d, *J* 2.0 Hz, H-2' and H-6'), 7.52 (1H, d, *J* 2.0 Hz, H-4), 8.03 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 28.31 (CH_3), 31.83 (CH_2), 35.24 (CH_2), 55.40 (CH_3), 82.87 (C), 107.43 (CH), 114.20 (CH), 115.79 (CH), 117.79 (CH), 122.66 (CH), 126.05 (CH), 128.26 (CH), 128.43 (CH), 128.64 (CH), 128.79 (C), 133.27 (C), 134.51 (C), 134.58 (C), 140.43 (C), 141.22 (C), 149.51 (C), 157.70 (C). (m/z): LRMS (EI^+): 427 ($M^{+\bullet}$, 52 %), 371 ($M^{+\bullet}$ – CH_2=$C(CH_3)_2$, 87), 280 (100). HRMS: 427.2148. $C_{28}H_{29}NO_3$ requires 427.2147.

***N*-Boc-2-(2"-phenylethyl)-5-(2'-thiophenyl)indole 352**.



In the same way, but using 2-iodothiophene (322 mg) as the aryl iodide in the Suzuki cross coupling gave indole **352** as a dark brown solid (81 mg, 62 %). Mp 108-110 ˚C. υ_{max}(Golden gate)/cm^{-1}: 1470 (Ar), 1726 (C=O), 2854 (CH), 2925 (CH). δ_H (400 MHz, $CDCl_3$): 1.68 (9H, s, ^{t}Bu), 3.03 (2H, t, *J* 8.0 Hz, CH_2Ph), 3.33 (2H, t, *J* 8.0 Hz, CH_2CH_2Ph), 6.35 (1H, s, H-3), 7.02-7.08 (1H, m, H-4'), 7.18-7.31 (7H, m, H-5', H-3'and Ph) 7.51 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.66 (1H, d, *J* 2.0 Hz, H-4), 8.07 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 28.25 (CH_3), 31.76 (CH_2), 35.12 (CH_2), 84.05 (C), 107.45 (CH), 115.90 (CH), 117.08 (CH), 121.76 (CH), 122.61 (CH), 124.08 (CH), 126.03 (CH), 127.94 (CH), 128.40 (CH), 128.42 (CH), 129.30 (C), 129.80 (C), 135.99 (C), 141.39 (C), 142.56 (C), 145.16 (C), 150.41 (C). m/z (EI): 403 ($M^{+\bullet}$, 43 %), 347 ($M^{+\bullet} - CH_2{=}C(CH_3)_2$, 67], 212 (100). HRMS: 403.1607. $C_{25}H_{25}NO_2S$ requires 403.1606.

***N*-Boc-2-(2"-phenylethyl)-5-(3'-pyridyl)indole 353**.

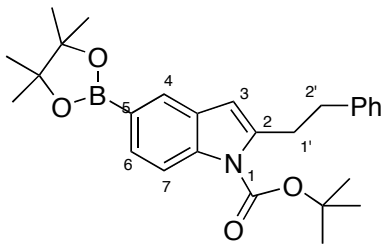


In the same way, but using 3-iodopyridine (312 mg) as the aryl iodide in the Suzuki cross coupling gave indole **353** as its TFA salt (105 mg) as a dark brown solid. A portion of the salt (40.0 mg) was treated with $NaHCO_3$ and extracted into DCM. The combined organics were concentrated under reduced pressure to give the indole **353** (27.6 mg, 58 %) as a brown oil. υ_{max} (KBr)/cm^{-1}: 1496 (Ar), 1733 (C=O), 2854 (CH), 2974 (CH). δ_H (400 MHz, $CDCl_3$): 1.64 (9H, s, ^{t}Bu), 2.98 (2H, t, *J* 7.8 Hz, C*H*$_2$Ph), 3.30 (2H, t, *J* 7.8 Hz, C*H*$_2$CH$_2$Ph), 6.35 (1H, s, H-3), 7.12-7.23 (5H, m, Ph) 7.40 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.58 (1H, d, *J* 2.0 Hz, H-4), 7.84-7.87 (1H, m, H-5'), 8.12 (1H, d, *J* 8.8 Hz, H-7), 8.52 (1H,

d, *J* 8.6 Hz, H-4'), 8.68 (1H, d, *J* 2.2 and 8.6 Hz, H-6'), 9.04 (1H, d, *J* 2.2 Hz, H-2'). δ_C (100 MHz, $CDCl_3$): 27.25 (CH_3), 30.74 (CH_2), 34.12 (CH_2), 83.15 (C), 106.41 (CH), 115.13 (CH), 117.30 (CH), 121.51 (CH), 125.03 (CH), 126.74 (CH), 127.39 (C), 128.14 (CH), 128.31 (CH), 130.21 (C), 137.14 (C), 139.21 (CH), 140.31 (CH), 141.72 (C), 140.07 (C), 142.73 (CH), 143.42 (C), 149.93 (C). m/z (EI): 398 ($M^{+\bullet}$, 21 %), 342 [$M^{+\bullet}$ – CH_2=C(CH_3)$_2$, 48], 251 (65), 207 (100), HRMS: 398.1996. $C_{26}H_{26}N_2O_2$ requires 398.1994.

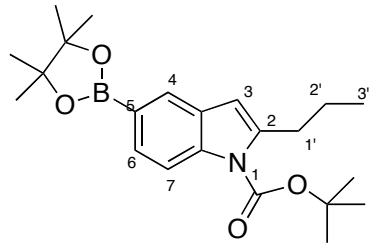
LIBRARY SYNTHESIS – GSK

N-Boc-2-(2'-phenylethyl)-5-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl)-indole 358 A.



One MiniKan^{TM} containing resin-bound enol ether **357 A** (93 μeq.) was shaken with trifluoroacetic acid (1 %) in DCM (5 mL) for 1.5 h. The solution was removed and the reactor was washed with DCM (3 ×). Combined organics were concentrated under reduced pressure gave indole **358 A** (23.7 mg, 57 %). ^{1}H NMR data as reported for indole **338** above.

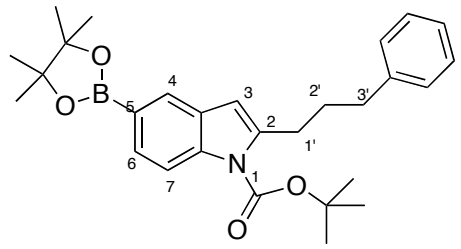
N-Boc-2-propyl-5-(4',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)indole 358 B.



In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 B** (93 μeq.) gave indole **358 B** (21.8 mg, 61 %). δ_H (400 MHz, $CDCl_3$): 1.03 (2H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.37

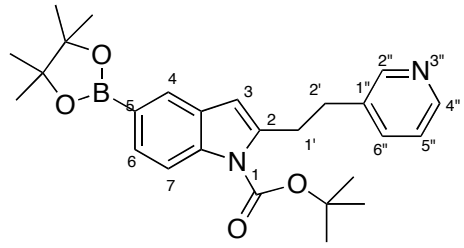
(12H, s, CH_3), 1.67 (9H, s, ^{t}Bu), 2.93–2.98 (4H, m, CH_2CH_2), 6.34 (1H, s, H-3), 7.65 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 8.06 (1H, d, *J* 1.2 Hz, H-4), 8.21 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-2-(3'-phenylpropyl)-5-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl)indole 358 C**.



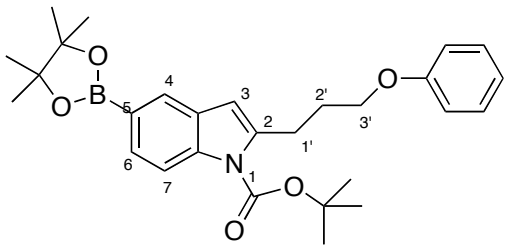
In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 C** (93 μeq.) gave indole **358 C** (25.7 mg, 60 %). δ_H (400 MHz, $CDCl_3$): 1.33 (12H, s, CH_3), 1.66 (9H, s, ^{t}Bu), 2.04 (2H, qn, *J* 7.4 Hz, $CH_2CH_2CH_2$), 2.73 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2Ph$), 3.03 (2H, t, *J* 7.4 Hz, CH_2Ph), 7.19–7.29 (5H, m, ArH), 6.34 (1H, s, H-3), 7.67 (1H, dd, 1.6 and 8.4 Hz, H-6), 7.93 (1H, d, *J* 1.6 Hz, H-4), 8.08 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-2-[2'-(3"-pyridyl)]-5-(4"',5"'-tetramethyl-1"',3"',2"'-dioxaborolan-2"'-yl)indole 358 D**.



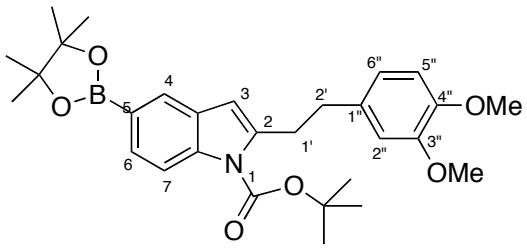
In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 D** (93 μeq.) gave indole **358 D** (24.2 mg, 58 %). δ_H NMR (400 MHz, DMSO-d_6): 1.21 (9H, s, ^{t}Bu), 1.24 (12H, s, CH_3), 2.76 (2H, t, *J* 7.2 Hz, CH_2CH_2), 3.17 (2H, t, *J* 7.2 Hz, CH_2CH_2), 6.32 (1H, s, H-3), 7.12 (1H, dd, 1.6 and 8.4 Hz, H-6), 7.22 (1H, d, *J* 1.6 Hz, H-4), 7.25 (1H, broad dd, *J* 4.8 Hz and 7.7 Hz, H-5"), 7.62 (1H, d, *J* 8.4 Hz, H-7), 7.67 (1H, broad d, *J* 7.8 Hz, H-4"), 8.41 (1H, broad s, H-2"), 8.43 (1H, broad d, 4.7 Hz, H-6").

***N*-Boc-2-(3'-phenoxypropyl)-5-(4",5"-tetramethyl-1",3",2"-dioxaborolan-2"-yl)indole 358 E**.



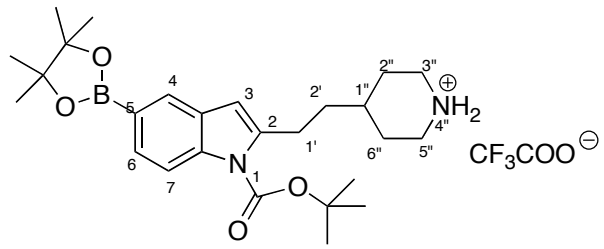
In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 E** (93 μeq.) gave indole **358 E** (17.5 mg, 42 %). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.68 (9H, s, ^{t}Bu), 2.19 (2H, qn, *J* 7.4 Hz, $CH_2CH_2CH_2$), 3.20 (2H, t, *J* 7.2 Hz, $CH_2CH_2CH_2OPh$), 4.04 (2H, t, *J* 7.4 Hz, CH_2OPh), 6.37 (1H, s, H-3), 6.88–6.95 (3H, m, ArH), 7.27–7.29 (2H, m, ArH), 7.67 (1H, dd, 1.2 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 1.2 Hz, H-4), 8.07 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-2-[2'-(3",4"-dimethoxyphenyl)ethyl]-5-(4"',5"'-tetramethyl-1"',3"',2"'-dioxaborolan-2"'-yl)indole 358 F**.



In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 F** (93 μeq.) gave indole **358 F** (27.1 mg, 58 %). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.67 (9H, s, ^{t}Bu), 2.96 (2H, t, *J* 7.2 Hz, H-2'), 3.30 (2H, t, *J* 7.4 Hz, H-1'), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.32 (1H, s, H-3), 6.71 (1H, d, *J* 1.6 Hz, H-2"), 6.77–6.78 (2H, m, H-5" and H-6"), 7.68 (1H, dd, 1.2 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 1.2 Hz, H-4), 8.06 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-2-[2'-(piperidin-4"-yl)ethyl]-5-(4"',5"'-tetramethyl-1"',3"',2"'-dioxaborolan-2"'-yl)indole, trifluoroacetate salt 358 G'**.



In the same way, one MiniKan^{TM} containing resin-bound enol ether **357 G** (93 μeq.) gave indole **358 G'** (36.6 mg, 73 %). δ_H (400 MHz, $CDCl_3$): 1.37 (12H, s, CH_3), 1.53–1.56 (5H, m, H-pip), 1.69 (9H, s, ^{t}Bu), 2.00-2.10 (2H, m, piperidine), 2.90-3.10 (4H, m, CH_2CH_2), 3.45-3.60 (2H, m, 2 × CH^AH^BN), 6.34 (1H, s, H-3), 7.68 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 7.93 (1H, s, H-4), 8.01 (1H, d, *J* 8.4 Hz, H-7), 9.11 (2H, bs, NH_2).

Indoles 359 Aa-Hl.

These were prepared as per (Library synthesis – GSK) solid-phase Suzuki cross-coupling reaction conditions. After evaporation, the resulting indoles **359 Aa-Hl** can be observed in Table 5 with corresponding yields and purities. Analysis of the library was by reversed phase HPLC/DAD-UV/ELSD/MS using a Waters Analytical 4-way MUX QC System with an Agilent Zorbax SB C8, 21.2 × 250 mm column and eluting with 0.1 % trifluoroacetic acid in MeCN:H_2O (4:1), Flow = 25 mL/min. HPLC MS data is displayed in Table 6 (library members in bold also have ^{1}H NMR data for the reversed phase HPLC-purified indoles as listed below).

Yields of indoles 359 synthesised (purities in parenthesis)								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
a	66 (89)	72 (97)	78 (81)	53 (70)	64 (88)	72 (94)	68 (71)	*
b	**62 (69)**	55 (77)	**35 (78)**	61 (84)	**67 (47)**	**74 (70)**	**59 (60)**	*
c	**53 (79)**	48 (80)	37 (83)	56 (69)	**57 (77)**	**37 (43)**	46 (16)	*
d	*	*	56 (54)	63 (44)	65 (50)	80 (46)	*	*
e	**60 (66)**	62 (91)	30 (73)	72 (87)	**64 (29)**	35 (32)	39 (24)	*
f	65 (41)	76 (8)	65 (39)	60 (64)	43 (27)	30 (35)	39 (18)	*
g	57 (36)	*	*	*	92 (33)	89 (21)	71 (20)	*
h	50 (70)	73 (64)	41 (59)	65 (100)	**52 (48)**	**41 (13)**	57 (43)	39 (84)
i	58 (21)	49 (55)	48 (15)	62 (41)	59 (18)	40 (35)	*	18 (12)
j	85 (64)	69 (57)	41 (61)	57 (55)	60 (51)	38 (67)	34 (63)	*
k	81 (86)	62 (91)	78 (71)	90 (75)	89 (78)	68 (77)	67 (84)	*
l	45 (91)	74 (91)	51 (94)	76 (86)	**64 (64)**	48 (70)	42 (13)	*

* MW of product not detected

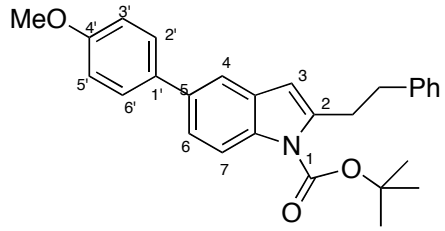
Table 5

HPLC retention times (min) for indoles **359** (detected $M+H^+$ in parenthesis)								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
a	1.73 (440.2)	1.61 (378.2)	1.88 (454.2)	1.44 (441.2)	1.73 (470.2)	1.49 (550.3)	2.00 (547.3)	*
b	5.30 (427.2)	4.75 (365.2)	6.32 (441.2)	1.42 (428.2)	5.33 (457.3)	3.93 (487.2)	7.46 (534.3)	*
c	7.22 (411.2)	6.41 (349.2)	8.72 (425.2)	1.58 (412.2)	7.23 (441.2)	5.17 (471.2)	5.24 (518.3)	*
d	*	*	6.03 (417.2)	1.40 (404.2)	5.14 (433.2)	3.79 (463.2)	*	*
e	4.90 (422.2)	4.43 (360.2)	5.87 (436.2)	1.35 (423.2)	4.92 (452.2)	3.66 (482.2)	6.86 (529.3)	*
f	5.64 (403.1)	1.44 (341.1)	6.78 (417.1)	1.45 (404.2)	5.99 (443.2)	4.19 (463.2)	8.02 (510.3)	*
g	1.26 (387.1)	*	*	*	3.83 (417.2)	1.52 (447.2)	2.06 (494.3)	*
h	4.34 (422.1)	3.93 (360.1)	5.15 (436.2)	1.33 (423.2)	4.40 (452.2)	3.35 (482.2)	5.92 (529.3)	1.45 (491.2)
i	3.89 (404.1)	3.46 (342.1)	4.59 (418.2)	1.26 (405.1)	3.92 (434.2)	2.98 (464.1)	*	1.48 (473.2)
j	8.57 (399.2)	7.55 (337.2)	11.52 (413.2)	1.49 (400.1)	9.12 (429.2)	6.17 (459.2)	5.33 (506.3)	*
k	1.51 (412.2)	1.44 (350.2)	4.97 (426.2)	1.28 (413.2)	1.53 (442.2)	1.37 (472.2)	1.72 (519.3)	*
l	5.10 (399.2)	4.50 (337.2)	6.36 (413.2)	1.30 (400.2)	5.22 (429.2)	3.84 (459.2)	7.81 (506.3)	*

* MW of product not detected

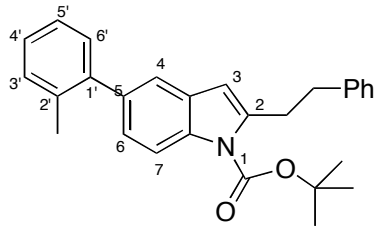
Table 6

***N*-Boc-5-(4'-methoxyphenyl)-2-(2''-phenylethyl)indole 359 Ab**.



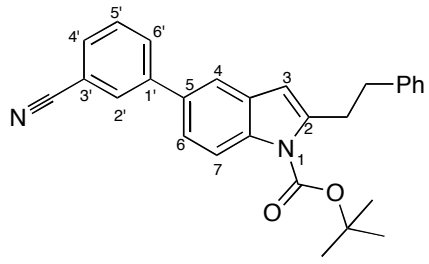
Data as reported under indole **351** above.

***N*-Boc-5-(2'-methylphenyl)-2-(2''-phenylethyl)indole 359 Ac**.



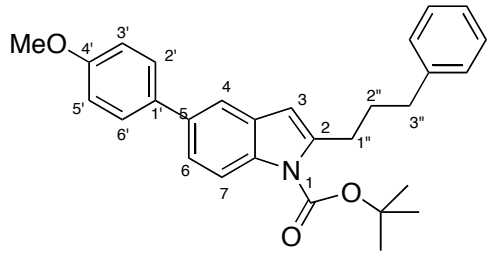
δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.28 (3H, s, CH_3) 3.04 (2H, t, *J* 7.6 Hz, C*H*$_2$Ph), 3.36 (2H, t, *J* 7.6 Hz, C*H*$_2$CH$_2$Ph), 6.39 (1H, s, H-3), 7.20 (1H, dd, 2.0 and 8.8 Hz, H-6) 7.22-7.32 (9H, m, Ph, H-3' to H-6'), 7.38 (1H, d, *J* 2.0 Hz, H-4), 8.09 (1H, d, *J* 8.8 Hz, H-7).

***N*-Boc-5-(3'-cyanophenyl)-2-(2''-phenylethyl)indole 359 Ae**.



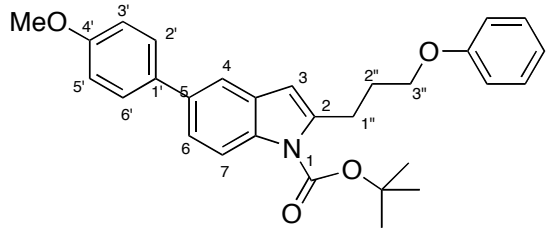
δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 3.05 (2H, t, *J* 7.8 Hz, C*H*$_2$Ph), 3.37 (2H, t, *J* 7.8 Hz, C*H*$_2$CH$_2$Ph), 6.41 (1H, s, H-3), 7.18-7.32 (5H, m, Ph) 7.44 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.53 (1H, dt, *J* 0.4 and 7.6 Hz, H-5'), 7.59-7.63 (2H, m, H-4 and H-6'), 7.86 (1H, ddd, *J* 1.2, 2.0 and 8.0 Hz, H-4'), 7.91-7.92 (1H, m, H-2'), 8.16 (1H, d, *J* 8.8 Hz, H-7).

***N*-Boc-5-(4'-methoxyphenyl)-2-(3''-phenylpropyl)indole 359 Cb**.



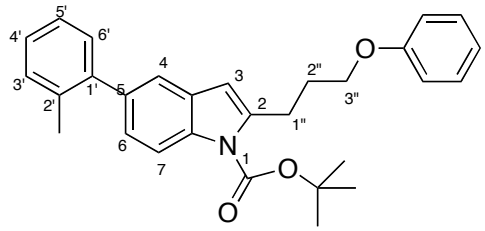
δ_H (400 MHz, $CDCl_3$): 1.68 (9H, s, ^{t}Bu), 2.00-2.10 (2H, m, $CH_2CH_2CH_2$) 2.75 (2H, t, *J* 7.6 Hz, CH_2Ph), 3.06 (2H, t, *J* 7.6 Hz, $CH_2CH_2CH_2Ph$), 3.85 (3H, s, OCH_3), 6.39 (1H, s, H-3), 6.98 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 7.17-7.32 (5H, m, Ph) 7.42 (1H, dd, 2.0 and 8.4 Hz, H-6), 7.56 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 7.60 (1H, d, *J* 1.6 Hz, H-4), 8.11 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-5-(4'-methoxyphenyl)-2-(3''-phenoxypropyl)indole 359 Eb**.



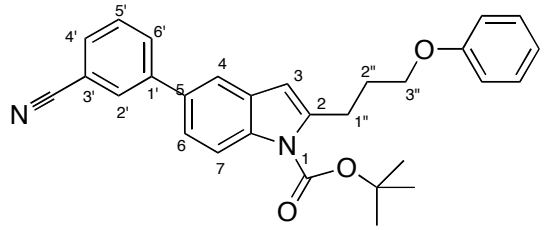
δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.21 (2H, tt, *J* 6.4 and 7.4 Hz, $CH_2CH_2CH_2$), 3.23 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2OPh$), 3.85 (3H, s, OCH_3) 4.06 (2H, t, *J* 6.4 Hz, CH_2OPh), 6.42 (1H, s, H-3), 6.89-6.98 (3H, m, Ph), 7.00 (2H, d, *J* 2.8 Hz, H-3' and H-5') 7.26-7.30 (2H, m, Ph) 7.43 (1H, dd, 2.0 and 8.4 Hz, H-6), 7.54 (2H, d, 8.8 Hz, H-2' and H-6'), 7.60 (1H, d, *J* 2.0 Hz, H-4), 8.10 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-5-(2'-methylphenyl)-2-(3"-phenoxypropyl)indole 359 Ec**.



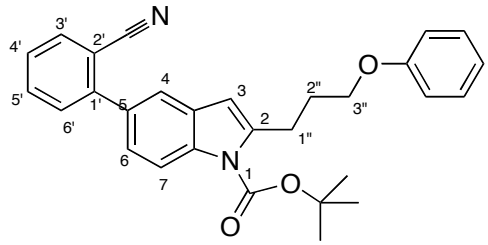
δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.22 (2H, tt, 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 2.28 (3H, s, CH_3) 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2OPh$), 4.07 (2H, t, *J* 6.2 Hz, CH_2OPh), 6.41 (1H, s, H-3), 6.90-6.96 (3H, m, Ph), 7.20 (1H, dd, 2.0 and 8.4 Hz, H-6), 7.22-7.26 (6H, m, H-3' to H-6' and Ph), 7.37 (1H, d, *J* 2.0 Hz, H-4), 8.10 (1H, d, *J* 8.4 Hz, H-7).

***N*-Boc-5-(3'-cyanophenyl)-2-(3"-phenoxypropyl)indole 359 Ee**.



δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.23 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2OPh$), 4.06 (2H, t, *J* 6.2 Hz, CH_2OPh), 6.44 (1H, s, H-3), 6.89-6.96 (3H, m, Ph), 7.26-7.31 (2H, m, Ph) 7.43 (1H, dd, *J* 2.0 and 8.8 Hz, H-6) 7.53 (1H, t, 7.6 Hz, H-5'), 7.59-7.63 (2H, m, H-4 and H-6'), 7.86 (1H, td, *J* 1.4 and 7.6 Hz, H-4'), 7.91 (1H, t, 1.6 Hz, H-2'), 8.17 (1H, d, *J* 8.8 Hz, H-7).

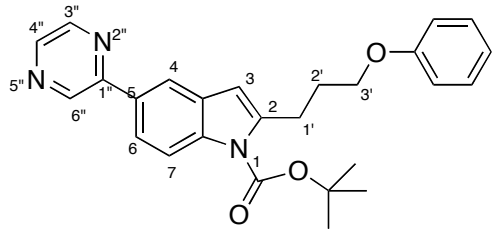
***N*-Boc-5-(2'-cyanophenyl)-2-(3"-phenoxypropyl)indole 359 Eh**.



δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$), 4.06 (2H, t, *J* 6.2 Hz, CH_2CH_2OPh), 6.45 (1H, s, H-3), 6.88-6.96 (3H, m, Ph), 7.26-7.31 (2H, m, Ph), 7.40-7.44 (2H, m, H-4' and H-6), 7.55 (1H,

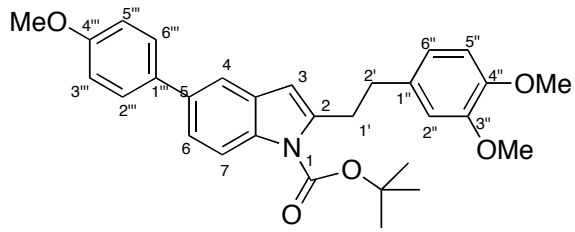
dd, 0.8 and 7.6 Hz, H-6'), 7.61-7.66 (2H, m, H-4 and H-5'), 7.77 (1H, dd, *J* 2.0 and 8.0 Hz, H-3'), 8.18 (1H, d, *J* 8.8 Hz, H-7).

_N_-Boc-2-(3'-phenoxypropyl)-5-(pyrazin-2"-yl)-indole 359 El.



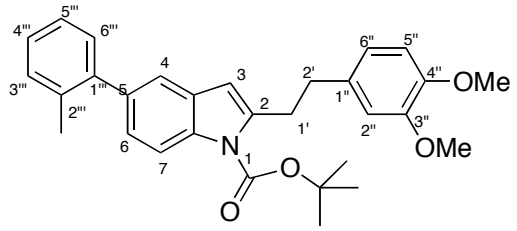
δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$), 4.07 (2H, t, *J* 6.2 Hz, CH_2CH_2OPh), 6.48 (1H, s, H-3), 6.89-6.97 (3H, m, Ph), 7.26-7.30 (2H, m, Ph) 7.90 (1H, dd, 1.6 Hz and 8.8 Hz, H-6), 8.12 (1H, d, 1.6 Hz, H-4), 8.21 (1H, d, *J* 8.8 Hz, H-7), 8.47 (1H, d, *J* 2.4 Hz, H-6"), 8.62 (1H, dd, *J* 1.6 and 2.4 Hz, H-5"), 9.08 (1H, d, *J* 1.6 Hz, H-3").

_N_-Boc-2-[2'-(3",4"-dimethoxyphenyl)ethyl]-5-(4"'-methoxyphenyl)indole 359 Fb.



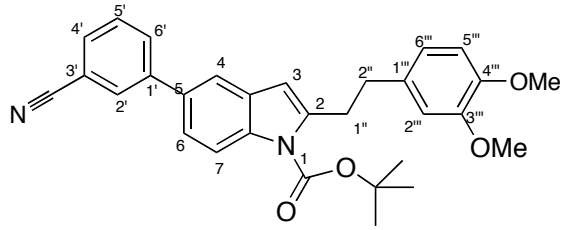
δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.97 (2H, t, *J* 7.8 Hz, CH_2Ph), 3.33 (2H, t, *J* 7.8 Hz, CH_2CH_2Ph), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.37 (1H, s, H-3), 6.73 (1H, d, *J* 1.6 Hz, H-2"), 6.77-6.80 (2H, m, H-5" and H-6"), 6.98 (2H, d, *J* 8.8 Hz, H-3"' and H-5"'), 7.44 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.55-7.60 (3H, m. H-4. H-2"' and H-6"'), 8.10 (1H, d, *J* 8.8 Hz, H-7).

***N*-Boc-2-[2'-(3'',4''-dimethoxyphenyl)ethyl]-5-(2'''-methylphenyl)indole 359 Fc**.



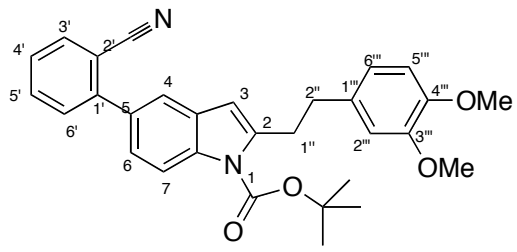
δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.29 (3H, s, ArC*H*$_3$), 2.98 (2H, t, *J* 7.8 Hz, H-2'), 3.33 (2H, t, *J* 7.8 Hz, H-1'), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.37 (1H, s, H-3), 6.73 (1H, s, H-2''), 6.81 (2H, s, H-5'' and H-6'', coincident), 7.20 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.23-7.28 (4H, m, H-3''' to H-6'''), 7.37 (1H, d, *J* 2.0 Hz, H-4), 8.09 (1H, d, *J* 8.8 Hz, H-7).

***N*-Boc-5-(3'-cyanophenyl)-2-[2''-(3''',4'''-dimethoxyphenyl)ethyl]indole 359 Fe**.



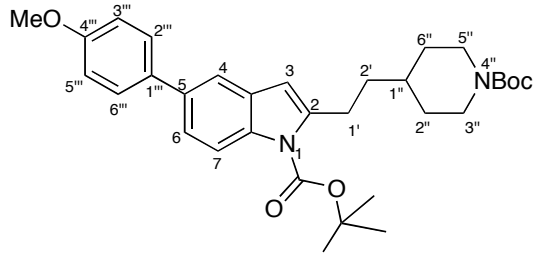
δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.98, (2H, t, *J* 7.6 Hz, H-2''), 3.34 (2H, t, *J* 7.6 Hz, H-1''), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.33 (1H, s, H-3), 6.73 (1H, d, *J* 1.6 Hz, H-2'''), 6.74-6.82 (2H, m, H-5''' and H-6'''), 7.45 (1H, dd, 2.0 and 8.4 Hz, H-6), 7.52 (1H, dt, *J* 0.4 and 7.8 Hz, H-5'), 7.59-7.63 (2H, m, H-4 and H-6'), 7.86 (1H, td, *J* 1.6 and 8.0 Hz, H-4'), 7.91 (t, *J* 1.4 Hz, H-2'), 8.17 (1H, d, *J* 8.8 Hz, H-7).

***N*-Boc-5-(2'-cyanophenyl)-2-[2''-(3''',4'''-dimethoxyphenyl)ethyl]indole 359 Fh**.



δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.98, (2H, t, *J* 7.8 Hz, H-2"), 3.34 (2H, t, *J* 7.8 Hz, H-1"), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.42 (1H, s, H-3), 6.72-6.82 (3H, m, H-2"', H-5"' and H-6"'), 7.40-7.45 (2H, m, H-4' and H-6), 7.55 (1H, dd, 0.8 and 7.6 Hz, H-6'), 7.62-7.66 (2H, m, H-4 and H-5'), 7.77 (1H, dd, *J* 0.8 and 7.6 Hz, H-3'), 8.18 (1H, d, *J* 8.4 Hz, H-7).

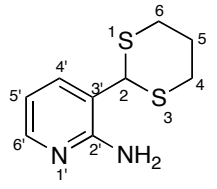
_N_-Boc-2-[2'-(_N_-Boc-piperidin-4"-yl)ethyl]-5-(4"'-methoxyphenyl)indole 359 Gb



δ_H (400 MHz, $CDCl_3$): 1.06-1.25 (2H, m, piperidine), 1.46 (9H, s, ^{t}Bu), 1.49-1.78 (5H, m, piperidine), 1.70 (9H, s, ^{t}Bu), 2.60-2.70 (2H, m, CH_2CH_2CH), 3.05 (2H, t, *J* 7.6 Hz, H-1'), 3.86 (3H, s. OCH_3), 4.05-4.20 (2H, m, 2 × CH^AH^BN), 6.37 (1H, s, H-3), 6.99 (2H, d *J* 8.8 Hz, H-3'" and H-5'") 7.43 (1H, dd, 2.0 and 8.8 Hz, H-6), 7.55 (2H, d, *J* 8.8 Hz, H-2'" and H-6'"), 7.58 (1H, d, *J* 2.0 Hz, H-4), 8.08 (1H, d, *J* 8.8 Hz, H-7).

7-AZAINDOLE WORK

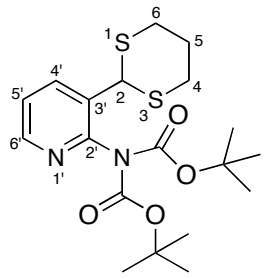
2-(2'Aminopyridin-3'-yl)-1,3-dithiane 363



Boron trifluoride diethyletherate (1.84 mL, 14.7 mmol) was added drop-wise to a stirred solution of 2-aminopyridin-3yl carboxyaldehyde **362** (1.510 g, 12.3 mmol) in toluene (25 mL) and the resulting cloudy suspension was stirred vigorously. The reaction mixture was then cooled with an ice bath as 1,3-propandithiol (1.48 mL, 14.7 mmol) was added drop-wise. The reaction was allowed to reach RT before being heated to reflux overnight. The cloudy suspension became transparent yellow during heating. After 24 h the mixture was

allowed to cool and stirred at RT for a further 48 h. After this time the reaction mixture was quenched with water. The organic layer extracted with DCM (2 × 250 mL) and the combined organics washed with 1M NaOH (2 × 250 mL), water (2 × 250 mL) and dried over ($MgSO_4$). Removal of solvent in *vacuo* gave yellow solid. The resulting solid was washed with ether to give target compound **363** as a yellow powder (1.86 g, 71 %). R_f [SiO_2; hexane: EtOAc (4:2)]: 0.14. υ_{max}(Golden gate)/cm^{-1}: 1573 (Ar-H), 1612 (NH_2), 2898 (C=N–C). δ_H (400 MHz, $CDCl_3$): 1.87-1.98 (1H, m, H_{ax}-5), 2.16-2.22 (1H, m, H_{eq}-5), 2.94 (2H, dt, *J* 3.3 Hz and 13.8 Hz, H_{eq}-4 and H_{eq}-6), 3.08 (2H, td, *J* 3.6 Hz and 14.0 Hz, H_{ax}-4 and H_{ax}-6), 5.00 (2H, broad s, NH_2), 5.18 (1H, s, H-2), 6.69 (1H, dd, *J* 4.8 Hz and 7.7 Hz, H-5'), 7.55 (1H, dd, *J* 1.8 Hz and 7.7 Hz, H-4'), 8.05 (1H, dd, *J* 1.8 Hz and 4.8 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 25.14 (CH_2), 31.78 (CH_2), 48.01 (CH), 114.59 (CH), 117.59 (C), 136.67 (CH), 148.13 (CH), 156.16 (C). (m/z): LRMS (EI^+): 212 ($M^{+\cdot}$, 92 %), 137 (100). HRMS 212.0442. $C_9H_{12}N_2S_2$ requires 212.0440.

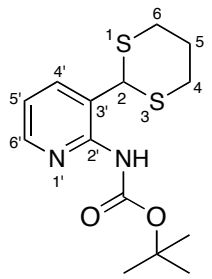
2-[2'-aminodicarbamate]-pyridin-3'-yl-1,3-dithiane 364



A solution of 2-(2'Aminopyridin-3'-yl)-1,3-dithiane **363** (3.011 g, 14.2 mmol) and di-tert-butyl dicarbonate (7.432 g, 34.1 mmol) in THF (50 mL) was heated until reflux for 15 h under argon. After this time the reaction mixture was quenched with water. The organic layer extracted with DCM (2 × 250 mL) and the combined organics washed with sat. $NaCl_{(aq)}$ (2 × 200 mL), water (2 × 200 mL) and dried over ($MgSO_4$). Removal of solvent in *vacuo* gave a thick pale green oil. The resulting oil was triturated with pet.ether (40/60 °C) to give a yellow powder. The powder was then washed copiously via soxhlet with pet.ether (40/60 °C) overnight, to give target compound **364** as a yellow powder. (2.620 g, 52 %). R_f [SiO_2, hexane: EtOAc (4:2)]: 0.41. υ_{max}(Golden Gate)/cm^{-1}: 1729 (C=O), 2929 (CH_3). δ_H (400 MHz, $CDCl_3$): 1.36 (18H, s, 2xCH_3), 1.87-1.99 (1H, m, H_{ax}-5), 2.15-2.21 (1H, m, H_{eq}-5), 2.88 (2H, dt, *J* 3.7 Hz and 14.2 Hz, H_{eq}-4 and H_{eq}-6), 3.03 (2H, dt, *J* 2.3 Hz and 14.7 Hz, H_{ax}-4 and H_{ax}-6), 5.25 (1H, s, H-2), 7.33 (1H, dd, *J* 4.8 Hz and 7.8 Hz, H-5'),

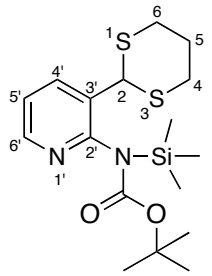
8.08 (1H, dd, *J* 1.8 Hz and 7.8 Hz, H-4'), 8.44 (1H, dd, *J* 1.8 Hz and 4.8 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 24.86 (CH_2), 27.79 (CH_3), 31.73 (CH_2), 45.13 (CH), 83.15 (C), 123.83 (CH), 132.35 (C), 138.26 (CH), 148.31 (CH), 149.07 (C), 150.08 (C). m/z (EI): 412 ($M^{+\cdot}$, 76 %), 256 (100). HRMS: 412.1491. $C_{19}H_{28}N_2O_4S_2$, requires 412.1490.

2-[2'-aminocarbamate]-3'-pyridine-1,3-dithiane 365



TFA (0.79 mL, 10.3 mmol) was added drop-wise to a solution of 2-[2'-aminodicarbamate]-pyridin-3'-yl-1,3-dithiane **364** (1.721 g, 4.1 mmol) in DCM (40 mL) and the mixture allowed to stir for 15 h at RT under argon. After this time the reaction mixture was washed with $NaHCO_3$ until neutral, then water and dried over ($MgSO_4$). Removal of solvent in *vacuo* yielded a green oil. The resulting oil was purified via column chromatography (hexane/ EtOAc 2:1 then DCM/ methanol 9:1), to furnish NHBoc derivative 2-[2'-aminocarbamate]-3'-pyridine-1,3-dithiane **365** as yellow solid (0.580 g, 44 %). R_f [SiO_2, hexane/ EtOAc (2:1)]: 0.46. υ_{max}(Golden Gate)/cm^{-1}: 1472 (Ar), 1686 (C=O). δ_H (400 MHz, $CDCl_3$): 1.88-1.90 (1H, m, H_{ax}-5), 2.09-2.15 (1H, m, H_{eq}-5), 2.86 (2H, dt, *J* 3.4 Hz and 14.0 Hz, H_{eq}-4 and H_{eq}-6), 3.00 (2H, dt, *J* 2.3 Hz and 14.4 Hz, H_{ax}-4 and H_{ax}-6), 5.22 (1H, s, H-2), 7.0 (1H, dd, *J* 4.8 Hz and 7.7 Hz, H-5'), 7.60 (1H, broad s, NH), 7.76 (1H, dd, *J* 1.8 Hz and 7.7 Hz, H-4'), 8.33 (1H, dd, *J* 1.8 Hz and 4.8 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 27.27 (CH_3), 30.75 (CH_2), 46.13 (CH_2), 79.95 (CH), 119.33 (CH), 124.77 (C), 136.89 (CH), 147.47 (CH), 148.03 (C), 152.84 (C). m/z (EI): 312 ($M^{+\cdot}$, 54 %), 267 (74), 256 (100). HRMS: 312.0966. $C_{14}H_{20}N_2O_2S_2$ requires 312.0967.

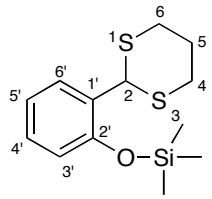
2-[2'-aminosilylcarbamate]-3'-pyridine-1,3-dithiane 366



A solution of lithium diisopropylamide (1.40 mL, 2.0M, 2.8 mmol) was added drop-wise to a cooled (–78 °C) stirred solution of carbamate **365** (0.751 g, 2.4 mmol) and TMSCl (0.36 mL, 2.9 mmol) in THF (10 mL) at –78 °C under an inert atmosphere of argon. The reaction mixture was then allowed to warm to RT over 45 min and was allowed to stir for a further 1 h at RT. After this time, the solvent was removed in *vacuo* and ether (20 mL) was added. The resulting white solid was filtered off and the ethereal solution concentrated to furnish target silylcarbamate **366** as an off white solid (0.890 g, 98 %). δ_H (400 MHz, $CDCl_3$): 0.33 (9H, s, Si-C$\underline{H}_3$), 1.87-1.89 (1H, m, H_{ax}-5), 2.06-2.12 (1H, m, H_{eq}-5), 2.83 (2H, dt, *J* 3.4 Hz and 14.0 Hz, H_{eq}-4 and H_{eq}-6), 2.98 (2H, dt, *J* 2.3 Hz and 14.4 Hz, H_{ax}-4 and H_{ax}-6), 5.19 (1H, s, H-2), 7.08 (1H, dd, *J* 4.8 Hz and 7.7 Hz, H-5'), 7.73 (1H, dd, *J* 1.8 Hz and 7.7 Hz, H-4'), 8.30 (1H, dd, *J* 1.8 Hz and 4.8 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 0.62 (CH_3), 27.24 (CH_3), 30.72 (CH_2), 46.10 (CH_2), 79.92 (CH), 119.31 (CH), 124.72 (C), 136.84 (CH), 147.43 (CH), 148.00 (C), 152.81 (C).

SPIROACETAL WORK

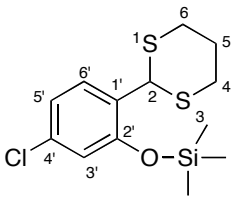
2-(2'-Trimethylsiloxyphenyl)-1,3-dithiane 105[81]



TMSCl (3.6 mL, 28 mmol, 1.2 eq) was added to a solution of 2-(2'-hydroxyphenyl)-1,3-dithiane (5.0 g, 24 mmol) in pyridine (50 mL). After 20 h, the reaction mixture was diluted with Et_2O (180 mL) and washed with water (5 ×), 1 M aqueous $CuSO_4$, water (2 ×) and brine and then dried over Na_2SO_4 and concentrated *in vacuo* to give TMS ether **105** as a

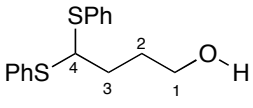
yellow oil (6.60 g, 98 %). δ_H (400 MHz, $CDCl_3$): 0.32 (9H, s, 3xCH_3) 1.84-1.98 (1H, m, H_{ax}-5), 2.12-2.29 (1H, m, H_{eq}-5), 2.90 (2H, td, *J* 3.7 Hz and 14.2 Hz, H_{eq}-4 and H_{eq}-6), 3.05 (2H, dt, *J* 2.5 Hz and 14.2 Hz, H_{ax}-4 and H_{ax}-6), 5.52 (1H, s, H-2), 6.78 (1H, dd, *J* 1.2 Hz and 8.2 Hz, H-3'), 6.92 (1H, dt, *J* 1.2 Hz and 7.6 Hz, H-5'), 7.15 (1H, dt, *J* 2.1 Hz and 7.9 Hz, H-4'), 7.52 (1H, d, *J* 7.6 Hz, H-6').

2-[4'-Chloro-2'-trimethylsiloxyphenyl]-1,3-dithiane 401



TMSCl (3.6 mL, 28 mmol, 1.2 eq) was added to a solution of 4'-chlorophenol-1,3 dithiane (5.0 g, 24 mol) in dry pyridine (50 mL). After 20 h, the reaction mixture was diluted with Et_2O (180 mL) and washed with water (5 ×), 1 M aqueous $CuSO_4$, water (2 ×) and brine and then dried over Na_2SO_4 and concentrated *in vacuo* to give TMS ether **401** as a yellow solid (6.60 g, 98 %). mp: 119 °C. υ_{max} (Golden Gate)/cm^{-1}: 1486 (Ar), 1568 (Ar), 2897 (CH), 2955 (CH). δ_H (400 MHz, $CDCl_3$): 0.44 (9H, s, Si-CH_3), 1.85-1.98 (1H, m, H_{ax}-5), 2.12-2.20 (1H, m, H_{eq}-5), 2.90 (2H, td, *J* 4.1 and 13.7 Hz, H_{eq}-4 and H_{eq}-6), 3.05 (2H, dt, *J* 2.5 and 13.6 Hz, H_{ax}-4 and H_{ax}-6), 5.44 (1H, s, H-2), 6.78 (1H, d, *J* 2.1 Hz, H-3'), 6.96 (1H, dd, *J* 2.1 and 8.3 Hz, H-5'), 7.47 (1H, d, *J* 8.3 Hz, H-6'). δ_C (100 MHz, $CDCl_3$): 0.04 (CH_3), 24.76 (CH_2), 31.99 (CH_2), 43.75 (CH), 119.14 (CH), 121.77 (CH), 128.25 (C), 129.62 (CH), 133.62 (C), 151.99 (C). m/z (CI^+): 321 [$(M+H)^+$ (^{37}Cl), 64 %)], 319 [$(M+H)^+$ (^{35}Cl), 100 %)]. HRMS: 319.0413 and 321.0385. $C_{13}H_{20}{}^{35}ClO_2S_2Si$ requires 319.0413, and $C_{13}H_{20}{}^{37}ClO_2S_2Si$ requires 321.0382.

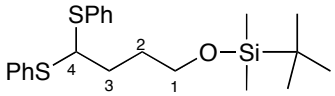
4,4-Bis(phenylthio)butan-1-ol 404[236]



2,3-Dihydrofuran (25 mL, 301 mmol) was added quickly to the rapidly stirred solution of thiophenol (68 mL, 661 mmol) in DCM (300 mL) at 0 °C, under argon and allowed to stir

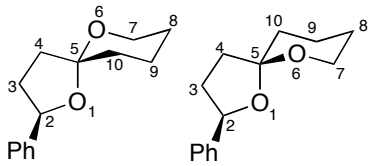
for 10 min. Boron triflouride diethyl etherate (42 mL) was added drop-wise to the cooled (0 °C) reaction mixture over a period of 45 min. The resulting mixture was then allowed to stir for 4 h at 0 °C before being quenched very carefully with water. The organic layer was extracted with DCM (3 × 250 mL) and the combined organics washed with 1 M NaOH (4 × 250 mL), sat. $NaCl_{(aq)}$ (1 × 200 mL) and dried ($MgSO_4$). Removal of solvent *in vacuo* gave the thioacetal **404** as an orange oil (94.2 g, 91 %), sufficiently pure for the next step. δ_H (400 MHz, $CDCl_3$): 1.48 (1H, broad s, OH), 1.79-1.92 (4H, m, H-2 and H-3), 3.63 (1H, t, *J* 6.4 Hz, H-4), 4.44 (1H, t, *J* 6.4 Hz, H-1), 7.38 (10H, m, 2 × SPh).

[4,4-Bis(phenylthio)but-1-oxy]-*tert*-butyl-dimethylsilane 405



1,1-Bis(phenylsulfanyl)butan-5-ol **404** (5.06 g, 17.2 mmol), was added to a solution of *tert*-butyl-dimethylsilyl chloride (2.73 g, 18.1 mmol) and imidazole (2.35 g, 34.5 mmol) in dry DCM (50 mL) at 0 °C, under argon. The resulting reaction mixture was then allowed to stir overnight at RT. After this time the reaction mixture was diluted with more DCM (100 mL), the resulting white precipitate removed by filtration and the organics concentrated to give a pale yellow oil. The oil was then treated with hot hexane-ethyl acetate (10:1), to give white needles that were removed by filtration. The filtrate was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the target compound **405** as a yellow oil (6.31 g, 91 %). υ_{max}: (Golden Gate)/cm^{-1}: 1439 (Ar), 1478 (Ar), 2928 (CH), 2953 (CH). δ_H (400 MHz, $CDCl_3$): 0.23 (6H, s, $SiMe_2$), 0.99 (9H, s, ^tBu), 1.93–1.99 (2H, m, H-2), 2.05–2.10 (2H, m, H-3), 3.74 (2H, t, *J* 6.0 Hz, H-4), 4.59 (1H, t, *J* 6.5 Hz, H-1), 7.36–7.52 (10H, m, 2 × SPh). δ_C (100 MHz, $CDCl_3$): –5.12 (CH_3), 18.37 (C), 25.74 (CH_3), 30.29 (CH_2), 32.53 (CH_2), 58.15 (CH), 62.52 (CH_2), 127.71 (CH), 129.07 (CH), 132.19 (CH), 134.06 (C). m/z (EI^+): 404 ($M^{+\bullet}$, 12 %), 295 ($M^{+\bullet}$ –$^\bullet$SPh, 100), 237 ($M^{+\bullet}$ –$^\bullet$SPh and –^{t}BuH, 78). HRMS: 404.1664. $C_{22}H_{32}OSiS_2$ requires 404.1663.

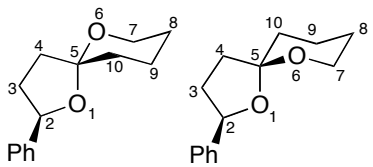
(2*RS*, 5*RS*)-2-Phenyl-1,6-dioxaspiro[4.5]decane and (2*RS*, 5*SR*)-2-Phenyl-1,6-dioxaspiro[4.5]decane 411



63:37 mixture of diastereomers

As per general method 1 for solution-phase synthesis of spiroacetals, thioacetal **405** (891 mg, 2.2 mmol, 1.2 eq) and γ-phenyl-γ-butyrolactone (302 mg 1.8 mmol, 1.0 eq) yielded a mixture of diastereomers of spiroacetals **411** as a brown oil. The resulting oil was purified *via* column chromatography (100 % Hexane then 100 % DCM), to furnish a 63:37 mixture of diastereomeric spiroacetals **411** as a yellow oil (189 mg, 47 %). R_f [SiO_2, 100 % DCM]: 0.26. ν_{max} (Golden Gate)/cm^{-1}: 1461 (Ar), 2894 (CH). δ_H (400 MHz, $CDCl_3$): 1.42-2.09 ($9H^{A\&B}$, m, CH_2), 2.10-2.18 ($1H^B$, m, H-3^B), 2.33-2.42 ($1H^A$, m, H-3^A), 3.51 ($1H^A$, ddt, *J* 2.2 Hz, 4.4 Hz and 11.3 Hz, H_{eq}-7^A), 3.60 ($1H^B$, dtd, *J* 2.2 Hz, 4.4 Hz and 11.3 Hz, H_{eq}-7^B), 3.81 ($1H^A$, dt, *J* 2.9 Hz and 11.3 Hz, H_{ax}-7^A), 3.89 ($1H^B$, dt, *J* 2.9 Hz and 11.5 Hz, H_{ax}-7^B), 4.88 ($1H^B$, dd, *J* 6.6 Hz and 9.6 Hz, H-2^B), 5.10 ($1H^A$, t, *J* 7.1 Hz, H-2^A), 7.15-7.36 ($5H^{A\&B}$, m, Ph). Assignment by COSY. δ_C (100 MHz, $CDCl_3$): 20.23 (CH_2), 20.27 (CH_2), 25.30 (CH_2), 25.37 (CH_2), 33.17 (CH_2), 33.86 (CH_2), 33.96 (CH_2), 34.40 (CH_2), 37.89 (CH_2), 39.59 (CH_2), 61.89 (CH_2), 61.99 (CH_2), 79.47 (CH), 83.18 (CH), 105.94 (C), 106.29 (C), 125.84 (CH), 126.74 (CH), 127.43 (CH), 127.56 (CH), 128.44 (CH), 128.50 (CH), 143.29 (C), 143.44 (C). m/z (CI^+): 219 [$(M+H)^+$, 100 %]. HRMS: 219.1385. $C_{14}H_{19}O_2$ requires $(M+H)^+$ 219.1384.

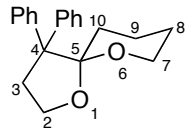
(2*RS*, 5*RS*)-2-Phenyl-1,6-dioxaspiro[4.5]decane and (2*RS*, 5*SR*)-2-Phenyl-1,6-dioxaspiro[4.5]decane 411



63:37 mixture of diastereomers

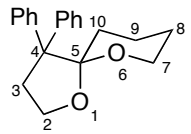
As per general method 2 for the synthesis of spiroacetals, thioacetal **405** (2.23 g, 5.5 mmol, 3.0 eq) and γ-phenyl-γ-butyrolactone (0.302 g 1.8 mmol, 1.0 eq) yielded a mixture of diastereomers of spiroacetals as a brown oil. The resulting oil was purified *via* column chromatography (100 % hexane then 100 % DCM), to furnish a 63:37 mixture of diastereomeric spiroacetals **411** A and B as a yellow oil (234 mg, 58 %). Data as above.

(5*RS*)-4,4-Diphenyl-1,6-dioxaspiro[4.5]decane 414



As per general method 1, α,α-diphenyl-γ-butyrolactone (311 mg 1.2 mmol, 1.0 eq) and thioacetal **405** (612 mg, 1.51 mmol, 1.2 eq), furnished spiroacetal **414** as yellow oil. Column chromatography eluting with hexane-DCM (1:1) gave the spiroacetal as a white solid (148 mg, 40 %). mp: 85 °C. R_f [SiO_2, hexane-DCM (1:1)]: 0.14. υ_{max}(Golden Gate)/cm^{-1}: 1442 (Ar), 1490 (Ar), 2941 (CH). δ_H (400 MHz, $CDCl_3$): 1.02 (1H, broad d, *J* 13.1 Hz, H_{eq}-10), 1.50-1.92 (5H, m, CH_2), 2.80-2.95 (2H, m, H-3), 3.72 (1H, broad dd, *J* 4.1 and 11.0 Hz, H_{eq}-7), 3.88 (1H, dt, *J* 2.6 and 11.1 Hz, H_{ax}-7), 4.09 (1H, ddd, *J* 4.9, 8.6 and 10.0 Hz, H-2), 4.22 (1H, dt, *J* 6.6 and 8.7 Hz, H-2), 6.97-6.99 (2H, m, ArH), 7.12-7.36 (6H, m, ArH), 7.44-7.46 (2H, m, ArH). δ_C (100 MHz, $CDCl_3$): 19.14 (CH_2), 23.88 (CH_2), 29.61 (CH_2), 39.11 (CH_2), 60.15 (CH_2), 60.67 (C), 62.56 (CH_2), 105.68 (C), 124.58 (CH), 124.80 (CH), 126.26 (CH), 126.45 (CH), 127.61 (CH), 128.32 (CH), 144.22 (C), 145.38 (C). m/z (CI^+): 295 ($M+H^+$, 100 %). HRMS: 295.1698. $C_{20}H_{23}O_2$ requires $M+H^+$, 295.1699.

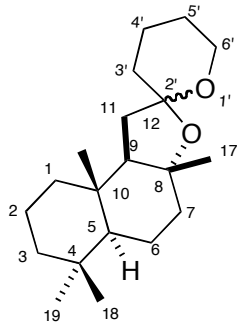
(5*RS*)-4,4-Diphenyl-1,6-dioxaspiro[4.5]decane 414



In the same way per general method 2, thioacetal **405** (1.52 g, 3.7 mmol, 3.0 eq) and α,α-diphenyl-γ-butyrolactone (311 mg 1.2 mmol, 1.0 eq) gave spiroacetal **414** as a yellow

solid, recrystallisation from methanol gave the purified spiroacetal as a solid (189 mg, 51 %). Date as above.

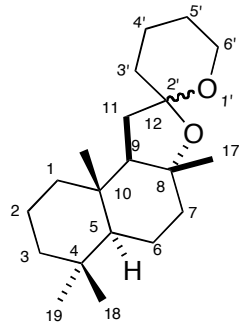
(12*R*)-4',5'-Dihydro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-pyran] and (12*S*)-4',5'-dihydro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-pyran] 416



73:27 mixture of diastereomers

As per general method 1, 3aR-(+)-sclareolide (312 mg, 1.2 mmol, 1.0 eq) thioacetal **405** (0.582 g, 1.4 mmol, 1.2 eq), furnished a 73:27 mixture of epimeric spiroacetals **416** as a yellow solid (226 mg, 60 %), recrystallisation from methanol isolated the major diastereomer as a solid (161 mg, 44 %). mp: 116 °C. $[\alpha]_D^{18}$ + 49.1 (*c* 0.1 M, DCM). ν_{max} (Golden Gate)/cm^{-1}: 2931 (CH). δ_H (400 MHz, $CDCl_3$): 0.78 (3H, s, CH_3), 0.84 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.89–0.95 (2H, m, CH_2), 1.05–1.12 (1H, m, CH_2), 1.21 (3H, s, CH_3), 1.21-1.77 (16H, m, CH_2), 1.87 (1H, td, *J* 3.2 Hz and 11.3 Hz), 3.56 (1H, broad d, *J* 11.6 Hz), 3.89 (1H, dt, *J* 3.1 Hz and 11.3 Hz). δ_C (100 MHz, $CDCl_3$): δ 15.18 (CH_3), 18.37 (CH_2), 19.62 (CH_2), 20.53 (CH_2), 21.08 (CH_3), 23.07 (CH_3), 25.30 (CH_2), 33.11 (C), 33.53 (CH_3), 36.02 (C), 36.89 (CH_2), 37.05 (CH_2), 39.75 (CH_2), 40.40 (CH_2), 42.50 (CH_2), 57.10 (CH), 60.24 (CH), 62.74 (CH_2), 82.31 (C), 106.04 (C). m/z (EI$^+$): 306 ($M^{+\bullet}$, 13 %), 291 ($M^{+\bullet}$ –$^{\bullet}CH_3$, 37), 111 (100). HRMS: 306.2559. $C_{20}H_{34}O_2$ requires 306.2562.

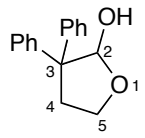
(12*R*)-4',5'-Dihydro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-pyran] and (12*S*)-4',5'-dihydro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-pyran] 416



73:27 mixture of diastereomers

In the same way per general method 2, thioacetal **405** (1.45 g, 3.6 mmol, 3.0 eq) and 3aR-(+)-sclareolide (312 mg, 1.2 mmol, 1.0 eq) gave a mixture of epimeric spiroacetals **416** (264 mg, 72 % as a yellow solid, recrystallisation from methanol gave the major diastereomer as a solid (191 mg, 52 %). Data as above.

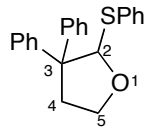
3,3-Diphenyltetrahydrofuran-2-ol 420



DiBAl-H (1.88 mL, 1.8 mmol) was added drop-wise to a cooled solution (–78 °C) of α,α-diphenyl-γ-butyrolactone (311 mg, 1.3 mmol) in dry toluene (10 mL). The resulting reaction mixture was then allowed to stir for 5 h at –78 °C. After this time the reaction was quenched by addition of methanol (1 mL) and the mixture warmed to 0 °C and diluted with water (1 mL). The mixture was then stirred with $MgSO_4$ and celite (5 g) for 20 min thereafter the resulting slurry was filtered through a pad of celite. The residue was washed with ether and the washings dried ($MgSO_4$). The organics were concentrated under reduced pressure to give lactol **420** as a yellow oil (243 mg, 81 %). υ_{max} (Golden Gate)/cm^{-1}: 1580 (Ar-H), 1598 (Ar-H) 3057 (OH). δ_H (400 MHz, $CDCl_3$): 2.42 (1H, ddd, *J* 1.7 Hz, 6.6 Hz, and 11.8 Hz, H-4), 3.02 (1H, ddd, *J* 8.8 Hz, 10.1 Hz and 11.8 Hz, H-4), 3.36 (1H, broad s, OH), 3.81 (1H, ddd, *J* 6.7 Hz, 8.3 Hz and 10.1 Hz, H-5), 4.27 (1H, dt, *J* 1.7 Hz and 8.8 Hz, H-5), 5.99 (1H, s, H-2), 7.15–7.45 (10H, m, Ar-H). δ_C (100 MHz, $CDCl_3$): 34.56 (CH_2), 59.98 (C), 66.34 (CH_2), 101.47 (CH), 126.44 (CH), 126.70 (CH), 127.33 (CH), 128.36

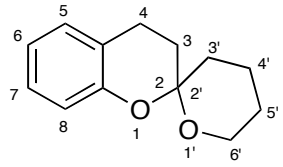
(CH), 128.46 (CH), 128.59 (CH), 143.37 (C), 145.01 (C). m/z, (CI^+): 241 [$(M+H)^+$, 43 %)], 223 (100, $(M+H)^+$, $-H_2O$). HRMS: 241.1229. $C_{16}H_{17}O_2$ requires 241.1226.

3,3-Diphenyl-2-phenylsulfanyltetrahydrofuran 422



Thiophenol (0.19 mL, 1.9 mmol) was added to a solution of lactol **420** (231 mg, 0.9 mmol), in dry DCM (10 mL) stirring under argon at 0 °C. $BF_3{\cdot}OEt_2$ (0.12 mL, 0.9 mmol) was added drop-wise to the cooled solution over 10 min. The resulting reaction mixture was then stirred for 4 h at 0 °C. After this time the reaction was quenched by addition of water. The organic layer separated, the aqueous layer washed with DCM (3 × 100 mL) and all organics combined. The organics were washed with 1 M NaOH (2 × 100 mL), then brine (100 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield **422** as orange oil (231 mg, 73 %). υ_{max} (Golden Gate)/cm^{-1}: 1582 (Ar), 1595 (Ar). δ_H (400 MHz, $CDCl_3$): 2.36 (1H, ddd, *J* 2.6 Hz, 7.3 Hz and 11.9 Hz, H-4), 3.15 (1H, td, *J* 9.4 Hz and 12.0 Hz, H-4), 3.83 (1H, ddd, *J* 7.4 Hz, 8.3 Hz and 9.3 Hz, H-5), 4.28 (1H, ddd, *J* 2.6 Hz, 8.4 Hz, 9.2 Hz, H-5), 6.21 (1H, s, H-2), 7.09–7.44 (15H, m, Ar-H). δ_C (100 MHz, $CDCl_3$): 30.14 (CH_2), 60.27 (C), 66.59 (CH_2), 94.46 (CH), 126.48 (CH), 127.07 (CH), 127.15 (CH), 127.30 (CH), 128.11 (CH), 128.33 (CH), 128.81 (CH), 128.88 (CH), 132.28 (CH), 135.16 (C), 143.26 (C), 146.08 (C). m/z, (EI^+): 332 ($M^{+\bullet}$, 7 %), 223 (100, $M^{+\bullet}$, $-{}^{\bullet}SPh$). HRMS: 332.1235. $C_{22}H_{20}OS$ requires 332.1238.

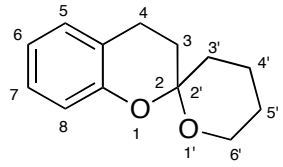
(2*RS*)-3,4,4',5'-Tetrahydrospiro[1-benzopyran-2,2'(3'*H*)-pyran] 424



As per general method 1, dihydrocoumarin (309 mg, 2.02 mmol, 1.0 eq) and thioacetal **405** (981 mg, 2.43 mmol, 1.2 eq), furnished the spiroacetal as a yellow oil. Column chromatography eluting with pet.ether-DCM (4:1) gave spiroacetal **424** as an oil (223 mg, 54 %). R_f [SiO_2, pet.ether-DCM (4:1)]: 0.22. υ_{max}(Golden Gate)/cm^{-1}: 1456 (Ar), 1491

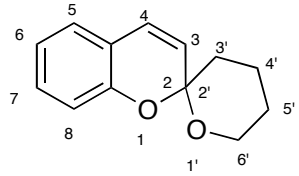
(Ar), 2845 (CH), 2874 (CH). δ_H (400 MHz, $CDCl_3$): 1.49–1.65 (4H, m), 1.72 (1H, dt, *J* 6.1 and 13.2 Hz), 1.77-1.83 (1H, m), 1.89 (1H, ddd, *J* 2.1, 6.4 and 13.4 Hz), 1.93–2.09 (1H, m), 2.53 (1H, ddd, *J* 1.9, 6.1 and 16.3 Hz), 2.93 (1H, ddd, *J* 6.4, 13.1, 16.3 Hz), 3.48–3.55 (1H, m), 3.73 (1H, dt, *J* 3.3 Hz and 11.5 Hz), 6.72–6.81 (2H, m), 6.95–7.06 (2H, m). δ_C (100 MHz, $CDCl_3$): 18.49 (CH_2), 21.04 (CH_2), 25.27 (CH_2), 31.94 (CH_2), 34.83 (CH_2), 61.84 (CH_2), 95.89 (C), 116.99 (CH), 120.56 (CH), 122.75 (C), 127.08 (CH), 129.25 (CH), 152.26 (C). m/z, (EI^+): 204 ($M^{+\bullet}$, 89 %), 131 (100, $M^{+\bullet}$, $-^{\bullet}C_4H_9O$). HRMS: 204.1150. $C_{13}H_{16}O_2$ requires 204.1151.

(2*RS*)-3,4,4',5'-Tetrahydrospiro[1-benzopyran-2,2'(3'*H*)-pyran] 424



In the same way per general method 2, thioacetal **405** (2.45 g, 6.1 mmol, 3.0 eq) and dihydrocoumarin (309 mg, 2.02 mmol, 1.0 eq) furnished the spiroacetal **424** as a yellow oil. Column chromatography eluting with pet.ether-DCM (4:1) gave the spiroacetal **424** as an oil (268 mg, 65 %). Data as above.

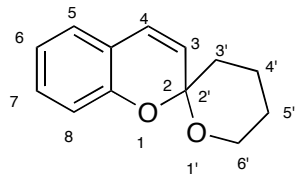
(2*RS*)-4',5'-Dihydrospiro[1-benzopyran-2,2'(3'*H*)-pyran] 425



As per general method 1, coumarin (308 mg, 2.05 mmol, 1.0 eq) and thioacetal **405** (992 mg, 2.46 mmol, 1.2 eq), furnished spiroacetal as a yellow oil. Column chromatography eluting with pet.ether-DCM (4:1) gave spiroacetal **425** as an oil (198 mg, 48 %). R_f [SiO_2, pet.ether-DCM (4:1)]: 0.24. υ_{max}(Golden Gate)/cm^{-1}: 1458 (Ar), 1488 (Ar), 1638 (C=C), 2851 (CH), 2923 (CH). δ_H (400 MHz, $CDCl_3$): 1.50–1.73 (4H, m), 2.00–2.18 (2H, m), 3.55 (1H, dd, *J* 4.6 Hz and 11.0 Hz), 3.93 (1H, dt, *J* 3.2 and 11.6 Hz), 5.67 (1H, d, *J* 9.6 Hz), 6.57 (1H, d, *J* 9.6 Hz), 6.83 (1H, t, *J* 7.4 Hz), 6.94 (1H, d, *J* 7.9 Hz), 7.06 (1H, dd, *J* 1.5 Hz and 7.5 Hz), 7.14 (1H, dt, *J* 1.6 Hz and 7.7 Hz). δ_C (100 MHz, $CDCl_3$): 18.55

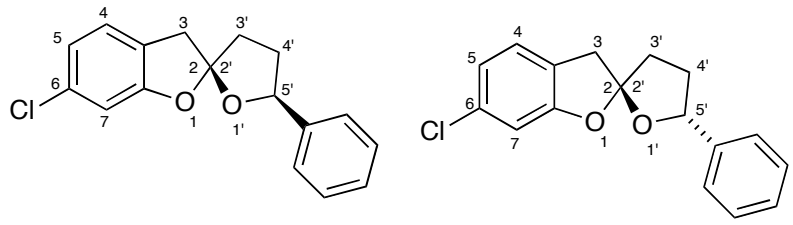
(CH_2), 24.77 (CH_2), 35.07 (CH_2), 61.79 (CH_2), 95.38 (C), 116.53 (CH), 121.23 (C), 121.45 (CH), 125.47 (CH), 126.04 (CH), 127.02 (CH), 129.19 (CH), 151.45 (C). m/z, (FAB^+): 203 [$(M+H)^+$, 100 %)]. HRMS: 203.1072. $C_{13}H_{15}O_2$ requires $M+H^+$ 203.1071.

(2*RS*)-4',5'-Dihydrospiro[1-benzopyran-2,2'(3'*H*)-pyran] 425



In the same way per general method 2, thioacetal **405** (2.48 g, 6.2 mmol, 3.0 eq) and coumarin (308 mg, 2.05 mmol, 1.0 eq) furnished spiroacetal as a yellow oil. Column chromatography eluting with pet.ether-DCM (4:1) gave spiroacetal **425** as an oil (238 mg, 57 %). Data as above.

(2'*RS*,5'*RS*)- and (2'*RS*,5'*SR*)-6-Chloro-4',5'-dihydro-5'-phenyl-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-furan} 426

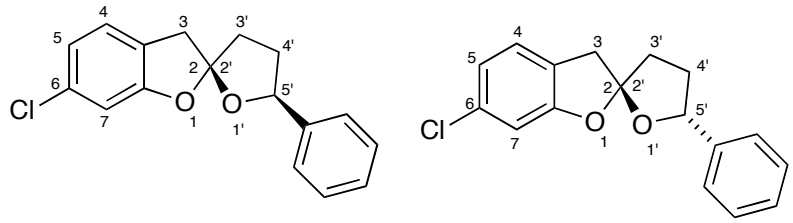


50:50 mixture of diastereomers

As per general method 1 for the synthesis of spiroacetals, dithiane **401** (0.71 g, 2.2 mmol, 1.2 eq.) and γ-phenyl-γ-butyrolactone (304 mg, 1.8 mmol, 1.0 eq.) yielded a mixture of diastereomeric spiroacetals as a yellow oil. The resulting oil was purified *via* column chromatography [pet.ether-DCM (1:1)], to furnish a 50:50 mixture of diastereomers **426** as an oil (181 mg, 38 %). R_f [SiO_2, pet.ether-DCM (1:1)]: 0.76. ν_{max} (golden gate)/cm^{-1}: 1451 (Ar), 1594 (Ar), 1609 (Ar), 2915 (CH), 2950 (CH). δ_H (400 MHz, $CDCl_3$): 2.01 ($1H^{A\ or\ B}$, dddd, *J* 4.4, 5.8, 9.7 and 12.4 Hz), 2.21-2.29 ($3H^{A\ or\ B}$), 2.44-2.53 ($3H^{A\ or\ B}$, m), 2.66 ($1H^{A\ or\ B}$, qd, *J* 8.3 and 12.4 Hz), 3.29 ($1H^{B}$, d, *J* 16.7 Hz), 3.34 ($1H^{B}$, d, *J* 16.7 Hz), 3.36 ($1H^{A}$, d, *J* 16.6 Hz), 3.45 ($1H^{A}$, d, *J* 16.6 Hz), 5.16-5.22 ($1H^{A\ or\ B}$, m), 5.34 ($1H^{A\ or\ B}$, dd, *J* 5.9 and 7.8 Hz), 6.80-6.86 ($2H^{A\&B}$, m), 7.05-7.09 ($1H^{A\&B}$, m), 7.24-7.44 ($5H^{A\&B}$, m, ArH). δ_C (100 MHz, $CDCl_3$): 32.28 (CH_2), 33.75 (CH_2), 35.60 (CH_2), 37.62 (CH_2), 37.77 (CH_2), 37.88

(CH_2), 80.61 (CH), 83.07 (CH), 109.58 (CH), 109.72 (CH), 118.73 (C), 118.97 (C), 119.93 (CH), 120.04 (CH), 123.94 (C), 123.96 (C), 124.51 (CH), 125.05 (CH), 125.36 (CH), 125.57 (CH), 126.97 (CH), 127.03 (CH), 127.83 (2xCH), 132.68 (C), 141.41 (C), 141.79 (C), 157.97 (C), 158.06 (C). m/z (CI^+): 289 [$(M+H)^+$ (^{37}Cl), 33 %], 287 [$(M+H)^+$ (^{35}Cl), 100 %)]. HRMS: 287.0839 and 289.0815. $C_{17}H_{16}{}^{35}ClO_2$ requires $(M+H)^+$ 287.0838, and $C_{17}H_{16}{}^{37}ClO_2$ requires $(M+H)^+$ 289.0816.

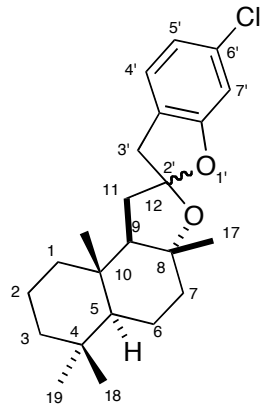
(2'*RS*,5'*RS*)- and (2'*RS*,5'*SR*)-6-Chloro-4',5'-dihydro-5'-phenyl-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-furan} 426



50:50 mixture of diastereomers

As per general method 2 for the synthesis of spiroacetals, dithiane **401** (1.76 g, 5.5 mmol, 3.0 eq.) and γ-phenyl-γ-butyrolactone (302 mg, 1.8 mmol, 1.0 eq.) yielded the epimeric spiroacetals **426** as a yellow oil. The resulting oil was purified by column chromatography [pet.ether-DCM (1:1)], to furnish a 50:50 mixture of diastereomers **426** A and B as an oil (249 mg, 47 %). Data as above.

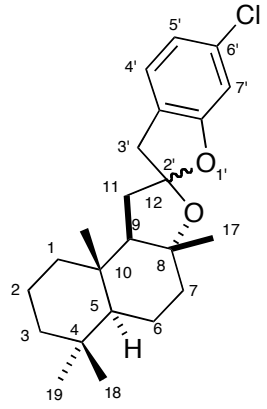
(12*R*)-6'-Chloro-spiro{8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-benzo[b]furan}
and (12*S*)-6'-chloro-spiro{8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-benzo[b]furan} 427



50:50 mixture of diastereomers

As per general method 1, 3aR-(+)-sclareolide (309 mg, 1.2 mmol, 1.0 eq) and dithiane **401** (464 mg, 1.44 mmol, 1.2 eq), gave a 50:50 mixture of epimeric spiroacetals as a yellow solid, recrystallisation from methanol gave a 60:40 mixture of spiroacetals **427** A and B as a white solid (229 mg, 51 %). mp: 128 °C. $[\alpha]_D^{18}$ + 11.7 (*c* = 0.1 M, DCM) ν_{max} (Golden Gate)/cm^{-1}: 1479 (Ar), 1610 (Ar), 2866 (CH), 2925 (CH). δ_H (400 MHz, $CDCl_3$): 0.84 ($3H^{A\&B}$, s, CH_3), 0.88 ($6H^B$ + $3H^A$, s), 0.91 ($3H^A$, s), 1.20 ($3H^B$, s), 1.35 ($3H^A$, s), 0.99–2.12 ($13H^{A\&B}$, m), 2.21 ($1H^B$, dd, *J* 3.4 and 10.1 Hz), 2.45 ($1H^A$, dd, *J* 12.8 and 14.1 Hz), 3.20 ($2H^A$, s), 3.23 ($2H^B$, s), 6.76–6.82 ($2H^{A\&B}$, m), 7.00–7.05 ($1H^{A\&B}$, m). δ_C (100 MHz, $CDCl_3$): δ 12.81 (CH_3), 13.13 (CH_3), 15.95 (CH_2), 15.98 (CH_2), 18.13 (CH_2), 18.49 (CH_2), 18.64 (CH_3), 18.67 (CH_3), 20.29 (CH_3), 20.59 (CH_3), 27.35 (CH_2), 31.11 (CH_3), 33.43 (CH_2), 33.98 (CH_2), 37.44 (CH_2), 37.59 (CH_2), 37.73 (CH_2), 39.10 (CH_2), 40.02 (CH_2), 40.05 (CH_2), 40.39 (CH_2), 54.40 (CH), 54.70 (CH), 56.35 (CH), 58.77 (CH), 81.91 (C), 82.33 (C), 107.73 (CH), 107.77 (CH), 115.70 (C), 116.73 (C), 118.08 (CH), 122.07 (C), 122.26 (C), 122.63 (CH), 122.68 (CH), 130.75 (C), 130.79 (C), 155.97 (C), 156.49 (C). m/z (EI^+): 376 [$M^{+\bullet}$ (^{37}Cl), 42 %)], 374 [$M^{+\bullet}$ (^{35}Cl), 78 %)], 191 (100, $M^{+\bullet}$ – $C_9H_8O_2Cl$). HRMS: 374.2013 and 374.1993. $C_{23}H_{31}{}^{35}ClO_2$ requires 374.2018, and $C_{23}H_{31}{}^{37}ClO_2$ requires 376.1989.

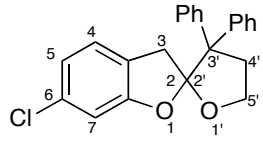
(12*R*)-6'-Chloro-spiro{8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-benzo[b]furan}
and (12*S*)-6'-chloro-spiro{8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'*H*)-benzo[b]furan} 427



50:50 mixture of diastereomers

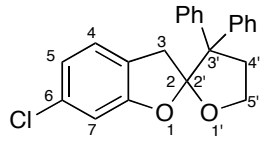
In the same way per general method 2, dithiane **401** (1.14 g, 3.6 mmol, 3.0 eq) and 3aR-(+)-Sclareolide (0.309 g, 1.2 mmol, 1.0 eq) gave a 50:50 mixture of epimeric spiroacetals as a yellow solid, recrystallisation from methanol gave a 60:40 mixture of spiroacetals **427** A and B as a white solid (277 mg, 62 %). Data as above.

6-Chloro-4',5'-dihydro-3',3'-diphenyl-spiro{benzo[b]furan-2(3*H*), 2'(3'*H*)-furan} 428



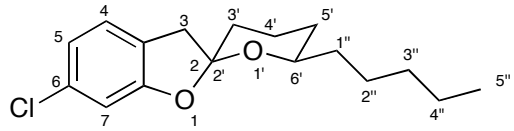
As per general method 1, α,α-diphenyl-γ-butyrolactone (306 mg, 1.3 mmol, 1.0 eq.) and dithiane **401** (482 mg, 1.5 mmol, 1.2 eq), yielded spiroacetal as a yellow powder. Recrystallisation from methanol gave purified spiroacetal **428** as a powder (209 mg, 46 %). mp: 138 °C. R_f [SiO_2, pet.ether-DCM (4:1)]: 0.19. υ_{max} (golden gate)/cm^{-1}: 1445 (Ar), 1596 (Ar), 1609 (Ar), 2889 (CH), 2985 (CH). δ_H (400 MHz, $CDCl_3$): 2.65 (1H, ddd, *J* 2.9 Hz, 7.6 Hz and 12.1 Hz, H-4'), 3.16 (1H, d, *J* 17.7 Hz, H-3), 3.25 (1H, ddd, *J* 8.7 Hz, 9.9 Hz and 12.2 Hz, H-4'), 3.55 (1H, d, *J* 17.7 Hz, H-3), 4.21 (1H, apparent q, *J* 8.3 Hz, H-5'), 4.35 (1H, ddd, *J* 2.9 Hz, 8.6 Hz and 9.9 Hz, H-5'), 6.59 (1H, d, *J* 2.1 Hz, H-7), 6.79 (1H, dd, *J* 2.1 and 8.0 Hz, H-5), 7.00 (1H, d, *J* 8.0 Hz, H-4), 7.10-7.14 (4H, m, Ar-H), 7.18-7.27 (6H, m, Ar-H). δ_C (100 MHz, $CDCl_3$): 36.59 (CH_2), 37.97 (CH_2), 61.39 (C), 65.54 (CH_2), 110.16 (CH), 120.44 (CH), 120.98 (C), 124.01 (C), 124.80 (CH), 126.42 (CH), 126.53 (CH), 127.86 (CH), 127.94 (CH), 128.07 (CH), 128.21 (CH), 133.11 (C), 142.70 (C), 144.96 (C), 158.10 (C). m/z, (CI^+): 365 [$(M+H)^+$ (^{37}Cl), 75 %], 363 [$(M+H)^+$ (^{35}Cl), 97 %], 211 (100 –C_8H_5OCl). HRMS: 363.1152 and 365.1132. $C_{23}H_{20}{}^{35}ClO_2$ requires $(M+H)^+$ 363.1151, and $C_{23}H_{20}{}^{37}ClO_2$ requires $(M+H)^+$ 365.1122.

6-Chloro-4',5'-dihydro-3',3'-diphenyl-spiro{benzo[b]furan-2(3*H*), 2'(3'*H*)-furan} 428



In the same way per general method 2, dithiane **401** (1.21 g, 3.8 mmol, 3.0 eq) and α,α-diphenyl-γ-butyrolactone (0.306 g, 1.3 mmol, 1.0 eq.) gave spiroacetal as a yellow powder. Recrystallisation from methanol gave purified spiroacetal **428** as a white powder (248 mg, 54 %). Data as above.

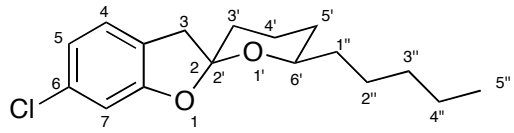
6-Chloro-4',5'-dihydro-6'-(pent-1"-yl)-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} 429



70:30 mixture of diastereomers

As per general method 1, δ-decanolactone (0.31 mL 1.7 mmol, 1.0 eq.) and dithiane **401** (671 mg, 2.1 mmol, 1.2 eq), yielded a 70:30 mixture of spiroacetals as a yellow oil. The resulting oil was purified via column chromatography [pet.ether-DCM (4:1)], to furnish the major diastereomer **429** as an oil (172 mg, 33 %). R_f [SiO_2, pet.ether-DCM (4:1)]: 0.36. ν_{max} (Golden Gate)/cm^{-1}: 1480 (Ar), 1591 **(**Ar), 1610 (Ar), 2858 (CH), 2951 (CH). δ_H (400 MHz, $CDCl_3$): 0.86 (3H, t, *J* 6.8 Hz, C-5"), 1.20-1.41 (8H, m, H-1" to H-4"), 1.42-1.49 (1H, m, H-3'), 1.65-1.80 (3H, m, H-3' and H-4'), 1.92-2.03 (2H, m, H-5'), 2.98 (1H, d, *J* 16.3 Hz, H-3), 3.06 (1H, d, *J* 16.3 Hz, H-3), 3.91-3.99 (1H, m, H-6'), 6.77-6.82 (2H, m, H-5 and H-7), 7.02 (1H, d, *J* 7.7 Hz, H-4). δ_C (100 MHz, $CDCl_3$): 13.07 (CH_3), 18.76 (CH_2), 21.60 (CH_2), 23.84 (CH_2), 29.07 (CH_2), 30.81 (CH_2), 33.00 (CH_2), 35.02 (CH_2), 41.44 (CH_2), 71.17 (CH), 109.41 (CH), 110.47 (C), 119.35 (CH), 124.00 (C), 124.40 (CH), 131.98 (C), 158.17 (C). m/z, (CI^+): 297 [$(M+H)^+$ (^{37}Cl), 85 %], 295 [$(M+H)^+$ (^{35}Cl), 100 %)]. HRMS: 295.1465 and 297.1441. $C_{17}H_{24}{}^{35}ClO_2$ requires $M+H^+$ 295.1461, and $C_{17}H_{24}{}^{37}ClO_2$ requires $M+H^+$ 297.1438.

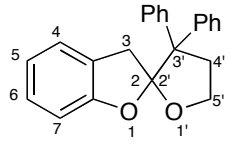
6-Chloro-4',5'-dihydro-6'-(pent-1"-yl)-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} 429



70:30 mixture of diastereomers

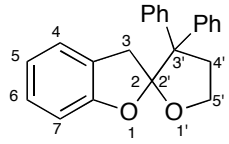
In the same way per general method 2, dithiane **401** (1.68 g, 5.3 mmol, 3.0 eq) and delta-decanolactone (0.31 mL, 1.7 mmol, 1.0 eq.) gave a 70:30 mixture of spiroacetals as a yellow oil. The resulting oil was purified via column chromatography [pet.ether-DCM (4:1)], to furnish the major diastereomer **429** as an oil (224 mg, 44 %). Data as above.

4',5'-Dihydro-3',3'-diphenylspiro{benzo[b]furan-2(3*H*),2'(3'*H*)-furan} 430



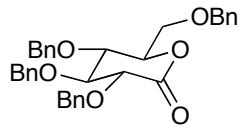
As per general method 1 for the synthesis of spiroacetals, dithiane **105** (0.42 g, 1.5 mmol, 1.2 eq) and α,α-diphenyl-γ-butyrolactone (306 mg, 1.3 mmol, 1.0 eq) yielded spiroacetal as a yellow powder. Recrystallisation from methanol gave spiroacetal **430** as a powder (191 mg, 46 %). mp: 142 °C. ν_{max} (Golden Gate)/cm^{-1}: 1461 (Ar), 1480 (Ar), 1598 (Ar), 2899 (CH). δ_H (400 MHz, $CDCl_3$): 2.70 (1H, ddd, *J* 3.1 Hz, 7.8 Hz and 12.3 Hz, H-4'), 3.17 (1H, d, *J* 17.4 Hz, H-3), 3.25 (1H, ddd, *J* 8.5 Hz, 9.9 Hz and 12.3 Hz, H-4'), 3.57 (1H, d, *J* 17.4 Hz, H-3), 4.22 (1H, apparent q, *J* 8.2 Hz, H-5'), 4.35 (1H, ddd, *J* 3.1 Hz, 8.6 Hz and 9.9 Hz, H-5'), 6.61 (1H, d, *J* 8.0 Hz, H-4), 6.81 (1H, dt, *J* 0.7 and 7.5 Hz, H-6), 7.03 (1H, t, *J* 7.5 Hz, H-5), 7.10 (1H, d, *J* 7.3 Hz, H-7), 7.13-7.29 (10H, m, Ar-H). δ_C (100 MHz, $CDCl_3$): 37.32 (CH_2), 38.39 (CH_2), 61.36 (C), 65.42 (CH_2), 109.59 (CH), 119.99 (C), 120.48 (CH), 124.43 (CH), 125.38 (C), 126.37 (CH), 126.56 (CH), 127.91 (CH), 128.00 (CH), 128.32 (CH), 128.40 (CH), 143.25 (C), 145.47 (C), 157.52 (C). m/z, (EI^+): 328 ($M^{+\bullet}$, 6 %), 194 (100, $M^{+\bullet}$, $-{}^{\bullet}C_8H_6O_2$). HRMS: 328.1463. $C_{23}H_{20}O_2$ requires 328.1465.

4',5'-Dihydro-3',3'-diphenylspiro{benzo[b]furan-2(3*H*),2'(3'*H*)-furan} 430



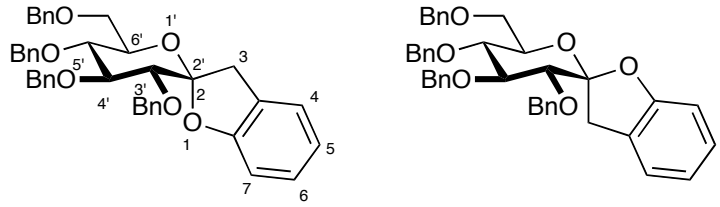
In the same way per general method 2, dithiane **105** (1.07 g, 3.8 mmol, 3.0 eq) and α,α-diphenyl-γ-butyrolactone (306 mg, 1.3 mmol, 1.0 eq) yielded spiroacetal as a yellow powder. Recrystallisation from methanol gave spiroacetal **430** as a powder (219 mg, 53 %). Data as above.

2,3,4,6-tetra-*O*-benzyl-D-glucolactone 432[254]



A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (0.811 g, 1.4 mmol) and activated 4 Å molecular sieves (1.48 g) in DCM (20 mL) was allowed to stir at RT for 15 min. Pyridinium chlorochromate (PCC) (1.462 g, 6.8 mmol) was then added and the resulting suspension allowed to stir at RT for 45 min. After this time, cyclohexane (20 mL) and Et_2O (40 mL) were added and the reaction mixture filtered through silica and concentrated under reduced pressure to give the lactone **432** as a thick oil (791 mg, 96 %). δ_H (400 MHz, $CDCl_3$): 3.59 (1H, dd, *J* 3.2 Hz and 11.2 Hz, H-6), 3.65 (1H, dd, *J* 2.4 Hz and 11.2 Hz, H-6), 3.82-3.90 (2H, m, H-3 and H-4), 4.05 (1H, d, *J* 6.4 Hz, H-2), 4.36-4.73 (8H, m, H-5 and C$\underline{H}_2$Ph), 4.92 (1H, d, *J* 11.2 Hz, C$\underline{H}^A$H^B).

(2*R*,3'*R*,4'*S*,5'*S*,6'*R*)-6'-(Benzyloxymethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} and (2*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6'-(Benzyloxymethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} 433

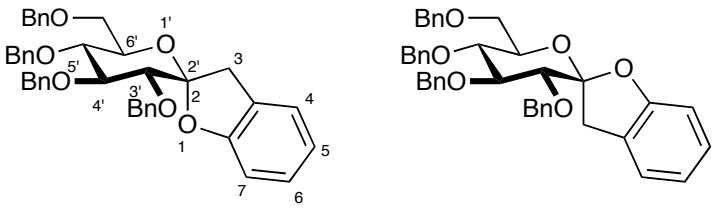


60:40 mixture of diastereomers

As per general method 1 for the synthesis of spiroacetals, dithiane **105** (189 mg, 0.67 mmol, 1.2 eq) and 2,3,4,6-tetra-*O*-benzyl-D-glucolactone **432** (306 mg, 0.56 mmol, 1.0 eq) yielded a 60:40 mixture of spiroacetals as a yellow oil. Column chromatography eluting with hexane-ethyl acetate (4:1) gave a 60:40 mixture of spiroacetals **433** as an oil (110 mg, 32 %). R_f [SiO_2, hexane-ethyl acetate (4:1)]: 0.51. υ_{max}(Golden Gate)/cm^{-1}: 1454 (Ar), 1496 (Ar), 1598 (Ar), 2856 (CH), 2925 (CH). δ_H (400 MHz, $CDCl_3$): 2.99 (1H^B, d, *J* 16.3 Hz, CCH^x *H*^{y} Ar), 3.13 (1H^A, d, *J* 16.4 Hz, CCH^x *H*^{y} Ar), 3.17 (1H^B, d, *J* 16.3 Hz, CC*H*^{x} H^y

Ar), 3.57 (1H^{A}, d, *J* 16.1 Hz, CC*H*^{x} H^{y} Ar), 3.57–4.26 (6H$^{A\&B}$, m, sugar CH and CH_2), 4.41–5.50 (8H$^{A\&B}$, m, 4 × C*H*$_2$Ph) 6.71–7.40 (24H$^{A\&B}$, m, ArH). Assignment by COSY. m/z, (FAB$^+$): 629 [(M+H)$^+$, 100 %)]. HRMS: 629.2824. $C_{41}H_{41}O_6$ requires M+H$^+$ 629.2821.

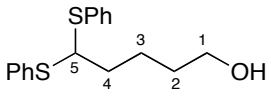
(2*R*,3'*R*,4'*S*,5'*S*,6'*R*)-6'-(Benzyloxymethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} and (2*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6'-(Benzyloxymethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3*H*),2'(3'*H*)-pyran} 433



60:40 mixture of diastereomers

In the same way per general method 2, dithiane **105** (474 mg, 1.67 mmol, 3.0 eq) and 2,3,4,6-tetra-*O*-benzyl-D-glucolactone **432** (306 mg 2.63 mmol, 1.0 eq) furnished a 60:40 mixture of spiroacetals as a yellow oil. Column chromatography eluting with hexane-ethyl acetate (4:1) gave a 60:40 mixture of spiroacetals **433** A and B as an oil (167 mg, 48 %). Data as above.

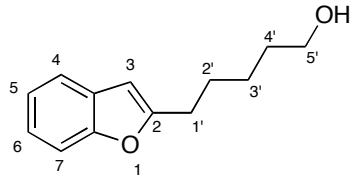
5,5-Bis(phenylthio)pentan-1-ol 435[236]



3,4-Dihydrofuran (3.8 mL, 50 mmol) was added quickly to the rapidly stirred solution of thiophenol (10.3 mL, 100 mmol) in DCM (50 mL) at 0 °C, under argon and allowed to stir for 10 min. Boron triflouride diethyl etherate (5.7 mL, 50 mmol) was added drop-wise to the cooled (0 °C) reaction mixture over a period of 45 min. The resulting mixture was then allowed to stir for 4 h at 0 °C before being quenched very carefully with water. The organic layer was extracted with DCM (3 × 100 mL) and the combined organics washed with 1 M $NaOH_{(aq)}$ (4 × 100 mL), sat. $NaCl_{(aq)}$ (1 × 50 mL) and dried ($MgSO_4$). Removal

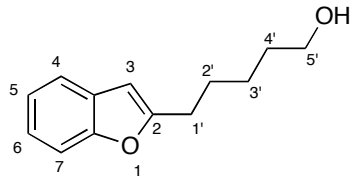
of solvent *in vacuo* gave target compound **435** as an orange oil (12.3 g, 83 %), sufficiently pure for the next step. δ_H (400 MHz, $CDCl_3$): 1.45 (1H, broad s, OH), 1.46-1.57 (2H, m, H-3), 1.63-1.74 (2H, m, H-2), 1.81-1.90 (2H, m, H-4), 3.59 (2H, t, *J* 6.4 Hz, H-1), 4.41 (1H, t, *J* 6.4 Hz, H-5), 7.23-7.47 (10H, m, 2 × SPh).

2-(5'-Hydroxypent-1'-yl)benzo[b]furan 442



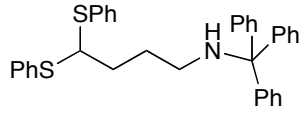
As per general method 1, ε-caprolactone (306 mg 2.63 mmol, 1.0 eq) and dithiane **105** (1.321 g, 3.15 mmol, 1.2 eq), furnished benzofuran as a yellow oil. Column chromatography eluting with hexane-DCM (4:1) gave benzofuran **442** as an oil (263 mg, 49 %). R_f [SiO_2, hexane-DCM (4:1)]: 0.21. υ_{max}(Golden Gate)/cm^{-1}: 1432 (Ar), 1587 (Ar), 2859 (CH), 2937 (CH), 3387 (OH). δ_H (400 MHz, $CDCl_3$): 1.33 (1H, s, OH), 1.33–1.38 (2H, m, H-4'), 1.46–1.53 (2H, m, H-3'), 1.68 (2H, quin, *J* 7.6 Hz, H-2'), 2.76 (2H, t, *J* 7.6 Hz, H-1'), 3.51 (2H, t, *J* 6.6 Hz, H-5'), 6.37 (1H, s, H-3), 7.04–7.13 (2H, m, ArH), 7.31 (1H, d, *J* 7.4 Hz, H-4), 7.38 (1H, dd, *J* 1.9 Hz and 7.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 25.31 (CH_2), 27.47 (CH_2), 28.38 (CH_2), 32.42 (CH_2), 62.78 (CH_2), 101.92 (CH), 110.69 (CH), 120.17 (CH), 122.38 (CH), 123.07 (CH), 128.93 (C), 154.58 (C), 159.32 (C). m/z, (CI^+): 205 [$(M+H)^+$, 100 %]. HRMS: 205.1229. $C_{13}H_{17}O_2$ requires $M+H^+$ 205.1225.

2-(5'-Hydroxypent-1'-yl)benzo[b]furan 442



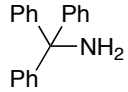
In the same way per general method 2, dithiane **105** (3.29 g, 7.9 mmol, 3.0 eq) and ε-caprolactone (306 mg 2.63 mmol, 1.0 eq) furnished benzofuran as a yellow oil. Column chromatography eluting with hexane-DCM (4:1) gave benzofuran **442** as an oil (328 mg, 61 %). Data as above.

_N_-[4,4-Bis(phenylsulfanyl)but-1-yl]-_N_-tritylamine 111[86]



Pyridine sulfur trioxide (5.481 g, 34.5 mmol) was added portion-wise to a stirred cooled (0 °C) solution of 1,1-bis(phenylsulfanyl)butan-5-ol **404** (2.521 g, 8.6 mmol), triethylamine (8.41 mL, 60.3 mmol) and DMSO (6.12mL, 86.2 mmol) in DCM (60 mL). The resulting reaction mixture was allowed to reach RT and stirred overnight. The reaction was cooled to 0 °C and quenched with water, followed by sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM (3 ×). All organics were combined, washed with water (3 ×) and then brine (1 ×). The organics were then dried ($MgSO_4$) and concentrated under reduced pressure to yield crude 1-bis(phenylsulfanyl)butyraldehyde **450** as a dark orange oil (4.561 g), which was used without further purification. Tritylamine (4.11 g, 15.8 mmol) was added to a solution containing crude aldehyde **450** (7.9 mmol) in dry MeOH (80 mL). 4Å Molecular sieves were added (2.0 g) and the mixture was heated under reflux overnight. After this time sodium borohydride (331 mg, 8.7 mmol) was added and the reaction left stirring for 4 h. After this time the reaction mixture was cooled to 0 °C and quenched with water. The layers separated and the aqueous layer extracted with DCM (3 ×). Combined organics were washed with brine and water alternately (3 ×), then dried ($MgSO_4$) and concentrated under reduced pressure to give crude **111** as orange oil. Column chromatography [pet.ether/ DCM (2:1), SiO_2)] gave a solid, which was then recrystallised in methanol to give _N_-[4,4-Bis(phenylsulfanyl)butyl]-_N_-tritylamine **111** as needles 1.26 g, 30 % yield, R_f [SiO_2, pet.ether- DCM, (2:1)] 0.12. δ_H (400 MHz, $CDCl_3$): 1.42 (1H, s, NH), 1.75-1.82 (2H, m, CH_2CH_2N), 1.90-1.95 (2H, m, $CH_2CH_2CH_2N$), 2.10 (2H, t, J 6.5 Hz, C$\underline{H_2}$N), 4.38 (1H, t, J 6.62 Hz, C$\underline{H}CH_2$), 7.16-7.21 (3H, m, Ar-H), 7.24-7.33 (12H, m, Ar-H), 7.38-7.52 (10H, m, Ar-H).

Tritylamine 451[255]



Following the procedure of Chadwick and co-workers, ammonia gas was condensed (300 mL) using a cold finger and dry ice. Trityl chloride (15 g, 54 mmol) was added and the reaction mixture stirred at –55 °C for 6 h. The reaction mixture was allowed to warm to RT and the ammonia evacuated overnight. After evaporation of ammonia, the resulting residue was washed with Et_2O. The white ppt formed upon addition of Et_2O was removed by filtration and the filtrate washed with 10 % Na_2SO_4 and then water. The organics were then dried ($MgSO_4$) and concentrated under reduced pressure to yield **451** as white solid (13.6 g, 97 %). δ_H (400 MHz, $CDCl_3$): 2.31 (2H, s, NH_2), 7.18-7.30 (15H, m, Ar-H).

REFERENCES

[1] Drews, J. *Science* **2000**, *287*, 1960.

[2] Farber, E. *The Evolution of Chemistry; a History of its Ideas, Methods and Materials*, Ronald Press, New York, **1952**, 173.

[3] Langley, J. N. *J. Physiol.* **1905**, *33*, 374.

[4] Tan, D. S. *Nat. Chem. Bio*. **2005**, *1*, 74.

[5] Lahana, R. *Drug Discovery Today* **1999**, *4*, 447.

[6] Kauver, L, M. *Chem. Bio*. **1995**, *2*, 107.

[7] Schreiber, S, L. *Science* **2000**, *287*, 1964.

[8] Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51.

[9] King, R. W. *Chem. Bio*. **1999**, *6*, 327.

[10] Dolle, R. E.; Nelson Jr, K. H. *J. Combinatorial Chem*. **1999**, *1*, 235.

[11] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893.

[12] Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfieldt, J. *J. Med. Chem*. **1988**, *31,* 2235.

[13] Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

[14] Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4708.

[15] Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954.

[16] Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 7430.

[17] Lewell, X. Q.; Judd, D. B.; Watson, S. P.; Hann, M. M. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 511.

[18] Merrifield, R. B. *J. Am. Chem. Soc.* **1963,** *85*, 2149.

[19] Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.

[20] Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82.

[21] Kerr, J. M.; Banville, S. C.; Zuckermann, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 2529.

[22] James, I. W. *Tetrahedron* **1999**, *55*, 4855.

[23] Wang, S. S. *J. Am. Chem. Soc*. **1973**, *95*, 1328.

[24] James, I. W. *Mol. Diversity* **1997**, *2*, 175.

[25] Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett*. **1998**, *29,* 4005.

[26] Chen, C.; Randall, L.; Miller, D.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc*. **1994**, *116*, 2661.

[27] Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev*. **2002**, *102*, 2607.

[28] Comely, A. C.; Gibson, S. E. *Angew. Chem. Int. Ed*. **2001**, *40*, 1012.

[29] Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.

[30] Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006.

[31] Spivey, A. C.; Diaper, C. M.; Adams, H. *J. Org. Chem.* **2000**, *65*, 5253.

[32] Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 211.

[33] Pourbaix, C.; Carreaux, F.; Carboni, B.; Deleuze, H. *J. Chem. Soc., Chem. Commun.* **2000**, 1275.

[34] Hughes, I. *Tetrahedron Lett.* **1996**, *37*, 7595.

[35] Gibson, S. E.; Hales, N. J.; Peplow, M. A. *Tetrahedron Lett.* **1999**, *40*, 1417.

[36] Bräse, S.; Enders, D.; Kobberling, J.; Avemarie, F. *Angew. Chem. Int. Ed.* **1998**, *37*, 3413.

[37] Pátek, M.; Lebl, M. *Biopoly*. **1998**, *47*, 353.

[38] Kenner, G. W.; Dermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636.

[39] Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia.* **1996**, *50*, 525.

[40] Ball, C. P.; Barrett, A. G. M.; Commerçon, A.; Compère, D.; Kuhn, C.; Roberts, R. S.; Smith, M. L.; Venier, O. *Chem. Commun.* **1998**, 2019.

[41] Barrett, A. G. M.; Procopiou, P. A.; Voigtmann, U. *Org. Lett*. **2001**, *3*, 3165.

[42] Gordon, D.W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47.

[43] Piscopio, A. D.; Miller, J. F.; Kock, K. *Tetrahedron Lett*. **1998**, *39*, 2667.

[44] Quabeck, U. *Synth. Commun*. **1985**, *15*, 855.

[45] Wothers, P.; Greeves, N.; Warren, S.; Clayden, J. *Organic Chemistry*, Oxford University Press Inc, New York, 2001, page 814.

[46] Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber*. **1958**, *91*, 61.

[47] Wadworth Jr. W. S.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733.

[48] Ager, D. J. *Org. React*. **1990**, *38*, 1.

[49] Julia, M. *Pure Appl. Chem*. **1985**, *57*, 763.

[50] Kelly, S. E. *Comprehensive Organic Synthesis* **1991**, *1*, 729.

[51] Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **1980**, 3270.

[52] Schrock, R. R. *Chem. Rev*. **2002**, *102*, 145.

[53] Hartley, R. C.; Jianfeng, Li.; Main, C, A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825.

[54] Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc*. **1978**, *100*, 3611.

[55] Dõrwald, F. W. *Metal Carbenes in Organic Synthesis* Wiley-VCH, **1999**.

[56] Hartley, R. C.; McKiernan, G, J. *J. Chem. Soc., Perkin Trans. 1*. **2002**, 2763.

[57] Fukuyama, T.; Liu, G. *Pure Appl. Chem*. **1997**, *69*, 501.

[58] Müller, M.; Lamottke, K.; Löw, E.; Magor-Veenstra, E.; Steglich, W. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 2483.

[59] Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem*. **1985**, *50*, 2316.

[60] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc*. **1990**, *112*, 6392.

[61] Payack, J. F.; Hughes, D. L.; Cai, D. W.; Cottrell, I. F.; Verhoeven, T. R. *Org. Prep. Proc. Int*. **1995**, *27*, 707.

[62] Hughes, D. L.; Payack, J. F.; Cai, D. W.; Verhoeven, T. R.; Reider, P. J. *Organometallics* **1996**, *15*, 663.

[63] Meurer, E. C.; Santos, L. S.; Pilli, R. A.; Eberlin, M. N. *Org. Lett.* **2003**, *5*, 1391.

[64] Petasis, A. N.; Lu, S.; Bzowej, E. I.; Fu, D.; Staszewski, J. P.; Akritopoulou-Zanze, I.; Patane, M. A.; Yong-Han, H. *Pure Appl. Chem*. **1996**, *68*, 667.

[65] Dollinger, L. M.; Howell, A. R. *J. Org. Chem*. **1996**, *61*, 7248.

[66] Dollinger, L. M.; Nakala, A. J.; Hashemzadeh, M.; Wang, G.; Wany, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem*. **1999**, *64*, 7074.

[67] Petasis, N. A.; Lu, S. *Tetrahedron Lett.* **1995**, *36*, 2393.

[68] Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909.

[69] Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327.

[70] Petasis, N. A.; Hu, Y. H. *J. Org. Chem*. **1997**, *62*, 782.

[71] Takeda, T.; Fujiwara, T. *Synlett* **1996**, 481.

[72] Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem. Int. Ed.* **1985**, *97*, 425.

[73] Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.

[74] Takeda, T.; Fujiwara, T. *Rev. Heteroatom. Chem*. **1999**, *21*, 93.

[75] Takeda, T.; Watanabe, M.; Nozaki, N.; Fujiwara, T. *Chem. Lett.* **1998**, 115.

[76] Takeda, T.; Saito, J.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 5571.

[77] Rahim, A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* **1998**, *39*, 2153.

[78] Takeda, T.; Sato, K.; Tsubouchi, A. *Synthesis* **2004**, 1457.

[79] Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Commun.* **2002**, 1974.

[80] Uddin, M. J.; Rao, P. N. P.; McDonald, R.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 439.

[81] Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387.

[82] Macleod, C.; Hartley, R. C.; Hamprecht, D. W. *Org. Lett.* **2002**, *4*, 75.

[83] McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389.

[84] Roberts, C. F.; Hartley, R. C. *J. Org. Chem.* **2004**, *69*, 6145.

[85] Macleod, C.; Austin, C. A.; Hamprecht, D. W.; Hartley, R. C. *Tetrahedron Lett.* **2004**, *45*, 8879.

[86] Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R, C. *Eur. J. Org. Chem*. 2006, 4998.

[87] Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

[88] Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

[89] Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Tetrahedron* **1995**, *51*, 1623.

[90] Takai, K.; Fujimura, O.; Katoaka, Y.; Utimoto, K. *Tetrahedron Lett*. **1989**, *30*, 211.

[91] Takai, K.; Katoaka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett*. **1988**, *29*, 1065.

[92] Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem*. **1987**, *52*, 4410.

[93] Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061.

[94] Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919.

[95] Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.

[96] Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209.

[97] Mortimore, M.; Kocienski, P. *Tetrahedron Lett.* **1988**, *29*, 3357.

[98] Takai, K.; Tezuka, M.; Kataoka, Y.; Utimoto, K. *Synlett* **1989**, 27.

[99] Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436.

[100] Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557.

[101] Guthrie, E. J.; Macritchie. J.; Hartley, R. C. *Tetrahedron Lett*. **2000**, *41*, 4987.

[102] Austin, A.; Smith, D.; Hartley, R. C. *J. Label. Compd. Radiopharm.* **2007**, *50*, 502.

[103] Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2005**, *105*, 2873.

[104] Davies, T. *Aromatic Heterocyclic Chemistry*, Oxford University Press Inc, New York, 1992, page 53.

[105] Bräse, S. *Bioorg. Med. Chem*. **2002**, *10*, 2415.

[106] Knepper, K.; Bräse, S. *Org. Lett*. **2003**, *5*, 2829.

[107] Armstrong, W. D.; liu, Y.-S.; He, L.; Ekborg-Ott, K. H. *J. Agric. Food Chem*. **2002**, 473.

[108] Humphrey, G.; Kuethe, J. *Chem. Rev*. **2006**, *106*, 2875.

[109] Spandoni, G.; Balsamini, C.; Bendini, A.; Diamantini, G.; Di Giacomo, B.; Tontini, A.; Tarzia, G. *J. Med. Chem*. **1998**, *41*, 3624.

[110] Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufeisen, S.; Lee, D. K. H, *J. Med. Chem.* **2000**, *43*, 1011.

[111] Mor, M.; Spandoni, G.; Di Giacomo, B.; Diamantini, G.; Bendini, A.; Tarzia, G.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Lucini, V.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *Bioorg. Med. Chem. Lett*. **2001**, *9*, 1045.

[112] Sebben, M; Ansanay, H; Bockaert, J; Dumuis. A. *Neuroreport* **1994**, *5*, 2553.

[113] Roth, B. L.; Craigo, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403.

[114] Sleight, A. J.; Monsma, F. J.; Borroni, E.; Austin, R. H.; Bourson, A. *Behav. Brain Res.* **1996**, *73*, 245.

[115] Grimaldi, B.; Bonnin, A.; Fillion, M.-P.; Ruat, M.; Traiffort, E.; Fillion, G. *Naunyn-Schmeideberg's Arch. Pharmacol.* **1998**, *357*, 393.

[116] Russell, M. G. N.; Baker, R. J.; Barden, L.; Beer, M. S.; Bristow, L.; Broughton, H. B.; Knowles, M.; McAllister, G.; Patel, S.; Castro, J. L. *J. Med. Chem*. **2001**, *44*, 3881.

[117] Sugimoto, Y.; Shimizu, A.; Kato, T.; Satoh, A.; Ozaki, S.; Ohta, H. Okamoto, O. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 3569.

[118] Meunier, J.-C. *Eur. J. Pharmacol*. **1997**, *1*, 340.

[119] Caron, S.; Vazquez, E.; Stevens, R. W.; Kazunari, N.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104.

[120] Riggs, J.; Kolesnikov, A.; Hendrix, J.; Young, W. B.; Shrader, W. D. Vijaykumar, D.; Stephens, R.; Liu, L.; Pan, L.; Mordenti. J.; Green, M. J.; Sukbuntherng. J. *Bioorg. Med. Chem. Lett*. **2006**, *16,* 2224.

[121] Kolesnikov, A.; Rai, R.; Young, W.B.; Mordenti, J.; Liu, L.; Torkelson, S.; Shrader, W.D.; Leahy, E. M.; Hu, H.; Gjerstad, E.; Janc, J.; Katz, B. A.; Sprengeler, P. A. *Bioorg. Med. Chem. Lett*. **2006**, *16,* 2243.

[122] Jablonski, J. A.; Grice, C. A.; Chai, W.; Dvorak, C. A.; Venable, J. D.; Kwok, A. K.; Ly, K. S.; Wei, J.; Baker, S. M.; Desai, P. J.; Jiang, W.; Wilson, S. J.; Thurmond, R. L.; Karlsson, L.; Edwards, J. P.; Lovenburg, T. W.; Carruthers, N. I. *J. Med. Chem.* **2003**, *46*, 3957.

[123] Perrault, W. R.; Shepard, P.; LaPean, L. A.; Krook, M. A.; Dobrowolski, P. J.; Lyster, M. A.; McMillan, M. W.; Knoechel, D. J.; Evenson, G. N.; Watt, W.; Pearlman, B. A. *Org. Process Res. Dev.* **1997**, *1*, 106.

[124] Yancopoulos, G. D.; Davis, S.; Gale, N. W.; Rudge, J. S.; Wiegand, S. J.; Holash, J. *Nature* **2000**, *407*, 242.

[125] Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M.; McNamara, J. *J. Org. Chem*. **2005**, *70*, 175.

[126] Masaki, Y. *Trends Pharmacol. Sci*. **2004**, *25*, 219.

[127] Kirchengast, M.; Luz, M. J. *Cardiovasc. Pharmacol*. **2005**, *45*, 182.

[128] Jeng, A. Y. *Curr. Opin. Invest. Drugs*. **2003**, *4*, 1076.

[129] Ergueden, J. K.; Krahn, T.; Schröder, C.; Stasch, J.-P.; Weigand, S.; Wild, H.; Brands, M.; Siegel, S.; Heimbach, D.; Keldenich, J. *Chem. Abstr*. **2003**, *138*, 3041.

[130] Brands, M.; Ergueden, J. K.; Hashimoto. K.; Heimbach, D.; Schröder, C.; Siegel, S.; Stasch, J.-P.; Weigand, S. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4201.

[131] Taber, D. F.; Tian, W. *J. Am. Chem. Soc*. **2006**, *128*, 1058.

[132] Tois, J.; Franzén, R.; Koskinen, A. *Tetrahedron* **2003**, *59*, 5395.

[133] Tois, J.; Franzén, R.; Aitio, O.; Laakso, I.; Kylänlahti, I. *J. Comb. Chem.* **2001**, *3*, 542.

[134] Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869.

[135] Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun*. **2003**, 1822.

[136] Mun, H.-S.; Ham, W. H.; Jeong, J.-H. *J. Comb. Chem*. **2005**, *7*, 130.

[137] Plunkett M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006.

[138] Wacker, D. A.; Kasireddy, P. *Tetrahedron Lett*. **2002**, *43*, 5819.

[139] Hughes, I. *Tetrahedron Lett*. **1996**, *37*, 7595.

[140] Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, *26*, 5963.

[141] Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.

[142] Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919.

[143] Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307.

[144] Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963.

[145] Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89.

[146] Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89.

[147] Wu, T. Y. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett.* **2001**, *3*, 3827.

[148] Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

[149] Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317.

[150] Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35,* 9333.

[151] Nicolaou, K. C.; Roecker, A. J.; Hughes, R.; Sumeren, R.; Pferfferkorn, J. A.; Winssinger, N. *Bioorg. Med. Chem*. **2003**, *11*, 465.

[152] Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed*. **2000**, *39*, 734.

[153] Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799.

[154] Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett.* **2000**, *41*, 6253.

[155] Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804.

[156] Kuo, E. A.; Hambleton, P. T.; Kay, D. P.; Evans, P. L.; Matharu, S. S.; Little, E.; McDowall, N.; Jones, C.B.; Hedgecock, C. J. R.; Yea, C. M.; Chan, A. W. E.; Hairsine, P. W.; Ager, I. R.; Tully, W. R.; Williamson, R. A.; Westwood, R. *J. Med. Chem.* **1996**, *39*, 4608.

[157] Lepia, A. J.; Morton, T. C. *Aust. J. Chem*. **1986**, *39*, 1747.

[158] Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* **1987**, 713.

[159] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem*. **1995**, *60*, 7508.

[160] Main, C. A.; Petersson, H. M.; Hartley, R. C.; Rahman, S. S. *Tetrahedron* **2008**, *64*, 901.

[161] Miki, Y.; Hachiken, H.; Yanase, N. J. *Chem. Soc. Perkin Trans 1*. **2001**, 2213.

[162] DiMauro, E. F.; Vitullo, J. R. *J. Org. Chem*. **2006**, *71*, 3959.

[163] Zhang, X-Q.; Li, Y-Y.; Zhang, H.; Gao, J-X. *Tetrahedron: Asymm*. **2007**, *18*, 2049.

[164] Miki, Y.; Aoki, Y.; Miyatake, H.; Minematsu, T.; Hibino, H. *Tetrahedron Lett*. **2006**, *47*, 5215.

[165] Yamabuki, A.; Fujinawa, H.; Choshi, T.; Tohyama, S.; Matsumoto, K.; Ohmura, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett*. **2006**, *47*, 5859.

[166] Data for the crystal structure appears in appendix B.

[167] Bamberger, E.; Lublin, *Chem. Ber*. **1909**, *42*, 1676.

[168] Wunsch, K. H.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1967**, *8*, 277.

[169] Bouillon, A.; Lancelot, J. –C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.

[170] For a similar synthesis employing 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxa-boralane; Garg, N. K.; Sarpong, R.; Stoltz, B. *J. Am. Chem. Soc*. **2002**, *124*, 13179.

[171] Sieh, D. H.; Wilbur, D. J.; Michejda, C. J. *J. Am. Chem. Soc*. **1980**, *102*, 3883.

[172] Farnsworth, D. W.; Wink, D. A.; Roscher, N. M.; Michejda, C. J.; Smith, R. H. *J. Org. Chem.* **1994**, *59*, 5942.

[173] Bräse, S. *Acc. Chem. Res*. **2004**, *37*, 805.

[174] Pilot, C.; Dahmen, S.; Lauterwasser, F.; Bräse, S. *Tetrahedron Lett*. **2001**, *42*, 9179.

[175] Lormann, M. E. P.; Walker, C. H.; Es-Sayed, M.; Bräse, S. *Chem. Commun.* **2002**, 1296.

[176] Zimmermann, V.; Avemaria, F.; Bräse, S. *Synlett* **2004**, 1163.

[177] Kabalka, G. W.; Li, G. *Tetrahedron Lett*. **1997**, *38*, 5777.

[178] Reeves, W. P.; Bahr, M. L. *Synthesis* **1976**, 823.

[179] Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103,* 2483.

[180] *Diversity-Based Synthesis of Nitrogen Heterocycles,* Austin, C. A.; PhD Thesis, University of Glasgow, **2006**, page 99.

[181] Moisés. C, L.; Clegg, W.; Demirtas, I.; Elsegood. M, R, J.; Maskill. H. *J. Chem. Soc., Perkin Trans 2*. **2000,** 85.

[182] *Novel Titanium Alkylidenes and their Application in the Synthesis of Indoles and Quinolines*, MacLeod, C.; PhD Thesis, University of Glasgow, **2003**, page 124.

[183] http://www.discoverypartners.com/Products/irori_prod_kanreact.html. (Accessed February 2008)

[184] *Stereoselective Synthesis of Piperidines*, Adriaenssens, L. V.; PhD Thesis, University of Glasgow, **2007**, page 65.

[185] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry 4th Ed.* Plenum Publishers, New York, 1990, page 276.

[186] D. Kadereit, P. Deck, I. Heinemann, H. Waldmann, *Chem. Eur. J.* **2001**, *7*, 1184.

[187] Song, Y-L.; Roller, P. P.; Long, Y-Q. *Bioorg. Med. Chem*. **2004**, *14*, 3205.

[188] Roby, J.; Voyer, N. *Tetrahedron Lett.* **1997**, *38*, 191.

[189] Piettre, S. R.; Baltzer, S. *Tetrahedron Lett*. **1997**. *38*, 1197.

[190] Kasahara, T.; Kondo, Y. *Heterocycles* **2006**, *67*, 95.

[191] Dolle, R. E.; Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Combi. Chem*. **2007**, *9*, 853.

[192] Wu, T. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett*. **2001**, *3*, 3827.

[193] Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J. Ed.; Wiley-VCH: Weinheim, Germany, **1998**, page 167.

[194] Malpass, J. R.; Hemmings, D.A.; Wallis, A. L.; Fletcher, S. R.; Patel, S. *J. Chem. Soc. Perkin Trans. 1*. **2001**, 1044.

[195] Collins, I. *J. Chem. Soc., Perkin Trans. 1*. **2002**, 1921.

[196] Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 3820.

[197] Zim. D.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 2413.

[198] Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

[199] Romero. M.; Harrak, Y.; Basset. J.; Ginet, L.; Constass, P.; Pujol, M. D. *Tetrahedron* **2006**, *62*, 9010.

[200] http://www.discoverypartners.com/accessories_DryResinFiller.html (Accessed February 2008)

[201] http://www.discoverypartners.com/CombiServices_containers.html (Accessed February 2008)

[202] Wong, A.; Kuethe, J, T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem*. **2004**, *69*, 7761.

[203] http://www.discoverypartners.com/X-Kan-10k_sm.html (Accessed February 2008)

[204] http://www.discoverypartners.com/CombiServices_clevap1.html (Accessed February 2008)

[205] http://www.discoverypartners.com/Clevap_sm.html (Accessed February 2008)

[206] http://www.discoverypartners.com/ X-Kan-illustration_2.html (Accessed February 2008)

[207] Conttineau, B.; O'Shea, D. F. *Tetrahedron* **2007**, *63*, 10354.

[208] Mérour, J-Y.; Joseph, B. *Curr. Org. Chem*. **2001**, *5*, 471.

[209] Wu, P-W.; Hsieh, W-T.; Cheng, Y-M.; Wei, C-Y.; Chou, P-T. *J. Am. Chem. Soc*. **2006**, *128*, 14426.

[210] Hénon, H.; Messaoudi, S.; Anizon, F.;Aboab, B.; Kucharczyk, N.; Leonce, S.; Golsteyn, R. M.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Pharmacol*. **2007**, *554*,106.

[211] Martin, M. J.; Trudell, M. L.; Arauzo, H. D.; Allen, M. S.; LaLoggia, A. J.; Deng, L.; Schultz, C. A.; Tan, Y.-C.; Bi, Y.; Narayanan, K.; Durn, L. J.; Koelher, K. F.; Skolnick, P.; Cook, J. M. *J. Med. Chem*. **1992**, *35*, 4105.

[212] Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 4526.

[213] Perron, F.; Albizati, K. F. *Chem. Rev*. **1989**, *89*, 1617.

[214] Basu, N.; Rastogi, R. P. *Phytochemistry* **1967**, *6*, 1249.

[215] Zhang, Y.; Zhang, Y-J.; Jacob, M. R.; Li, X-C.; Yang, C-R. *Phytochemistry* **2008**, *69*, 264.

[216] Heftmann, E. *Phytochemistry* **1983,** *22*, 1843**.**

[217] Kitchin, W.; Lewis, J. A.; Fletcher, M. T.; Drew, R. A. I.; Moore, C. J.; Francke, W. *J. Chem. Soc. Chem., Commun.* **1986**, 853**.**

[218] Entzeroth, M.; Blackman, A. J.; Mynderse, J. S.; Moore, R. E. *J. Org. Chem*. **1985**, *50*, 1255.

[219] Dekker, K. A.; Inagaki, T.; Gootz, T. D.; Kaneda, K.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Sugie, Y.; Yamauchi, Y.; Yoshikawa, N.; Kojima, N. *J. Antibiot*. **1997**, *50*, 833.

[220] Brimble, M. A.; Bryant, C. J. *Chem Commun*. **2006**, 4506.

[221] Kirby, A.J. *Stereoelectronic Effects*. Oxford University Press Inc, New York, 1996, page 18.

[222] Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, 59, 1105.

[223] Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc*. **1988**, *110*, 5768.

[224] Evans, D. A.; Sacks, C. E.; Whitney, R. A,; Mandel, N. G. *Tetrahedron Lett.* **1978**, 727.

[225] Hayes, P.; Maignan, C. *Synthesis* **1999**, 783.

[226] Tietze, L. F.; Schneider, G.; Wölfling, J.; Fecher, A.; Nöbel, T.; Peterson, S.; Schuberth, I.; Wulff, C. *Chem. Eur. J.* **2000**, *6*, 3755.

[227] Zhou, G.; Zheng, D.; Da, S.; Xie, Z.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 3349.

[228] Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001**, *66*, 2382.

[229] Chang, C.-F.; Yang, W.-B.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2002**, *43*, 6515.

[230] Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323.

[231] Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903.

[232] Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997.

[233] Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4569.

[234] Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-Feng, Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773.

[235] Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* **2004**, *6*, 4965.

[236] Rahim, M. A.; Fujiwara, T.; Takeda, T. *Tetrahedron* **2000**, *56*, 763.

[237] Phukan, P.; Sasmal, S.; Maier, M. E. *Eur. J. Org. Chem*. **2003**, 1733.

[238] Santos, A. A-D.; Princival, J. L.; Comasseto, J. V.; Barros, S. M-G.; Neto, J. E. B. *Tetrahedron* **2007**, *63*, 5167.

[239] Wantanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.

[240] http://www.phytochemicals.info/phytochemicals/coumarin.php (Accessed March 2008)

[241] Pisklak M.; Maciejewska D.; Herold F.; Wawer I. *J. Mol. Struct*. **2003**, *1*, 169.

[242] Häser, K.; Wenk, H. H.; Schwab, W. *J. Agric. Food Chem*. **2006,** *17,* 6236.

[243] Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.

[244] Dondoni, A.; Scherrmann. *J. Org. Chem*. **1994**, *59*, 6404.

[245] Marino, K.; Baldoni, L.; Marino, C. *Carbohyd. Res*. **2006**, *13,* 2286.

[246] Wothers, P.; Greeves, N.; Warren, S.; Clayden, J. *Organic Chemistry*, Oxford University Press Inc, New York, 2001, page 1140.

[247] Roddick, J. G. *Phytochemistry* **1974**, *13*, 9-25.

[248] Sinibaldi, M. E.; Canet, I. *Eur. J. Org. Chem*. **2008**, 4391.

[249] Overman, L. E.; Rhee, Y-H. *J. Am. Chem. Soc*. **2005**, *127*,15652.

[250] Nguyen, S.; Xu, J.; Forsyth, C. J. *Tetrahedron* **2006**, *62*, 5338.

[251] James, K. J.; Moroney, C.; Roden, C.; Satake, M.; Yasumoto, T.; Lehane, M.; Furey, A. *Toxicon* **2003**, *41*, 145.

[252] Malpass, J. R.; Hemmings, D. A.; Wallis, A. L.; Fletcher, S. R.; Patel, S. *J. Chem. Soc., Perkins Trans. 1*. **2001**, 1044.

[253] Mohan, B.; Nagarathnan, D.; Vedachalam, M.; Srinivasan, P. C. *Synthesis* **1985**, 188.

[254] Overkleeft, H. S.; Wiltenburg, J. v.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215.

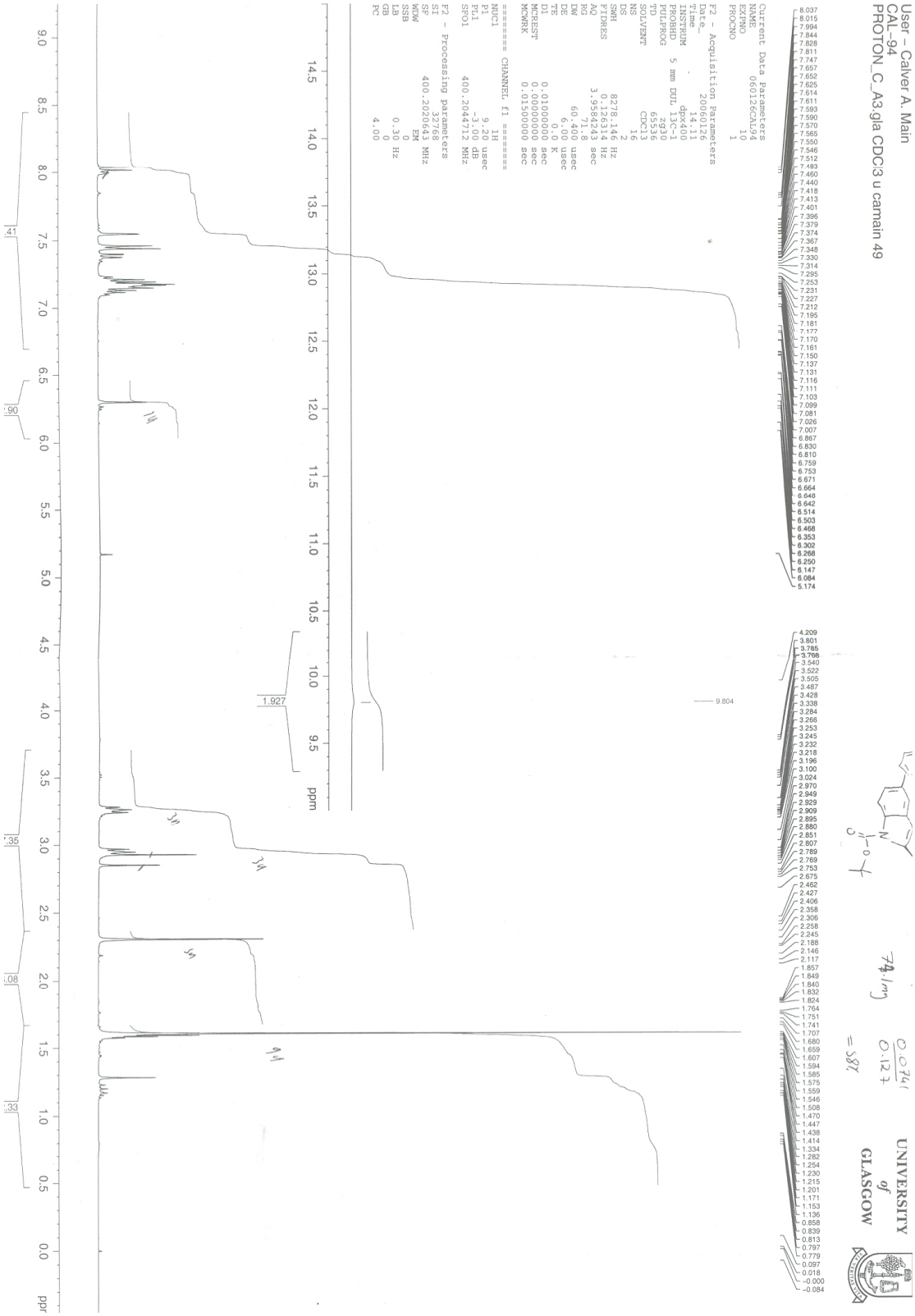
[255] Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans*. *1*. **1983**, *93*.

APPENDIX – A

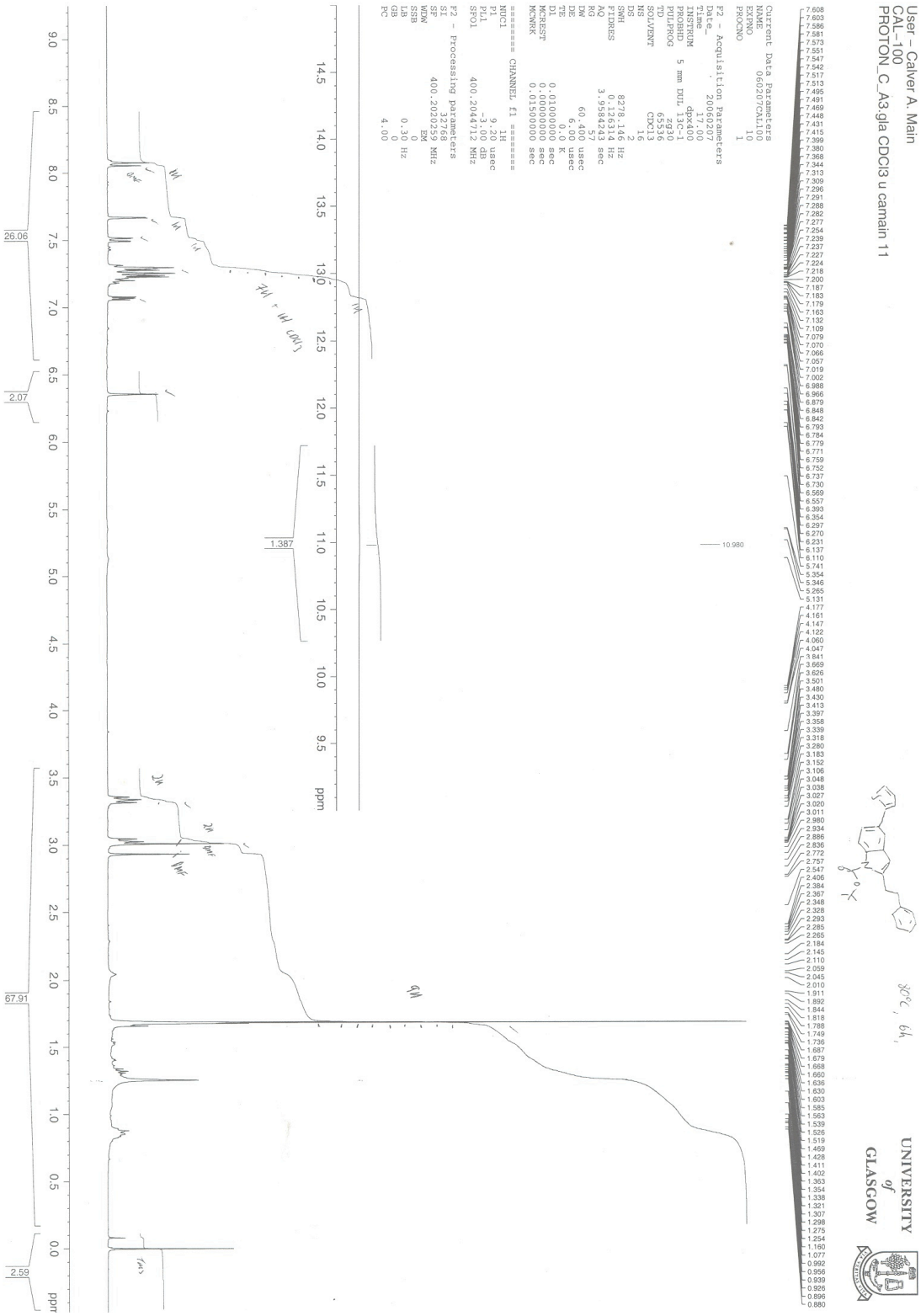
Representative NMR spectra of selected products

N-Boc-2-Phenylethyl-5-(4'',5''-tetramethyl-1'',3'',2''-dioxaborolan-2''-yl]-indole 338

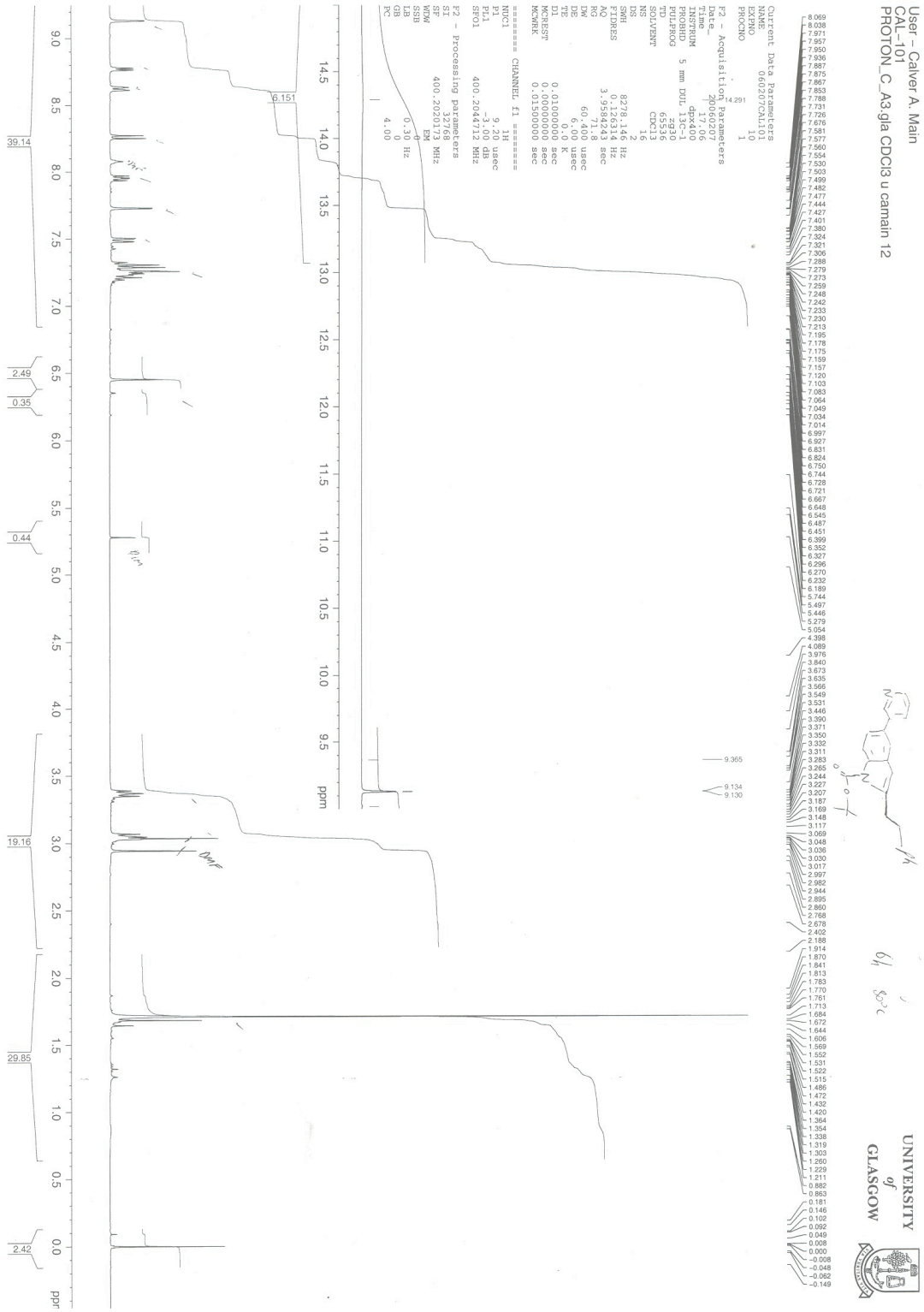
N-Boc-2-Phenylethyl-5-(para-toluyl)-indole 350



_N_-Boc-2-(2”-phenylethyl)-5-(2’-thiophenyl)indole 352.



_N_-Boc-2-(2”-phenylethyl)-5-(3’-pyridyl)indole 353.



APPENDIX – B

Crystal Structure of 5-Bromoanthranil 290

Data for crystal structure collected on: COLLECT (Nonius, 2004); cell refinement: SCALEPACK (Otwinowski & Minor, 1997); data reduction: SCALEPACK and DENZO (Otwinowski & Minor, 1997); program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997); soft-ware used to prepare material for publication: WinGX (Farrugia,1999).

5-Bromoanthranil 290