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

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

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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-isoproxy-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 \textit{ix} for the attempted conversion of resin-bound esters \textit{i} into functionalised 7-azaindole
\textit{x} after cleavage from resin. Further investigation with a different \textit{ortho}-nitrogen protecting group may yet prove successful.

Alkyldenation of lactones \textit{xi} with functionalized titanium carbenoid reagents \textit{xii} followed by acid-induced cyclisation of the resulting enol ethers \textit{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) \textit{xiv}. The titanium carbenoids \textit{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.


**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-butylxocarbanoyl  
Bu  butyl  
t-Bu/ tert-Bu  tertiary butyl  
b.p.  boiling point  
bs  broad singlet (NMR spectroscopy)  
°C  degrees centigrade  
cat.  catalytic  
Cl  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(1H)-pyrimidinone
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
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<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td>Ln</td>
<td>ligand</td>
</tr>
<tr>
<td>LVT</td>
<td>low valent titanium</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
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<tr>
<td>m</td>
<td>multiplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
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</tr>
<tr>
<td>meq</td>
<td>milliequivalents</td>
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<tr>
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<td>minute(s)</td>
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<tr>
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<tr>
<td>m.p.</td>
<td>melting point</td>
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<tr>
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<tr>
<td>NMR</td>
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<td>PG</td>
<td>protecting group</td>
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<td>Ph</td>
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<tr>
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<tr>
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<td>toluene</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium <em>para</em>-toluenesulfonate</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectroscopy)</td>
</tr>
<tr>
<td>quin</td>
<td>quintet (NMR spectroscopy)</td>
</tr>
<tr>
<td>Rac</td>
<td>racemic</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Rt</td>
<td>retention time</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectroscopy)</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>SPS</td>
<td>solid-phase synthesis</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectroscopy)</td>
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<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
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<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (para-toluenesulfonyl)</td>
</tr>
<tr>
<td>TsOH</td>
<td>para-toluene sulfonic acid</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>Vis</td>
<td>visible light</td>
</tr>
</tbody>
</table>
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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, \textit{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.\textsuperscript{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”.\textsuperscript{11} Defined by Evans \textit{et al.} as “a single molecular framework to produce ligands for diverse receptors” or in essence descriptors of biological activity.\textsuperscript{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.\textsuperscript{11}

\section{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.\textsuperscript{13} After developing a synthetic route for the synthesis of a number of 1,4-benzodiazepin-2-ones \textsuperscript{1}, Bunin \textit{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 \textsuperscript{14} (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.\textsuperscript{15} This work was achieved in order to contribute to screening programmes against a number of biological targets (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. 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 olomucine (7 \mu M), which had been observed as the most effective inhibitor up until that point (Figure 3).

![Purine derivative 3](image)

**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.
The substrate is immobilised by attachment to the solid support (resin) \textit{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.\textsuperscript{20} This “one Kan, one compound” strategy produces libraries consisting of thousands of separate individual compounds for screening.\textsuperscript{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. 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).

![Figure 4](image_url)
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](image)

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).\(^ {24}\)
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
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](image)

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 Ellman29 (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.\(^\text{30}\)

Many groups went onto modify Ellman’s original linker and develop their own linkers by utilising germanium\(^\text{31}\), sulfur\(^\text{32}\), boron\(^\text{33}\), phosphorous\(^\text{34}\) and chromium\(^\text{35}\). 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).\(^\text{36}\)
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 H₃PO₄ 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. 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. 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).
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 mCPBA in DCM to give the corresponding sulfone 27, S_{Na} substitution of the sulfone group with a range of nucleophiles, gave products 28 in high yields and purities (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, 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.

[Diagram showing the reaction scheme]

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).
Barrett’s most recent contribution to chameleon catch strategy has been from the SPS of isoxazole moieties. Methylation 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).

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

![Scheme 15](image_url)
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.\textsuperscript{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](image_url)

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](image_url)
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. 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-Wadsworth-Emmons (HWE) reaction] (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).
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.\textsuperscript{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 (\textit{e.g.} the Wittig reaction), above all the ability to alkylidenate carboxylic acid derivatives.\textsuperscript{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 (\textit{e.g.} titanium), in a high formal oxidation state, gives rise to the Schrock carbene 60. The metal is a good $\sigma$ acceptor and a good $\pi$ 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.\textsuperscript{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.

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.\textsuperscript{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.\textsuperscript{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 metalla-cycle 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.\textsuperscript{55} The driving force in the methyleneation of a carbonyl group is the irreversible formation of the strong Ti-O double bond in oxide 63 (Scheme 18).

![Scheme 18](image)

The Tebbe reagent is capable of methyleneating a broad range of carbonyl groups including aldehydes, ketones, esters, thioesters, amides and carbonates.\textsuperscript{56} Selective methyleneation can also be achieved in the presence of carbonyl groups of differing electrophilicity. Aldehydes and ketones are methyleneated 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).\textsuperscript{57}
Regioselectivity can also be achieved in the Tebbe methylation of esters and, with methylation 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.\(^\text{58}\)

Methylation of tertiary amides and carbonates to give enamines and ketene acetics have also been reported. However, methylation 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.\(^\text{59}\) Additionally, methylation 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 methylation.\(^\text{53}\) 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).\footnote{60} Definitive procedures for the preparation of DMT have been published by Hughes and also by Payack’s team at Merck Research Laboratories.\footnote{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](image_url)

Confirmation that the titanocene methylidene 62 is the active species in the mechanism of methylenation comes from the work of Hughes \textit{et al.}\footnote{62} They have shown that titanocene methylidene formation proceeds \textit{via} heat-induced \(\alpha\)-elimination, and that this is the overall rate-determining step of the alkylideneation reaction. Additionally, the recent work of Meurer \textit{et al.}\footnote{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 Cp₂Ti=OH⁺ and R₁R₂CCH₂H⁺.

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 methylation of cyclobutenedione derivative 72 to give exo-methylene compound 73 (Scheme 22).⁶⁴

![Scheme 22](image)

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

![Scheme 23](image)
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. 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).

![Scheme 24](image)

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). 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: Bis(benzylic)titanocenes are easily generated from substituted and non-substituted benzylmagnesium chlorides and titanocene dichloride and upon heating effectively alkylidenate carbonyl compounds. In addition, bis(vinyllic)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. 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](image)

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

![Scheme 26](image)

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).\(^7\)

![Scheme 27](image)

In order to generate a low-valent titanium species for the desulfurization of thioacetals, the group also prepared Cp\(_2\)Ti(PMe\(_3\))\(_2\), first reported by Kool \textit{et al.} by the reduction of titanocene dichloride with magnesium.\(^7\) However the preparation of Cp\(_2\)Ti(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).\(^7\)
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 \textit{en route} to the titanium alkylidene species \( 96 \), which is capable of alkylidenating esters \( 97 \) \textit{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 alkylideneation 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 dechlorination can often occur.\(^{81}\)

Scheme 31

\[ R^1 = H, F \\
R^2 = H, Me, SMe, F, Cl \]

\[ R^3 = H, Me, F, Cl \]

\[ R^4 = Me, SMe, F, Cl \]
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, which could then be employed in the diversity-orientated synthesis of aromatic and non aromatic heterocycles (See Chapter 4).

The few drawbacks of Takeda’s method include poor stereoselectivity in the alkylidenation of ketones and aldehydes and methylation 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.
3.2.4 1,1 Bimetallic Reagents

Takai and co-workers were the first to report the methylation of ketones at RT with a reagent generated from the addition of TiCl₄ 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](image)

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](image)
In 1995, the work by Tochtermann 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 TiCl₄, to give alkene 121 in good yield (Scheme 34).³⁸

![Scheme 34](image)

### 3.2.5 Takai Reagents

Takai reagents are also derived from TiCl₄ but differ in their preparation and reactivity. The reagents are prepared by the addition of 4 equivalents of titanium(IV) chloride (TiCl₄) 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).³⁸ 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](image)
A definitive procedure for the preparation of this reagent has been published and in comparison to the Tebbe reagent offers superior allenation. Takai reagents alkylidenate esters to give enol ethers in excellent yields and will convert thioesters into vinyl sulfides with good Z-selectivity. They are also capable of alkylidenating other carboxylic and carbonic acid derivatives. Stereoselectivity is generally governed by steric interactions, where enol ethers are generated from esters with a branch in R' 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).

![Scheme 36](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>Z/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>90</td>
<td>73:27</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>79</td>
<td>92:8</td>
</tr>
<tr>
<td>PhCH=CH</td>
<td>Bu</td>
<td>79</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 1

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

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.
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). 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 benzylidene 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.

![Scheme 37](image)

Nu = O, S, NR'
PG = acid-labile protecting group
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.\textsuperscript{101}

The benzofurans were synthesised utilising a titanium benzylidene 129 with a masked oxygen nucleophile in the \emph{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-butylimethyldisilane (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-butylimethyldisilyl (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).\textsuperscript{101}

![Scheme 38](image-url)
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.\textsuperscript{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.\textsuperscript{81}

\begin{center}
\textbf{Scheme 39}
\end{center}

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.\textsuperscript{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. Cp₂Ti[P(OEt)₃]₂.\textsuperscript{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.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

Scheme 40

Silyl protection had been employed to good effect in the original synthesis of the 2-substituted 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 Benzo[b]thiophenes

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-substituted benzo[b]thiophenes 142 from a novel masked sulfur-containing titanium benzylidene 140 (Scheme 41).\textsuperscript{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-butylidimethylsilyl 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-substituted benzo[b]thiophenes 142 (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.\(^\text{82}\)

![Scheme 42](image)

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 benzylidene 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).\(^\text{82}\)

![Scheme 43](image)

\(R^1 = \text{Me, Bn, CH} = \text{CMe}_2\)
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). 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). Titanium benzylicene 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 Et₃SiH and the solvent removed to give ammonium salts 156 (Scheme 45). The addition of Et₃SiH was required to reduce the trityl cation during cleavage so that the only side product was Ph₃CH. 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](image)

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 purity86 (Scheme 46).
Asymmetric synthesis of piperidines 162 was achieved using the enantiopure titanium alkylidene compounds (S)-158 and (R)-158. Alkyldenation 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

![Diagram](image_url)

**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 GlaxoSmithKline 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-substituted 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 indigo (the natural dye) and oleum (used for isolation) (Figure 10).\(^\text{103}\)

![Figure 10](image)

Indole is composed of a ten-\(\pi\) 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 \((4n+2\pi\) electrons) Hückel rule (Figure 11).\(^\text{104}\)

![Figure 11](image)

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, \textit{e.g.} with ethylene oxide to give indole \(165\) (Scheme 47).\(^\text{104}\)
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, \textit{e.g.} as the plant growth hormone heterauxin \(169\) (Figure 12).\(^ {107}\)

![Diagram of chemical structures](image)

**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).\textsuperscript{108}

\begin{center}
\includegraphics[width=0.3\textwidth]{indomethacin.png}
\end{center}

\textit{Indomethacin}

\textit{anti-inflammatory drug}

\textbf{Figure 13}

In addition to the more abundant, naturally occurring, 3-substituted 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).\textsuperscript{109,110}

\begin{center}
\includegraphics[width=0.3\textwidth]{melatonin.png}
\end{center}

\textit{melatonin 171}

\textit{hormone}

\textbf{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.\textsuperscript{109,111} Melatonin acts with high affinity on the G-protein membrane methoxytryptamine receptors MT\textsubscript{1} and MT\textsubscript{2}.\textsuperscript{111} The 2-substituted melatonin analogue \textbf{172} (Figure 15) has higher affinity for the MT\textsubscript{1} receptor than the native hormone melatonin.\textsuperscript{109} Additionally, indole \textbf{173} (Figure 15) exhibits an affinity similar to that of melatonin for the MT\textsubscript{1} receptor, but it has lower affinity for the MT\textsubscript{2} receptor.\textsuperscript{111} It is therefore the hope that 2-substituted melatonin analogues may eventually become useful drugs to help with disorders associated with melatonin imbalance.

![Figure 15](image)

In the mammalian system, the neurotransmitter serotonin \textbf{168} (5-hydroxytryptamine, 5-HT) is synthesized from the amino acid tryptophan \textbf{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\textsubscript{1}–5HT\textsubscript{7}.\textsuperscript{112} Of particular interest is the 5-HT\textsubscript{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\textsubscript{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\textsubscript{6} receptors.\textsuperscript{113} Therefore 5-HT\textsubscript{6} ligands might be of value in the treatment of anxiety and mood related disorders.\textsuperscript{114} Additional studies of the 5-HT\textsubscript{6} receptor suggest involvement in motor function, mood-dependent behaviour and the early growth process involving serotonin.\textsuperscript{115} A study of 2-substitued analogues of serotonin identified indole \textbf{174} as the most selective 5-HT\textsubscript{6} agonist reported,\textsuperscript{110} with another 2-substitued analogues \textbf{175} acting as an antagonist (Figure 16).\textsuperscript{116}
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.\textsuperscript{117} Although the ORL1 receptor is known to have a 47\% overall identity to classical opioid receptors (µ, δ, κ), native opioid peptides and synthetic agonists for µ, δ, κ receptors show no significant affinity for ORL1 receptors.\textsuperscript{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.

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.\textsuperscript{119}
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

![Figure 19](image)

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

![Figure 20](image)

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
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, congestive 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 possess 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 \textit{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).\(^{130}\)
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. 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. 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, 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](image)

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
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). 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 (HOt) 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-susbtituted and 2,3 disubstituted examples were synthesised in modest yield after chromatography.
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).\textsuperscript{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 \textit{et al.} consists of a carbon chain, as the spacer group, between resin and the silicon-bound reagent.\textsuperscript{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 NH₂ resin 200 swollen in DMF using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Scheme 51). 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-disubstituted indoles were obtained in moderate to good yields (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. 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-substituted 3-cyanoindoles 212.

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). 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.

\[
\begin{align*}
213 & \xrightarrow{\text{DMF, 70 °C, 48 h}} 214 \quad \xrightarrow{+PPh_2} \quad (i) \text{Na}_2\text{S}_2\text{O}_4, \text{EtOH, reflux, 90 min} \quad \xrightarrow{+PPh_2} \quad 215 \quad \xrightarrow{\text{HBr, MeOH, Dioxane}} \quad 216 \quad \xrightarrow{\text{Pyridine, DCM, 5 h}} \quad 217 \\
& \quad \xrightarrow{(i) \text{PhMe/ DMF distill}} \quad (ii) \text{KO'Bu, PhMe/ DMF reflux, 45 min} \quad 218, 78\% \quad \xrightarrow{\text{OMe}} \quad \xrightarrow{\text{NH}}
\end{align*}
\]

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.\textsuperscript{103} The first solution-phase example of palladium-catalysed cyclisation of an ortho-alkynylanilide to give an indole was by Taylor and McKillop\textsuperscript{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).\textsuperscript{141}

\begin{equation}
\begin{array}{c}
\text{CuI, (Ph}_3\text{P)}_2\text{PdCl}_2 \\
\text{Et}_3\text{N}
\end{array}
\quad
\begin{array}{c}
\text{NH} \\
\text{SO}_2\text{Me}
\end{array}
\quad
\begin{array}{c}
\text{NH} \\
\text{SO}_2\text{Me}
\end{array}
\quad
\begin{array}{c}
\text{R} \\
\text{NH} \\
\text{SO}_2\text{Me}
\end{array}
\end{equation}

\textbf{Scheme 54}

The proposed reaction mechanism for the palladium-catalysed cyclisation, is comprised of the following steps: (i) initial formation of a $\pi$-alkynepalladium complex 221, (ii) intramolecular nucleophilic attack of the nitrogen nucleophile onto the activated carbon-carbon triple bond to give the $\alpha$-indolypalladium complex 222, (iii) proton transfer with loss of palladium(II), which enters a new catalytic cycle, and formation of indole 223 (Scheme 55).\textsuperscript{103}
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®\textsuperscript{142}, TentaGel-S®\textsuperscript{143} or Wang\textsuperscript{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).\textsuperscript{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.
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. 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 based on Yamanaka’s cyclisation procedure. Resin-bound arylsulfonfyl 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-idoaniline 232 can also be electron-donating or electron-withdrawing. The sulfonyl linker also proved effective duringmercuration, organomercurial species 235, generated from resin-bound indole 233, was coupled with methyl acrylate 236 in the presence of \(\text{Pd(OAc)}_2\) and after cleavage of 237 with TBAF, 2,3-disubstituted indole 238 was isolated in good yield (Scheme 58).

![Scheme 57](image-url)
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
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™ 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). 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](image)

This was adapted to SPS route by Smith et al., 2-Iodoaniline 245 was successfully loaded onto Ellman’s THP resin through PPTS mediated aminal linkage to give resin-bound 252 (Scheme 61). Coupling with internal alkynes used Pd(PPh₃)₂Cl₂ 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 R¹ = TMS. In total, six indoles were isolated however information on purities was not supplied.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

Scheme 61
5.2.5 Cycloaddition Route to Indole Synthesis

K.C. Nicolaou and co-workers have also developed a strategy to access 2-substituted indole derivatives in a traceless manner from solid phase.\textsuperscript{151} The method is an extension of their previous work: the selenium-based approach for the solid phase combinatorial synthesis of benzopyran derivatives.\textsuperscript{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\textsubscript{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\textsubscript{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).\textsuperscript{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](image-url)
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.\(^\text{151}\)

### 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.\(^\text{153}\) 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](image_url)
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.\(^3\) 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.

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**Scheme 64**
6.2 Preparation of a Boronate-Bearing Titanium Benzyldene

The first aim was to investigate the synthesis of the titanium benzyldene 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-fluorobenzaldehyde 270 as the starting material for the synthesis. Adapting the method of Kuo et al. for the aromatic nucleophilic displacement (SNAr) 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-coupling159 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, Cp2Ti[P(OEt)3]2 90, gave a titanium carbenoid, presumed to be titanium benzyldene 278 (Scheme 65).
6.2.1 Alkylidenation and Cross-Coupling to give N-Benzyl Indoles

Hanna Petersson used boronate-bearing titanium benzyldiene 278 immediately, without isolation, to benzylidene 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 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. The products were isolated in high purity without the need for chromatography.
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.\textsuperscript{161}

The Miyaura cross-coupling failed when amine 273 or primary carbamate 274 was the substrate\textsuperscript{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,\textsuperscript{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.\textsuperscript{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-\textit{tert}-butylcarbamate protection. We hoped to develop a route to a boronate-bearing titanium alkylidenating reagent that would be capable of optimal alkylideneation and producing N-Boc protected indoles. As although there are reports in the literature that N-benzyl indoles can be deprotected to give indoles,\textsuperscript{164} N-Boc protecting groups are more easily removed.\textsuperscript{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 benzyldiene 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 acetics are easily transposed into 1,3-dithianes upon addition of propandithiol and BF₃.OEt₂.\(^{83}\) 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 diborinate 286, after which the acetal 287 would be easily converted into the corresponding 1,3-dithiane 288.\(^{83}\)

![Scheme 67](image-url)
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\(^\text{166}\) showed it was 5-bromoanthranil 290 (Figure 23).

![Scheme 68](image)

**Figure 23**

### 6.2.3 5-Bromoanthranil

5-Bromoanthranil, which was first reported by Bamberger & Lublin\(^\text{167}\) (1909) and more recently synthesised by Wünsch & Boulton\(^\text{168}\) (1967), is a 10 \(\pi\) 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).

![Scheme 69](image)
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\text{Pr})_3 and transesterification with pinacol in one pot. 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).

![Scheme 73](image)

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(OiPr)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-bromoantranil with 1,3-propanedithiol.

![Scheme 74](image)
In order to clarify whether or not pinacol was involved in the reduction, pinacol, B(O\textsuperscript{IPr})\textsubscript{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.

![Scheme 75](image)

Replacing B(O\textsuperscript{IPr})\textsubscript{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 '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.\textsuperscript{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 %.

![Scheme 76](image)
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, 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. 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).
6.2.7 Triazenes – Linkers in Solid Phase

Interestingly, 1,3-disubstituted triazenes are often employed as electrophile-cleavable linkers in solid-phase synthesis. 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.

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. Currently the group are designing routes, utilizing their resin-bound triazene toward traceless synthesis of indoles amongst other heterocycles.

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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{178} The resulting allyl azide is preferably used without purification since organic azides are potentially explosive.\textsuperscript{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.\textsuperscript{177}

![Scheme 80](image)

Although the reaction of allyl azide with aryllithiums, followed by acid-induced decomposition is a known method for preparing anilines,\textsuperscript{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.
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).\(^{181}\)
6.3.2 Synthesis of Resin-Bound Esters

Before alkylidation 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).

Scheme 82

Scheme 83

Scheme 84
Merrifield resin 4 is swollen in DMF and then reacted with cesium carboxylate 321. The cesium salt possesses 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 (SN2) 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) 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.
6.3.3 Alkyldenation of Trityl-Protected Substrate

Treatment of dithiane 319 with 4 equivalents of freshly prepared Takeda reagent, Cp₂Ti[P(OEt)₃]₂, gave the titanium carbenoid reagent thought to be titanium benzylidene 322. It should be noted that formation of Cp₂Ti[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 Cp₂Ti[P(OEt)₃]₂ reagent. He developed a CaH₂/ 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 alkyldenate resin-bound ester 279 contained within an IRORI MacroKan™. Cleavage of the resulting resin-bound enol ether 323 with mild acid, under our standard conditions, gave a mixture of compounds from the resin, with indole 325 isolated from column chromatography (Scheme 85).

![Scheme 85](image_url)
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 benzyldiene, 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\textsuperscript{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).

$N$-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.\textsuperscript{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.
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.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

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, 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).

\[ \text{Scheme 89} \]

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™. However treatment with TFA, failed to yield the expected boronate-bearing indole 333 (Scheme 90).

\[ \text{Scheme 90} \]
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 NH 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).
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).
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 than 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. 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(PPh₃)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).

\[
\begin{align*}
339 & \rightarrow 340 \\
& \text{4 eq. } \text{Cp}_2\text{Ti[PO}(\text{OE})_2]_2 \\
& \text{0.33 eq. } \text{O} \text{O} \text{Ph} \\
& \text{4 mol % Pd(PPh}_3)_4, 5 \text{ eq. Cs}_2\text{CO}_3 \\
& \text{5 eq. } \text{I} \\
& \text{9:1 DMF/H}_2\text{O} \\
341 & \text{, 75 %}
\end{align*}
\]

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.\textsuperscript{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\textsuperscript{196,197,198} (Scheme 94).

![Scheme 94](image_url)

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

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. 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-iodobenzene were attempted. The results of which are presented in table 2.

<table>
<thead>
<tr>
<th>Time (h) at 80 °C</th>
<th>Number of equivalents of para-nitro-4-iodobenzene</th>
<th>Yields % (Combined)</th>
<th>Ratio 343:342</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>5</td>
<td>64</td>
<td>4:1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>54</td>
<td>5:1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>61</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>68</td>
<td>5:1</td>
</tr>
</tbody>
</table>

**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).

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.
6.6 Conclusion

We had developed good conditions for the alkylidenation, cross-coupling and cleavage sequence to convert resin-bound esters into 2,5-disubstituted 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-disubstituted 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 aryloboronate 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.
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

\[
\begin{align*}
354 & \quad \xrightarrow{5 \text{ eq. } \text{Cs}_2\text{CO}_3, \ 5 \text{ eq. } \text{KI}} \quad 355 \\
\end{align*}
\]

Scheme 101
7.2 Alkylidenation and Cleavage

The sacrificial eight MiniKans™ containing the resin-bound esters 356 A-H were alkylidenated together to give enol ethers 357 A-H. Each MiniKan™ 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).
7.2.1 Synthesis of 96-Member Library

With the confirmation that the sensitive alkylidenation conditions had been successful, the remaining 96 MiniKans™, arranged as 8 batches of 12, with each of the 12 Kans containing the same resin-bound esters 356 A-H were alkylated in exact fashion to the 8 sacrificial Kans. The entire 96 MiniKans™ 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™ 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™ 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™ should go into which batch.

Figure 27, X-Kan sorter203
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).

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).
Addition of mild acid initiated cleavage from resin and the cyclisation. The MiniKans\textsuperscript{TM} 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\textsuperscript{TM} vessel in each separate well. The process in the Clevap is illustrated in Figure 30.

![Figure 30, illustration of residue collection\textsuperscript{206}](image)

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\textsuperscript{TM}. 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 iodosides 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 \textit{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 (1H-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.\textsuperscript{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.\textsuperscript{208}

![Figure 31](image)

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 $\text{360}$ has been used widely in biology (Figure 32).\textsuperscript{209} Furthermore, 7-azaserotonin $\text{361}$, 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.\textsuperscript{210}

![Figure 32](image)
The majority of routes to 7-azaindole derivatives have focused primarily on modified indole synthses such as the Fischer and the Madelung synthses. Other popular routes include transition-metal catalysed cross-coupling/ heteroannulation of 2-amino-3-halo-pyridines with alkynes or ketones. 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).

### 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 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. 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).
8.1.2 Attempted Alkyldenation 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 coordinated the pyridine nitrogen atom during generation of the titanium benzylidene 367, and this may have led to decomposition (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 coordinating 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).
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

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. Spiroacetals are key sub-units in a wide range of biologically active natural products and the pharmacological properties they possess 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). 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.

![Figure 33](image)

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), new glycosides of which continue to be discovered.
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).\(^{213}\)

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. who isolated several new 5,7-dimethoxyphthalide antibiotics with specific anti-

*Helicobacter pylori* activity, 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. 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.

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. If the second ring is also a tetrahydropyran, then the C-O bonds of each will be axial to the other ring.

![Figure 38](image-url)

**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.
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).

![Scheme 109](image)

### 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. 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).

![Scheme 110](image)
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 \(\beta\)-alkoxyalkyl iodides,\(^{226}\) by Ramberg-Baeklund rearrangement,\(^{230}\) by Wittig reaction between exocyclic \(\alpha\)-alkoxyphosphorus 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 \(\text{380}\) gave enol ether \(\text{381}\) in excellent yield (Scheme 111).\(^{235}\)

\[
\begin{array}{c}
\text{380} \quad 2 \text{eq. TiCl}_4 \\
\text{8 eq. Mg} \\
toluene-THF \\
\text{CH}_2\text{Cl}_2 \\
\rightarrow \text{381, 82 %}
\end{array}
\]

Scheme 111

Yan \textit{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 \(\text{CH}_2\text{Cl}_2\) 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](image)

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).

![Figure 39](image)
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 K₂CO₃ proceeded smoothly, providing [5.5] spiroacetal 386 as one diastereomer in good yield (Scheme 114).²²₈
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).
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).

![391 Aplysiatoxin](image)

**Figure 40**

Aplysiatoxin is a potent marine toxin isolated from the sea hare *Stylocheilus longicauda* as well as the blue green algae *Lyngbya 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. They envisioned using the spiroacetal framework of spiroacetal 377 as the chassis for synthesising alysiatoxin. 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-butylidimethylsilyl ether (TBS) and reaction of the lactone with the Tebbe reagent (Scheme 116).

![Scheme 116](image)
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-hydroxy-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](image)

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 TiCl₄ 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).

![Scheme 119](image)

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

![Scheme 120](image)
9.2.1 Synthesis of Spiroacetals from Titanium Alkyldiene 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 \textit{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](image)

With these early results to hand we repeated the generation of titanium carbenoid 406, and then added a slightly heavier phenyl \(\gamma\)-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).
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 steric well, with the formation of [4.5] spiroacetal 414 in modest yield (Scheme 123).

Scheme 122

Scheme 123
We then decided to apply our spiroacetal-forming conditions to another \( \gamma \)-lactone, 3aR(+) sclareolide 415. Lactone 415 was added to the titanium alkylidene 406, generated from the dithiane 405 using low valent titanium species, \( \text{Cp}_2\text{Ti}[\text{P(OEt)}_3]_2 \). 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](image)

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](image)
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).

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-mown 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 flavoring 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.
9.2.2 Synthesis of Spiroacetals from Titanium Benzyldene 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. Therefore, it was used to generate a [4.4] benzo-fused spiroacetal 426 from lactone 410 (Scheme 129).
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

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](image)

Scheme 130

![Scheme 131](image)

Scheme 131

![Scheme 132](image)

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 \( \alpha \) to the carbonyl group and \( \alpha \) 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, \( \text{Cp}_2\text{Ti}[\text{POEt}_3]_2 \), used in the Takeda reaction.\(^8\) Emma Guthrie, who worked on the titanium benzylidene mediated SPS of 2-substituted 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-disubstituted 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.\(^8\) Additionally, Calum McLeod also experienced similar problems during his work on the SPS of 2-substituted indoles from titanium benzylidenes.\(^8\)

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 Benzylidation 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).

![Scheme 133](image)

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).

![Scheme 134](image)
Titanium benzyldiene 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).

![Scheme 135](image)

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](image)

Formation of TBS-protected thioacetal 436 from pyran 434 was straightforward and presented few problems. Addition of thioacetal 436 to Cp₂Ti[P(OEt)₃]₂ followed by the lactone 412 and then cyclisation conditions did not prove encouraging. The ¹H 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. 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).
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.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

Figure 41

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactone</th>
<th>Titanium reagent</th>
<th>Spiroacetal</th>
<th>% Isolated yield using 1.2 eq. of titanium reagent</th>
<th>% Isolated yield using 3 eq. of titanium reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>133</td>
<td>430</td>
<td>46</td>
<td>53</td>
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<td>62*</td>
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<td>426</td>
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<td>44</td>
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<td>406</td>
<td>416</td>
<td>44*</td>
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<td>439</td>
<td>133</td>
<td>442</td>
<td>49</td>
<td>61</td>
</tr>
</tbody>
</table>

*Isolated yield of major diastereomer.

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

Table 4
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

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.\textsuperscript{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 \textbf{448} found in marine sponges\textsuperscript{249} and azaspiracid-1, isolated from mussels the spiroaminal domain \textbf{449}, of which is shown\textsuperscript{250} (Figure 44).

![Figure 44](image.png)

Diverse biological activities have been reported for crambescidin alkaloids including cytotoxicity, antifungal activity and antiviral activity towards, amongst others, human immuno deficiency virus (HIV).\textsuperscript{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.\textsuperscript{251}

\textbf{9.3.1 Proposed Route to Spiroaminals and Preliminary Studies}

Titanium alkylidene \textbf{154} bearing an \textit{N}-trityl protected amine had been used by Carolyn Austin, in the Hartley group, to make imines\textsuperscript{86} (Chapter 4). We considered using this reagent to prepare spiroaminal \textbf{453} from lactone \textbf{412} (Scheme 140). Thioacetal \textbf{111} was prepared by Carolyn Austin’s procedure\textsuperscript{86} and then converted into the corresponding titanium carbenoid \textbf{154} under our standard conditions (Scheme 139).
Unfortunately, studies into the alkylidenation of \( \alpha,\alpha \)-diphenyl-\( \gamma \)-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.
An alternative route to spiroaminals investigated the addition of an N-substituted lactam \textit{454} to titanium benzylidene \textit{133}, followed by treatment of enol ether \textit{455} with acid in order to form target spiroaminal \textit{456} (Scheme 141).

\textbf{Scheme 141}

The crude \textsuperscript{1}H NMR spectrum of the final compound appeared to contain a geminal CH\textsubscript{2} signal at 3.44 ppm perhaps belonging to spiroaminal \textit{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.

\textbf{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 alkylidene 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$_2$O 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$_2$TiCp$_2$ (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.

$^1$H 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 (MSstation) 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$_2$O (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/H₂O (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 Et₂O. 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 Et₂O. The reactor containing the resin-bound enol ether 336 was then dried under vacuum.

10.1.4 Solid-Phase Suzuki Cross-Coupling Reaction

Pd(PPh₃)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™, Cs₂CO₃ (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 H₂O (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™ was separated from the reaction mixture and washed with 9:1 DMF-H₂O (3 ×), alternately with MeOH and DCM (3 ×), and finally with MeOH and Et₂O. The MacroKan™ 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™ 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™ (x 13 containing Merrifield Resin, 46.5 mg per IRORI MiniKan™), 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™ washed: 9:1 DMF/H₂O (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). The IRORI MiniKans™ were then dried under vacuum. Loading ~ 2.0 meq/ IRORI MiniKan™.

10.2.2 Resin-Bound Enol Ethers 357 A-H

Cp₂TiCl₂ (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™, each containing one of the resin-bound esters 356 A-H [93 μeq./MiniKan™ 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™ were removed from the flask and washed with THF (5 x) then alternately with MeOH and DCM (5 x), and finally with MeOH then Et₂O. The 13 MiniKans™ 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™ in total.
10.2.3 Solid-Phase Suzuki Cross-Coupling

Pd(PPh₃)$_4$ (15 mg, 4 mol %) was added to a flask containing 8 MiniKans™ each containing a different resin-bound enol ether 357A-H (93 µeq./MiniKan™), stirring with Cs₂CO₃ (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™ were separated from the reaction mixture and washed with 9:1 DMF-H₂O (3 ×), alternately with MeOH and DCM (3 ×), and finally with MeOH and Et₂O. The MiniKans™ 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™, each containing a different resin-bound enol ether, were placed in an IRORI Clevap™ (automatic cleavage and evaporation) station, so that each MiniKan™ 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™ were collected separately and evaporated.

10.3 SPIROACETALS

10.3.1 Synthesis of Spiroacetics from tert-butyl-dimethylsilyl Protected Thioacetal 405

Method 1

Cp₂TiCl₂ (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 (K₂CO₃), 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 (MgSO₄) and concentrated under reduced pressure.

**Method 2**

Cp₂TiCl₂ (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, 1 eq.) 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 (K₂CO₃) 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 FeCl₃ (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 (MgSO₄) and concentrated under vacuo.

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

**Method 1**

Cp₂TiCl₂ (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 (K₂CO₃), 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 (MgSO₄) and concentrated under reduced pressure.

**Method 2**

Cp₂TiCl₂ (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 (K₂CO₃) 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 FeCl₃ (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 (MgSO₄) and concentrated under vacuo.
10.3.3 Synthesis of Spiroacetals from tert-methylsilyl Protected Dithiane 105

Method 1

Cp₂TiCl₂ (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 (K₂CO₃), 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 (MgSO₄) and concentrated under reduced pressure.

Method 2

Cp₂TiCl₂ (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 (K₂CO₃) 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 FeCl₃ (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 (MgSO₄) and concentrated under vacuo.
10.4 Experimental Data

2-Azido-5-bromobenzaldehyde 271

\[
\text{Br} \quad \text{N}_3 \quad \text{H}
\]

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 (MgSO₄) 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 PrOH). \( R_t \) [SiO₂, hexane-DCM (2:1)]: 0.58. \( \nu_{\max } \) (Golden Gate)/cm⁻¹: 1670 (CHO), 2129 (N₂), 2759 (CH stretch), 2877 (CH stretch). \( \delta_{\text{n}} \) (400 MHz, CDCl₃): 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). \( \delta_c \) (100 MHz, CDCl₃): 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⁺(81Br), 6 %], 225 [M⁺(79Br), 6], 199 [M⁺(81Br) – N₂, 27], 197 [M⁺(79Br) – N₂, 27], 83 (100). HRMS: 226.9513 and 224.9541. \( \text{C}_5\text{H}_4\text{BrN}_2\text{O} \) requires 226.9518, [M⁺(79Br)], and \( \text{C}_7\text{H}_7\text{BrN}_2\text{O} \) requires 224.9538.

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

\[
\text{Br} \quad \text{N}_3 \quad \text{S} \quad \text{S}
\]

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 BF₃OEt₂ (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 (MgSO₄) 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.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

272 as yellow needles; mp 162-164 °C. Rf[SiO2, hexane-DCM (2:1)]: 0.74. νmax(Golden Gate)/cm⁻¹: 2093 cm⁻¹ (N=N), 2135 (N-H), 2898 (CH stretch). δH (400 MHz, CDCl₃): 1.86-1.97 (1H, m, Hax-5), 2.14-2.21 (1H, m, Heq-5), 2.91 (2H, dt, J 13.7 and 4.1 Hz, Heq-4 and Hax-6), 3.09 (2H, dt, J 2.3 and 13.5 Hz, Hax-4 and Hax-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'). δc (100 MHz, CDCl₃): 24.95 (CH₃), 32.13 (CH₂), 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⁺(¹¹Br), 20 %], 315 [M⁺(⁷⁹Br), 20], 215 [M⁺(⁸¹Br) – N₂ and CH₂CH₂SH, 30], 213 [M⁺(⁷⁹Br) – N₂ and CH₂CH₂SH, 30], 83 (100). HRMS: 316.9484 and 314.9503. C₁₀H₁₀¹¹Br₃N₂S₂ requires 316.9478, and C₁₀H₁₀⁷⁹Br₃N₂S₂ requires 314.9500. Microanalysis: C, 38.05; H, 3.13; N, 13.08 %. C₁₀H₁₀¹¹Br₃N₂S₂ requires C, 37.98; H, 3.19; N, 13.29 %.

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

[tet-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(OiPr)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 (MgSO₄). Removal of solvent in vacuo gave dark brown oil. Column chromatography, (DCM), gave aniline 295 as a yellow solid (0.143 g, 26 %). Rf [SiO2, DCM]: 0.71. νmax(Golden Gate)/cm⁻¹: 1618 (NH₂ bend), 2898 (CH stretch), 2931 (CH stretch), 3353 (NH stretch), 3443 (NH stretch). δH (400 MHz, CDCl₃): 1.72-1.84 (1H, m, Hox-5), 2.01-2.08 (1H, m, Heq-5), 2.80 (2H, dt, J 13.7 and 4.0 Hz, Hox-4 and Heq-6), 2.94 (2H, dt, J 2.4 and 13.5 Hz, Hox-4 and Hax-6), 4.09 (2H, s, NH₂), 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, CDCl₃): 24.60 (CH₂), 31.05 (CH₂), 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⁺(81Br), 45 %], 289 [M⁺(79Br), 45], 216 [M⁺(81Br) – 'CH₂CH₂CH₂SH, 57], 214 [M⁺(79Br) – 'CH₂CH₂CH₂SH, 57], 83 (100). HRMS: 290.9570 and 288.9598. 
C₁₀H₁₂⁸¹BrNS₂ requires 290.9573, and C₁₀H₁₂⁷⁹BrNS₂ requires 288.9595. Microanalysis:

C, 41.32; H: 4.11; N, 4.70 %. C₁₀H₁₂BrNS₂ requires C, 41.38; H, 4.17; N, 4.83 %.

2-[2'-Azido-5'-bromophenyl]-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 NaHCO₃ (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. Rₖ[SiO₂; hexane: EtOAc (10:1)]:

0.69. v_max(Golden Gate)/cm⁻¹: 1145 (C-O), 2074 (N₃). δ_H (400 MHz, CDCl₃): 1.19 (6H, s, CH₃), 1.23 (6H, s, CH₃), 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, CDCl₃): 22.19 (CH₃), 24.28 (CH₂), 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⁺(81Br), 9 %], 325 [M⁺(7⁹Br) 9 %], 197 (100)]. HRMS 327.0410 and 325.0424. C₁₃H₁₆⁸¹BrN₃O₂ requires 327.0415, [M⁺(7⁹Br)], and C₁₃H₁₆⁷⁹BrN₃O₂ 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 (MgSO₄). 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. Rf [SiO₂, hexane-EtOAc (4:1)]: 0.45. v_max(Golden Gate)/cm⁻¹: 1366 (B-O), 1478 (Ar), 1682 (C=O). δ_H (400 MHz, CDCl₃): 1.32 (12H, s, CH₃), 1.54 (9H, s, "Bu), 1.91 (1H, tdd, 3.0, 12.5 and 14.1 Hz, Hₙ=5), 2.17 (1H, ttd, J 2.3, 3.9 and 14.2 Hz, Hₐq=5), 2.93 (2H, ddd, J 3.3 , 3.9 and 14.4 Hz, Hₐq=4 and Hₐq=6), 3.06 (2H, ddd, J 2.3, 12.5 and 14.4 Hz, Hₐq=4 and Hₐq=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, CDCl₃): 24.86 (CH₃), 25.17 (CH₂), 28.40 (CH₃), 31.93 (CH₂), 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⁺, 6 %), 380 (71), 274 (M⁺, -C(CH₃)₃ and HSCH=CHCH₂SH, 100). HRMS: 437.1866. C₂₁H₃₂BNO₄S₂ 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. Rf[SiO2; hexane: EtOAc (10:1)]: 0.23. δmax(Golden Gate)/cm⁻¹: 1633 (Ar), 2363 (C=N). δH (400 MHz, CDCl₃): 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). δC (100 MHz, CDCl₃): 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⁺ (⁸¹Br), 59 %], 197 [M⁺(⁷⁹Br) 60 %], 83 (100). HRMS 198.9456 and 196.9476.

C₇H₄⁸¹BrNO requires 198.9460, [M⁺(⁷⁹Br)], and C₇H₄²H⁷⁹BrNO requires 196.9478.

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

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\begin{align*}
\text{\textbf{294}} \\
\text{\textbf{294}}
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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 (MgSO₄). 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. Rf[SiO₂, DCM/Hexane]: 0.70. νmax(Golden Gate)/cm⁻¹: 1607 (Ar), 3402 (NH₂). δH (400 MHz, CDCl₃): 1.23 (12H, s, CH₃), 1.82-1.99 (1H, m, Hax-5), 2.09-2.21 (1H, m, Heq-5), 2.83 (2H, td, J 4.0 and 13.0 Hz, Heq-4 and Heq-6), 3.01 (2H, dt, J 2.0 and 13.0 Hz, Hax-4 and Hax-6), 4.40 (2H, broad s, NH₂), 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'). δC (100
MHz, CDCl₃): 24.89 (CH₃), 25.29 (CH₂), 32.00 (CH₂), 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⁺, 79 %), 262 (100), HRMS: 337.1338. C₁₆H₂₄BNO₂S₂ requires 337.1341. Microanalysis: C, 57.02; H: 7.17; N: 4.22 %. C₁₆H₂₄BNO₂S₂ requires C, 56.97; H, 7.17; N, 4.15 %.

2-(2'-Aminophenyl)-1,3-dithiane 296

![Chemical Structure](image)

*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(Pr))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 (MgSO₄). Removal of solvent in *vacuo* gave dark brown oil. Column chromatography, (DCM), gave compound 296 as a yellow solid (370 mg, 8 %). R$_r$[SiO₂, DCM]: 0.51. δ$_H$ (400 MHz, CDCl₃): 1.85-1.91 (1H, m, H₆-5), 2.16-2.19 (1H, m, H₇eq-5), 2.94 (2H, td, J 4.0 Hz and 13.2 Hz, H₆eq-4 and H₇eq-6), 3.11 (2H, dt, J 2.2 Hz and 13.2 Hz, H₆ax-4 and H₆ax-6), 3.99 (2H, broad s, NH₂), 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, CDCl₃): 25.31 (CH₂), 32.05 (CH₂), 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⁺, 56 %), 136 [(M⁺ – 'C₃H₅S, 100)]. HRMS: 211.0487. C₁₀H₁₃NS₂ requires 211.0485.
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 (MgSO₄). 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, CDCl₃): 1.97-2.01 (1H, m, H₃C-5), 2.18-2.21 (1H, m, H₅eq-5), 2.94 (2H, dt, J 3.7 Hz and 14.1 Hz, H₃C=4 and H₅eq-6), 3.16 (2H, dt, J 2.2 Hz and 12.7 Hz, H₃C-4 and H₅ax-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, CDCl₃): 25.01 (CH₂), 32.27 (CH₂), 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⁺, 15 %), 224 [(M⁺– ‘OH, 53)], 106 [(M⁺– ‘C₄H₇S₂O, 100)], HRMS: 241.0230. C₁₀H₁₁NS₂O₂ requires 241.0229.

2-(2′-Aminophenyl)-1,3-dithiane 317

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 (MgSO₄). Removal of solvent in vacuo gave the target aniline 317.
as yellow solid (1.44 g, 76 %). $\delta_{H}$ (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'). $\delta_{C}$ (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$^+$, 56 %), 136 (M$^+$ – C$_3$H$_2$S, 100). HRMS: 211.0487. C$_{10}$H$_{13}$NS$_2$ requires 211.0485.

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

![Diagram of 2-(2'-Aminotrityl)-1,3-dithiane 319](image)

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 %). $\nu_{\max}$(Golden Gate)/cm$^{-1}$: 1439 (Ar), 1488 (Ar), 2846 (CH). $\delta_{H}$ (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). $\delta_{C}$ (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$^+$, 2 %), 210 [(M$^+$ – C(Ph)$_3$, 100)]. HRMS: 453.1585. C$_{29}$H$_{27}$NS$_2$ requires 453.1583.
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

2-(2’-Phenylethyl)indole 324

A MacroKan™ 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 °C. ν<sub>max</sub>(Golden Gate)/cm<sup>−1</sup>: 2926 (CH), 2856 (CH), 1452 (Ar). δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 2.99-3.10 (4H, m, CH<sub>2</sub>CH<sub>2</sub>), 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<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 30.19 (CH<sub>2</sub>), 35.66 (CH<sub>2</sub>), 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 (El<sup>+</sup>): 221 (M<sup>+</sup>, 23 %), 130 (M<sup>+</sup>−CH<sub>2</sub>Ph, 75), 91 (M<sup>+</sup>−CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>N, 100), HRMS: 221.1204. C<sub>16</sub>H<sub>13</sub>N requires 221.1202.

2-(2’-Phenylethyl)-3-tritylindole 325

A MacroKan™ 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 °C. Rf[SiO<sub>2</sub>; DCM-hexane (6:1)]: 0.81. ν<sub>max</sub>(Golden Gate)/cm<sup>−1</sup>: 1446 (Ar), 1490 (Ar), 2849 (CH), 2918 (CH). δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 2.28 (2H, t, J 8.4 Hz, CH<sub>2</sub>CH<sub>2</sub>), 2.40 (2H, t, J 8.4 Hz, CH<sub>2</sub>CH<sub>2</sub>), 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<sub>3</sub>), 7.32-7.39 (5H, m, ArH), 7.60 (1H, bs, NH). δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 28.68 (CH<sub>2</sub>), 33.95
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

(CH₂), 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⁺, 95 %), 386 (M⁺– Ph, 100), HRMS: 463.2300. C₃₅H₃₈BNO₂S₂ requires 463.2301.

2-(2’-Aminotriptyl)-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 (MgSO₄) 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 °C. vₑₘₐₓ(Golden Gate)/cm⁻¹: 1446 (Ar), 1490 (Ar), 2897 (CH), 2932 (CH). δₘ (400 MHz, CDCl₃): 1.19 (12H, s, CH₃), 1.61-1.72 (1H, m, Hₐx-5), 1.98-2.05 (1H, m, Hₐq-5), 2.78 (2H, td, J 4.1 Hz and 13.2 Hz, Hₐq-4 and Hₐq-6), 2.91 (2H, dt, J 2.1 Hz and 13.1 Hz, Hₐx-4 and Hₐx-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’). δₜ (100 MHz, CDCl₃): 24.82 (CH₃), 31.15 (CH₂), 31.74 (CH₂), 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⁺*, 3 %), 336 [(M⁺– C(Ph)₃, 100)]. HRMS: 579.2437. C₃₅H₃₈BNO₂S₂ 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 %). δH (400 MHz, CDCl3): 0.24 (9H, s, Si-CH3), 1.33 (12H, s, CH3), 1.54 (9H, s, t-Bu), 1.92-2.05 (1H, m, Hax-5), 2.14-2.22 (1H, m, Heq-5), 2.88-3.07 (4H, m, Heq-4, Heq-6, Hax-4 and Hax-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'). δC (100 MHz, CDCl3): 0.60 (CH3), 23.52 (CH3), 23.82 (CH2), 27.05 (CH3), 30.59 (CH2), 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'', 3 %), 452 [(M'' - 'C(CH3)3 55)], 408 [(M'' - 'C(CH3)3 and CO2 60)], 346 (M'', - 'C(CH3)3 and HSCH=CHCH2SH, 100). HRMS: 509.2263. C24H40BNS2SiO4 requires 509.2261.

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

A MacroKan™ 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. Rf [SiO2, DCM]: 0.76. v_max(Golden Gate)/cm⁻¹: 1734 (C=O), 2976 (CH). δ_H (400 MHz, CDCl3): 1.36 (12H, s, CH₃), 1.68 (9H, s, ‘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, CDCl3): 24.93 (CH₃), 28.27 (CH₃), 31.76 (CH₂), 35.20 (CH₂), 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 (El): 447 (M⁺, 19 %), 391 (M⁺ – CH₂=C(CH₃)₂, 44), 300 (82), 83 (100). HRMS: 447.2577. C₂₇H₃₆BNO₄ requires 447.2571.

1-[4’-(4’’-Methylphenyl)phenyl]-4-phenylbutan-2-one 341

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 Et₂O. 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, CDCl₃): 2.39 (3H, s, ArCH₃), 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, CDCl₃): 21.50 (CH₃), 30.16 (CH₂), 43.19 (CH₂), 50.37 (CH₂), 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). Rf [SiO2, DCM]: 0.85. νmax(Golden Gate)/cm⁻¹: 1341 (NO2), 1516 (NO2), 1595 (Ar), 1734 (C=O), 2926 (CH), 2968 (CH). δH (400 MHz, CDCl3): 1.63 (9H, s, CH3), 2.97 (2H, t, J 7.9 Hz, CH2Ph), 3.28 (2H, t, J 7.9 Hz, CH2CH2Ph), 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'), 7.51 (1H, d, J 17 Hz, H-4), 7.57 (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") δC (100 MHz, CDCl3): δ 28.30 (CH3), 31.77 (CH3), 35.16 (CH3), 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⁺, 16 %), 386 (M⁺ – CH2=CH(CH3)2, 63), 295 (86), 57 (100), HRMS: 442.1893. C27H26N2O4 requires 442.1893. Ketone 342 was isolated as an orange solid (13 mg). Rf [SiO2, DCM]: 0.48. νmax(Golden Gate)/cm⁻¹: 1342 (NO2), 1517 (NO2), 1592 (Ar), 1717 (C=O), 2924 (CH). δH (400 MHz, CDCl3): δ 1.38 (9H, s, CH3), 2.71 (4H, m, CH2CH2Ph), 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, J 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''). δC (100 MHz, CDCl3): 28.09 (CH3), 29.60 (CH2), 45.18 (CH2), 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)⁺- CH₂=CH(CH₃)₂; 40], 482 (58), 481 (32), 59 (100), HRMS: 582.2240. C₃₃H₃₂N₃O₇ 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. Rf [SiO₂, DCM]: 0.76. νmax(Golden Gate)/cm⁻¹: 1468 (Ar), 1731 (C=O), 2929 (CH), 2077 (CH), 3025 (Ar-H). δH (400 MHz, CDCl₃): 1.63 (9H, s, 'Bu), 2.33 (3H, s, CH₃), 2.97 (2H, t, J 8.4 Hz, CH₂Ph), 3.28 (2H, t, J 8.4 Hz, CH₂CH₂Ph), 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). δC (100 MHz, CDCl₃): 21.12 (CH₃), 28.32 (CH₃), 32.52 (CH₂), 35.25 (CH₂), 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⁺, 34 %), 355 (M⁺ – CH₂=CH(CH₃)₂, 56), 264 (95), 290 (100). HRMS: 411.2199. C₂₉H₂₉NO₂ requires 411.2198.
**N-Boc-5-(4'-methylphenyl)-2-(2"'-phenylethyl)indole 350**

![Structure](image)

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. Rf [SiO2, DCM]: 0.76. Analytical data as reported for previous indole 350 above.

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

![Structure](image)

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. υmax (Golden gate)/cm⁻¹: 1468 (Ar), 1731 (C=O), 2929 (CH). δH (400 MHz, CDCl3): δ 1.61 (9H, s, 3'Bu), 2.95 (2H, t, J 7.8 Hz, CH₂Ph), 3.26 (2H, t, J 7.8 Hz, CH₂CH₂Ph), 3.76 (3H, s, OCH₃), 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). δC (100 MHz, CDCl3): 28.31 (CH₃), 31.83 (CH₂), 35.24 (CH₂), 55.40 (CH₃), 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⁺, 52 %), 371 (M⁺ – CH₂=C(CH₃)₂, 87), 280 (100). HRMS: 427.2148. C₂₈H₂₉NO₃ requires 427.2147.
**N-Boc-2-(2''-phenylethyl)-5-(2'-thiophenyl)indole 352.**

![Chemical structure](image)

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. $\nu_{\text{max}}$(Golden gate)/cm$^{-1}$: 1470 (Ar), 1726 (C=O), 2854 (CH), 2925 (CH). $\delta_H$ (400 MHz, CDCl$_3$): 1.68 (9H, s, 'Bu), 3.03 (2H, t, $J$ 8.0 Hz, CH$_2$Ph), 3.33 (2H, t, $J$ 8.0 Hz, CH$_2$CH$_2$Ph), 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). $\delta_C$ (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$^+$, 43 %), 347 (M$^+$ – CH$_2$=C(CH$_3$)$_2$, 67), 212 (100). HRMS: 403.1607. C$_{25}$H$_{25}$NO$_2$S requires 403.1606.

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

![Chemical structure](image)

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. $\nu_{\text{max}}$(KBr)/cm$^{-1}$: 1496 (Ar), 1733 (C=O), 2854 (CH), 2974 (CH). $\delta_H$ (400 MHz, CDCl$_3$): 1.64 (9H, s, 'Bu), 2.98 (2H, t, $J$ 7.8 Hz, CH$_2$Ph), 3.30 (2H, t, $J$ 7.8 Hz, CH$_2$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’). δC (100 MHz, CDCl3): 27.25 (CH3), 30.74 (CH2), 34.12 (CH2), 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+ , 21 %), 342 [M+ – CH2=C(CH3)2, 48], 251 (65), 207 (100), HRMS: 398.1996. C26H26N2O2 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 MiniKanTM 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 %). 1H 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 MiniKanTM containing resin-bound enol ether 357 B (93 µeq.) gave indole 358 B (21.8 mg, 61 %). δH (400 MHz, CDCl3): 1.03 (2H, t, J 7.2 Hz, CH3CH2), 1.37
(12H, s, CH₃), 1.67 (9H, s, 'Bu), 2.93–2.98 (4H, m, CH₂CH₂), 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.**

![Structural formula of N-Boc-2-(3'-phenylpropyl)-5-(4'',5''-tetramethyl-1'',3'',2''-dioxaborolan-2''-yl)indole 358 C.]

In the same way, one MiniKan™ containing resin-bound enol ether 357 C (93 μeq.) gave indole 358 C (25.7 mg, 60 %). δ_H (400 MHz, CDCl₃): 1.33 (12H, s, CH₃), 1.66 (9H, s, 'Bu), 2.04 (2H, qn, J 7.4 Hz, CH₂CH₂CH₂), 2.73 (2H, t, J 7.4 Hz, CH₂CH₂CH₂Ph), 3.03 (2H, t, J 7.4 Hz, CH₂Ph), 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.**

![Structural formula of 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™ containing resin-bound enol ether 357 D (93 μeq.) gave indole 358 D (24.2 mg, 58 %). δ_H NMR (400 MHz, DMSO-d₆): 1.21 (9H, s, 'Bu), 1.24 (12H, s, CH₃), 2.76 (2H, t, J 7.2 Hz, CH₂CH₂), 3.17 (2H, t, J 7.2 Hz, CH₂CH₂), 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™ containing resin-bound enol ether 357 E (93 µeq.) gave indole 358 E (17.5 mg, 42 %). $\delta_H$ (400 MHz, CDCl₃): 1.36 (12H, s, CH₃), 1.68 (9H, s, $^{t}$Bu), 2.19 (2H, qn, $J$ 7.4 Hz, CH₂CH₂CH₂), 3.20 (2H, t, $J$ 7.2 Hz, CH₂CH₂CH₂OPh), 4.04 (2H, t, $J$ 7.4 Hz, CH₂OPh), 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™ containing resin-bound enol ether 357 F (93 µeq.) gave indole 358 F (27.1 mg, 58 %). $\delta_H$ (400 MHz, CDCl₃): 1.36 (12H, s, CH₃), 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, OCH₃), 3.86 (3H, s, OCH₃), 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).
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

\( N\text{-Boc-2-[2’-(piperidin-4”-yl)ethyl]-5-(4”’,5”’-tetramethyl-1”’,3”’,2”’-dioxaborolan-2”’-yl)indole, trifluoroacetate salt 358 G’}. \)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{NH}_2 \\
\text{CF}_3\text{COO}^- & \\
\text{N} & \quad \text{B} \\
\text{O} & \quad \text{B} \\
\text{N} & \quad \text{H} \\
\end{align*}
\]

In the same way, one MiniKan™ containing resin-bound enol ether \( 357 \text{ G} \) (93 µeq.) gave indole \( 358 \text{ G’} \) (36.6 mg, 73 %), \( \delta_H \) (400 MHz, CDCl3): 1.37 (12H, s, CH\(_3\)), 1.53–1.56 (5H, m, H-pip), 1.69 (9H, s, ’Bu), 2.00-2.10 (2H, m, piperidine), 2.90-3.10 (4H, m, CH\(_2\)CH\(_2\)), 3.45-3.60 (2H, m, 2 \times CH\(_4\)H\(_3\)N), 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:H2O (4:1), Flow = 25 mL/min. HPLC MS data is displayed in Table 6 (library members in bold also have 1H 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
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<th>C</th>
<th>D</th>
<th>E</th>
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* MW of product not detected

Table 6
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

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

\[
\text{MeO-}\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{O}
\end{array}
\]

Data as reported under indole 351 above.

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

\[
\text{Ph-}\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\(\delta_H\) (400 MHz, CDCl\(_3\)): 1.70 (9H, s, \text{^3}Bu), 2.28 (3H, s, CH\(_3\)) 3.04 (2H, t, \(J\ 7.6\ Hz, CH_2Ph\)), 3.36 (2H, t, \(J\ 7.6\ Hz, CH_2CH_2Ph\)), 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 Ac.*

\[
\text{Ph-}\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\(\delta_H\) (400 MHz, CDCl\(_3\)): 1.71 (9H, s, \text{^3}Bu), 3.05 (2H, t, \(J\ 7.8\ Hz, CH_2Ph\)), 3.37 (2H, t, \(J\ 7.8\ Hz, CH_2CH_2Ph\)), 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.**

\[
\begin{align*}
\text{MeO} & \quad \text{4} \quad 3 \quad 2' \\
 & \quad \text{5} \quad 6 \quad 7 \\
\end{align*}
\]

\[
\begin{align*}
\delta_H (400 \text{ MHz, CDCl}_3): & \quad 1.68 (9H, s, \text{tBu}), 2.00-2.10 (2H, m, CH_2CH_2CH_2) \quad 2.75 (2H, t, J 7.6 \\
& \quad \text{Hz, CH}_2\text{Ph}), 3.06 (2H, t, J 7.6 \text{ Hz, CH}_2\text{CH}_2\text{CH}_2\text{Ph}), 3.85 (3H, s, OCH}_3), \quad 6.39 (1H, s, H-3), \\
& \quad 6.98 (2H, d, J 8.8 \text{ Hz, H-3' and H-5'}), 7.17-7.32 (5H, m, Ph) \quad 7.42 (1H, dd, 2.0 \text{ and } 8.4 \text{ Hz,} \\
& \quad \text{H-6}), \quad 7.56 (2H, d, J 8.8 \text{ Hz, H-2' and H-6'}), \quad 7.60 (1H, d, J 1.6 \text{ Hz, H-4}), \quad 8.11 (1H, d, J 8.4 \\
& \quad \text{Hz, H-7}).
\end{align*}
\]

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

\[
\begin{align*}
\text{MeO} & \quad \text{4} \quad 3 \quad 2' \\
 & \quad \text{5} \quad 6 \quad 7 \\
\end{align*}
\]

\[
\begin{align*}
\delta_H (400 \text{ MHz, CDCl}_3): & \quad 1.70 (9H, s, \text{tBu}), 2.21 (2H, tt, J 6.4 \text{ and } 7.4 \text{ Hz, CH}_2\text{CH}_2\text{CH}_2), \quad 3.23 \\
& \quad (2H, t, J 7.4 \text{ Hz, CH}_2\text{CH}_2\text{CH}_2\text{OPh}), \quad 3.85 (3H, s, OCH}_3), \quad 4.06 (2H, t, J 6.4 \text{ Hz, CH}_2\text{OPh}), \\
& \quad 6.42 (1H, s, H-3), \quad 6.89-6.98 (3H, m, Ph), \quad 7.00 (2H, d, J 2.8 \text{ Hz, H-3' and H-5'}), \quad 7.26-7.30 \\
& \quad (2H, m, Ph) \quad 7.43 (1H, dd, 2.0 \text{ and } 8.4 \text{ Hz, H-6}), \quad 7.54 (2H, d, 8.8 \text{ Hz, H-2' and H-6'}), \quad 7.60 \\
& \quad (1H, d, J 2.0 \text{ Hz, H-4}), \quad 8.10 (1H, d, J 8.4 \text{ Hz, H-7}).
\end{align*}
\]
**N-Boc-5-(2'-methylphenyl)-2-(3''-phenoxypropyl)indole** 359 Ec.

![Chemical structure of N-Boc-5-(2'-methylphenyl)-2-(3''-phenoxypropyl)indole 359 Ec.]

δ\(\text{H} (400\text{ MHz, CDCl})\): 1.70 (9H, s, 'Bu), 2.22 (2H, tt, 6.2 and 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)), 2.28 (3H, s, CH\(_3\)), 3.24 (2H, t, J 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)OPh), 4.06 (2H, t, J 6.2 Hz, CH\(_2\)OPh), 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 Ec.

![Chemical structure of N-Boc-5-(3'-cyanophenyl)-2-(3''-phenoxypropyl)indole 359 Ec.]

δ\(\text{H} (400\text{ MHz, CDCl})\): 1.71 (9H, s, 'Bu), 2.22 (2H, tt, J 6.2 and 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)), 3.23 (2H, t, J 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)OPh), 4.06 (2H, t, J 6.2 Hz, CH\(_2\)OPh), 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, J 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.

![Chemical structure of N-Boc-5-(2'-cyanophenyl)-2-(3''-phenoxypropyl)indole 359 Eh.]

δ\(\text{H} (400\text{ MHz, CDCl})\): 1.70 (9H, s, 'Bu), 2.22 (2H, tt, J 6.2 and 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)), 3.24 (2H, t, J 7.4 Hz, CH\(_2\)CH\(_2\)CH\(_2\)), 4.06 (2H, t, J 6.2 Hz, CH\(_2\)CH\(_2\)OPh), 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.**

\[
\begin{array}{c}
\text{C}_5N_2O_7 H_3 \text{O} \text{O} \\
\end{array}
\]

\[\delta_H (400 \text{ MHz, CDCl}_3): 1.71 (9H, s, '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}_2O\text{Ph}, 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.**

\[
\begin{array}{c}
\text{MeO} \text{O} \text{O} \text{O} \\
\end{array}
\]

\[\delta_H (400 \text{ MHz, CDCl}_3): 1.70 (9H, s, 'Bu), 2.97 (2H, t, J 7.8 Hz, CH}_2\text{Ph}, 3.33 (2H, t, J 7.8 Hz, CH}_2CH}_2\text{Ph}, 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 Fe.**

δ_H (400 MHz, CDCl₃): 1.70 (9H, s, 'Bu), 2.29 (3H, s, ArCH₃), 2.98 (2H, t, J 7.8 Hz, H-2″), 3.33 (2H, t, J 7.8 Hz, H-1″), 3.82 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 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, CDCl₃): 1.71 (9H, s, '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, OCH₃), 3.86 (3H, s, OCH₃), 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.**
Novel Titanium Carbenoid Reagents: Diversity Orientated Synthesis of Indoles and Spirocycles

\( \delta_H \) (400 MHz, CDCl\(_3\)): 1.71 (9H, s, '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**

![Structure of N-Boc-2'-[2'-(N-Boc-piperidin-4'-yl)ethyl]-5-(4''-methoxyphenyl)indole](image)

\( \delta_H \) (400 MHz, CDCl\(_3\)): 1.06-1.25 (2H, m, piperidine), 1.46 (9H, s, 'Bu), 1.49-1.78 (5H, m, piperidine), 1.70 (9H, s, 'Bu), 2.60-2.70 (2H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 3.05 (2H, t, \( J 7.6 \) Hz, H-1''), 3.86 (3H, s, OCH\(_3\)), 4.05-4.20 (2H, m, 2 \times CH\(_3\)H\(_2\)N), 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**

![Structure of 2-(2’Aminopyridin-3’-yl)-1,3-dithiane](image)

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-propanedithiol (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
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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 (MgSO₄). 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 %). Rf [SiO₂; hexane: EtOAc (4:2)]: 0.14. ν_max(Golden gate)/cm⁻¹: 1573 (Ar-H), 1612 (NH₂), 2898 (C=N–C). δ_H (400 MHz, CDCl₃): 1.87-1.98 (1H, m, Hax-5), 2.16-2.22 (1H, m, Heq-5), 2.94 (2H, dt, J 3.3 Hz and 13.8 Hz, Heq-4 and Heq-6), 3.08 (2H, td, J 3.6 Hz and 14.0 Hz, Hax-4 and Hax-6), 5.00 (2H, broad s, NH₂), 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, CDCl₃): 25.14 (CH₂), 31.78 (CH₂), 48.01 (CH), 114.59 (CH), 117.59 (C), 136.67 (CH), 148.13 (CH), 156.16 (C). (m/z): LRMS (EI⁺): 212 (M⁺, 92 %), 137 (100). HRMS 212.0442. C₉H₁₂N₂S₂ 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 (MgSO₄). 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 [SiO₂, hexane: EtOAc (4:2)]: 0.41. ν_max(Golden Gate)/cm⁻¹: 1729 (C=O), 2929 (CH₃). δ_H (400 MHz, CDCl₃): 1.36 (18H, s, 2xCH₃), 1.87-1.99 (1H, m, Hax-5), 2.15-2.21 (1H, m, Heq-5), 2.88 (2H, dt, J 3.7 Hz and 14.2 Hz, Heq-4 and Heq-6), 3.03 (2H, dt, J 2.3 Hz and 14.7 Hz, Hax-4 and Hax-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’). δC (100 MHz, CDCl3): 24.86 (CH2), 27.79 (CH3), 31.73 (CH2), 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+, 76 %), 256 (100). HRMS: 412.1491. C19H28N2O4S2 requires 412.0967.

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

![Chemical structure](attachment:image.png)

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 NaHCO3 until neutral, then water and dried over (MgSO4). 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 %). Rf [SiO2, hexane/ EtOAc (2:1)]: 0.46. v_max(Golden Gate)/cm⁻¹: 1472 (Ar), 1686 (C=O). δH (400 MHz, CDCl3): 1.88-1.90 (1H, m, Hax-5), 2.09-2.15 (1H, m, Heq-5), 2.86 (2H, dt, J 3.4 Hz and 14.0 Hz, Heq-4 and Heq-6), 3.00 (2H, dt, J 2.3 Hz and 14.4 Hz, Hax-4 and Hax-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’). δC (100 MHz, CDCl3): 27.27 (CH3), 30.75 (CH2), 46.13 (CH2), 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+, 54 %), 267 (74), 256 (100). HRMS: 312.0966. C14H20N2O2S2 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%). δH (400 MHz, CDCl3): 0.33 (9H, s, Si-CH3), 1.87-1.89 (1H, m, Hax-5), 2.06-2.12 (1H, m, Heq-5), 2.83 (2H, dt, J 3.4 Hz and 14.0 Hz, Heq-4 and Heq-6), 2.98 (2H, dt, J 2.3 Hz and 14.4 Hz, Hax-4 and Hax-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’). δC (100 MHz, CDCl3): 0.62 (CH3), 27.24 (CH3), 30.72 (CH2), 46.10 (CH2), 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

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 Et2O (180 mL) and washed with water (5 ×), 1 M aqueous CuSO4, water (2 ×) and brine and then dried over Na2SO4 and concentrated in vacuo to give TMS ether 105 as a
yellow oil (6.60 g, 98 %). δ_H (400 MHz, CDCl₃): 0.32 (9H, s, 3xCH₃) 1.84-1.98 (1H, m, H₃x-5), 2.12-2.29 (1H, m, Hₑq-5), 2.90 (2H, td, J 3.7 Hz and 14.2 Hz, Hₑq-4 and Hₑq-6), 3.05 (2H, dt, J 2.5 Hz and 14.2 Hz, Hₓ-4 and Hₓ-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'-trimethylsiloxypyphenyl]-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 Et₂O (180 mL) and washed with water (5 ×), 1 M aqueous CuSO₄, water (2 ×) and brine and then dried over Na₂SO₄ and concentrated in vacuo to give TMS ether 401 as a yellow solid (6.60 g, 98 %). mp: 119 °C. ν_max (Golden Gate)/cm⁻¹: 1486 (Ar), 1568 (Ar), 2897 (CH), 2955 (CH). δ_H (400 MHz, CDCl₃): 0.44 (9H, s, Si-CH₃) 1.85-1.98 (1H, m, Hₓ-5), 2.12-2.20 (1H, m, Hₑq-5), 2.90 (2H, td, J 4.1 and 13.7 Hz, Hₑq-4 and Hₑq-6), 3.05 (2H, dt, J 2.5 and 13.6 Hz, Hₓ-4 and Hₓ-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, CDCl₃): 0.04 (CH₃), 24.76 (CH₂), 31.99 (CH₂), 43.75 (CH), 119.14 (CH), 121.77 (CH), 128.25 (C), 129.62 (CH), 133.62 (C), 151.99 (C). m/z (Cl⁺): 321 [(M+H)⁺ (³⁵Cl), 64 %], 319 [(M+H)⁺ (³⁵Cl), 100 %]. HRMS: 319.0413 and 321.0385. C₁₃H₂₀⁴ClO₂S₂Si requires 319.0413, and C₁₃H₂₀⁴ClO₂S₂Si requires 321.0382.

4,4-Bis(phenylthio)butan-1-ol 404²³⁶

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 trifluoride 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 (MgSO₄). Removal of solvent in vacuo gave the thiaoacetal 404 as an orange oil (94.2 g, 91 %), sufficiently pure for the next step. δH (400 MHz, CDCl₃): 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

\[
\begin{align*}
\text{PhS} & \quad \text{Si} \\
\text{PhS} & \quad \text{O} \\
\text{PhS} & \quad \text{Si} \\
\text{PhS} & \quad \text{O} \\
\text{PhS} & \quad \text{Si} \\
\text{PhS} & \quad \text{O} \\
\text{PhS} & \quad \text{Si} \\
\text{PhS} & \quad \text{O} \\
\text{PhS} & \quad \text{Si} \\
\end{align*}
\]

1,1-Bis(phenylsulfonyl)butan-5-ol 404 (5.06 g, 17.2 mmol), was added to a solution of tert-butyl-dimethylsilyle 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 (MgSO₄) and the solvent removed in vacuo to give the target compound 405 as a yellow oil (6.31 g, 91 %). νmax: (Golden Gate)/cm⁻¹: 1439 (Ar), 1478 (Ar), 2928 (CH), 2953 (CH). δH (400 MHz, CDCl₃): 0.23 (6H, s, SiMe₂), 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). δC (100 MHz, CDCl₃): −5.12 (CH3), 18.37 (C), 25.74 (CH3), 30.29 (CH2), 32.53 (CH2), 58.15 (CH), 62.52 (CH2), 127.71 (CH), 129.07 (CH), 132.19 (CH), 134.06 (C). m/z (EI⁺): 404 (M⁺, 12 %), 295 (M⁺ – SPh, 100), 237 (M⁺ – 2SPh and –tBuH, 78). HRMS: 404.1664. C₂₂H₃₂OSiS₂ requires 404.1663.
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(2RS, 5RS)-2-Phenyl-1,6-dioxaspiro[4.5]decane and (2RS, 5SR)-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 %). Rf[SiO2, 100 % DCM]: 0.26. νmax (Golden Gate)/cm⁻¹: 1461 (Ar), 2894 (CH). δH (400 MHz, CDCl3): 1.42-2.09 (9HAA&BB, m, CH2), 2.10-2.18 (1Hβ, m, H-3B), 2.33-2.42 (1Hα, m, H-3A), 3.51 (1HAB, ddt, J 2.2 Hz, 4.4 Hz and 11.3 Hz, Heq-7A), 3.60 (1Hβ, ddt, J 2.2 Hz, 4.4 Hz and 11.3 Hz, Hax-7B), 3.81 (1Hα, dt, J 2.9 Hz and 11.3 Hz, Hax-7A), 3.89 (1Hβ, dt, J 2.9 Hz and 11.5 Hz, Hax-7B), 4.88 (1Hβ, dd, J 6.6 Hz and 9.6 Hz, H-2B), 5.10 (1HAB, t, J 7.1 Hz, H-2A), 7.15-7.36 (5HAA&BB, m, Ph). Assignment by COSY. δC (100 MHz, CDCl3): 20.23 (CH2), 20.27 (CH2), 25.30 (CH2), 25.37 (CH2), 33.17 (CH2), 33.86 (CH2), 33.96 (CH2), 34.40 (CH2), 37.89 (CH2), 39.59 (CH2), 61.89 (CH2), 61.99 (CH2), 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 (Cl⁻): 219 [(M+H)+, 100 %]. HRMS: 219.1385. C14H19O2 requires (M+H)+ 219.184.

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

63:37 mixture of diastereomers

186
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.

(5RS)-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. Rf [SiO2, hexane-DCM (1:1)]: 0.14. νmax(Golden Gate)/cm⁻¹: 1442 (Ar), 1490 (Ar), 2941 (CH). δH (400 MHz, CDCl3): 1.02 (1H, broad d, J 13.1 Hz, Heq-10), 1.50-1.92 (5H, m, CH₂), 2.80-2.95 (2H, m, H-3), 3.72 (1H, broad dd, J 4.1 and 11.0 Hz, Ha₂-7), 3.88 (1H, dt, J 2.6 and 11.1 Hz, Hax-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). δC (100 MHz, CDCl3): 19.14 (CH₂), 23.88 (CH₂), 29.61 (CH₂), 39.11 (CH₂), 60.15 (CH₂), 60.67 (C), 62.56 (CH₂), 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 (Cl⁺): 295 (M+H⁺, 100 %). HRMS: 295.1698. C20H23O2 requires M+H⁺, 295.1699.

(5RS)-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.

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

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. [\(\alpha\)]\text{D}\text{18} + 49.1 (c 0.1 M, DCM). \(\nu_{\text{max}}\) (Golden Gate)/\text{cm}^{-1}: 2931 (CH). \(\delta_{\text{H}}\) (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). \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)): \(\delta\) 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\(^{+}\), 13 %), 291 (M\(^{+}\)–CH\(_3\), 37), 111 (100). HRMS: 306.2559. C\(_{20}\)H\(_{34}\)O\(_2\) requires 306.2562.
(12R)-4',5'-Dihydro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'H)-pyran] and (12S)-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, thioacetals 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 MgSO₄ 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 (MgSO₄). The organics were concentrated under reduced pressure to give lactol 420 as a yellow oil (243 mg, 81%). νmax (Golden Gate)/cm⁻¹: 1580 (Ar-H), 1598 (Ar-H) 3057 (OH). δH (400 MHz, CDCl₃): 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). δC (100 MHz, CDCl₃): 34.56 (CH₂), 59.98 (C), 66.34 (CH₂), 101.47 (CH), 126.44 (CH), 126.70 (CH), 127.33 (CH), 128.36
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(CH), 128.46 (CH), 128.59 (CH), 143.37 (C), 145.01 (C). m/z, (Cl⁻): 241 [(M+H)⁺, 43 %], 223 (100, (M+H)⁺, –H₂O). HRMS: 241.1229. C₁₆H₁₇O₂ 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. BF₃·OEt₂ (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 (MgSO₄) and then concentrated in vacuo to yield 422 as orange oil (231 mg, 73 %). νmax (Golden Gate)/cm⁻¹: 1582 (Ar), 1595 (Ar). δH (400 MHz, CDCl₃): 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). δC (100 MHz, CDCl₃): 30.14 (CH₃), 60.27 (C), 66.59 (CH₂), 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⁺⁺, 7 %), 223 (100, M⁺⁺, –SPh). HRMS: 332.1235. C₂₂H₂₂OS requires 332.1238.

(2RS)-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 %). Rf [SiO₂, pet.ether-DCM (4:1)]: 0.22. νmax(Golden Gate)/cm⁻¹: 1456 (Ar), 1491
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(Ar), 2845 (CH), 2874 (CH). δH (400 MHz, CDCl3): 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). δC (100 MHz, CDCl3): 18.55

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

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

(2RS)-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 thiaoacetel 405 (992 mg, 2.46 mmol, 1.2 eq), furnished spiroacetel as a yellow oil. Column chromatography eluting with pet.ether-DCM (4:1) gave spiroacetel 425 as an oil (198 mg, 48 %). Rf[SiO2, pet.ether-DCM (4:1)]: 0.24. νmax(Golden Gate)/cm⁻¹: 1458 (Ar), 1488 (Ar), 1638 (C=C), 2851 (CH), 2923 (CH). δH (400 MHz, CDCl3): 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). δC (100 MHz, CDCl3): 18.55
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(CH₂), 24.77 (CH₂), 35.07 (CH₂), 61.79 (CH₂), 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. C₁₃H₁₅O₂ requires M+H⁺ 203.1071.

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

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 %). Rf [SiO₂, pet.ether-DCM (1:1)]: 0.76. νmax (golden gate)/cm⁻¹: 1451 (Ar), 1594 (Ar), 1609 (Ar), 2915 (CH), 2950 (CH). δH (400 MHz, CDCl₃): 2.01 (1Hₐ or B, dddd, J 4.4, 5.8, 9.7 and 12.4 Hz), 2.21-2.29 (3Hₐ or B), 2.44-2.53 (3Hₐ or B, m), 2.66 (1Hₐ or B, qd, J 8.3 and 12.4 Hz), 3.29 (1H₈, d, J 16.7 Hz), 3.34 (1H₈, d, J 16.7 Hz), 3.36 (1Hₐ, d, J 16.6 Hz), 3.45 (1Hₐ, d, J 16.6 Hz), 5.16-5.22 (1Hₐ or B, m), 5.34 (1Hₐ or B, dd, J 5.9 and 7.8 Hz), 6.80-6.86 (2Hₐ&B, m), 7.05-7.09 (1Hₐ&B, m), 7.24-7.44 (5Hₐ&B, m, ArH). δC (100 MHz, CDCl₃): 32.28 (CH₂), 33.75 (CH₂), 35.60 (CH₂), 37.62 (CH₂), 37.77 (CH₂), 37.88
(CH₂), 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 (Cl⁺): 289 [(M+H)⁺ ^{37}Cl], 33 %, 287 [(M+H)⁺ ^{35}Cl], 100 %]. HRMS: 287.0839 and 289.0815. C₁₇H₁₆^{35}ClO₂ requires (M+H)⁺ 287.0838, and C₁₇H₁₆^{37}ClO₂ requires (M+H)⁺ 289.0816.

(2'SS,5'SS)- and (2'R'S,5'R'S)-6-Chloro-4',5'-dihydro-5'-phenyl-spiro[benzo[b]furan-2(3'H),2'(3'H')-furan] 426

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, 3αR-(+)-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. [α]_D^18 + 11.7 (c = 0.1 M, DCM) νmax (Golden Gate)/cm⁻¹: 1479 (Ar), 1610 (Ar), 2866 (CH), 2925 (CH). δH (400 MHz, CDCl₃): 0.84 (3H^A&^B, s, CH₃), 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). δC (100 MHz, CDCl₃): δ 12.81 (CH₂), 13.13 (CH₃), 15.95 (CH₂), 15.98 (CH₂), 18.13 (CH₂), 18.49 (CH₂), 18.64 (CH₃), 18.67 (CH₃), 20.29 (CH₃), 20.59 (CH₃), 27.35 (CH₂), 31.11 (CH₃), 33.43 (CH₂), 33.98 (CH₂), 37.44 (CH₂), 37.59 (CH₂), 37.73 (CH₂), 39.10 (CH₂), 40.02 (CH₂), 40.05 (CH₂), 40.39 (CH₂), 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⁺ (37Cl, 42 %)], 374 [M⁺ (35Cl, 78 %)], 191 (100, M⁺ – CsH₆O₂Cl). HRMS: 374.2013 and 374.1993. C₂₃H₃₁ClO₂ requires 374.2018, and C₂₃H₃₁³⁷ClO₂ requires 376.1989.

(12R)-6'-Chloro-spiro[8,12-epoxy-13,14,15,16-tetranorlabdan-12,2'(3'H)-benzo[b]furan]
and (12S)-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 3αR-(+)-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(3H), 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. Rf [SiO2, pet.ether-DCM (4:1)]: 0.19. v_max (golden gate)/cm⁻¹: 1445 (Ar), 1596 (Ar), 1609 (Ar), 2889 (CH), 2985 (CH). δ_H (400 MHz, CDCl₃): 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, ddd, 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, CDCl₃): 36.59 (CH₂), 37.97 (CH₂), 61.39 (C), 65.54 (CH₂), 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, (Cl⁻): 365 [(M+H)⁺ (37Cl), 75 %], 363 [(M+H)⁺ (35Cl), 97 %], 211 (100 –C₈H₂OCl). HRMS: 363.1152 and 365.1132. C₂₃H₂₀³⁵ClO₂ requires (M+H)⁺ 363.1151, and C₂₃H₂₀³⁷ClO₂ requires (M+H)⁺ 365.1122.

6-Chloro-4',5'-dihydro-3',3'-diphenyl-spiro{benzo[b]furan-2(3H), 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.
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 (224 mg, 44 %). Data as above.
4',5'-Dihydro-3',3'-diphenylspiro{benzo[b]furan-2(3H),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<sub>max</sub> (Golden Gate)/cm<sup>-1</sup>: 1461 (Ar), 1480 (Ar), 1598 (Ar), 2899 (CH). δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 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<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 37.32 (CH<sub>2</sub>), 38.39 (CH<sub>2</sub>), 61.36 (C), 65.42 (CH<sub>2</sub>), 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<sup>+</sup>): 328 (M<sup>+</sup>, 6%), 194 (100, M<sup>+</sup>, <sup>13</sup>C<sub>8</sub>H<sub>6</sub>O<sub>2</sub>). HRMS: 328.1463. C<sub>23</sub>H<sub>20</sub>O<sub>2</sub> requires 328.1465.

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

![Chemical Structure of 2,3,4,6-tetra-O-benzyl-D-glucolactone 432](image)

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 Et3O (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 %). δH (400 MHz, CDCl3): 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 CH2Ph), 4.92 (1H, d, J 11.2 Hz, CH3H6).

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

![Chemical Structure of (2R,3'R,4'S,5'S,6'R)-6'-(Benzyloxyethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3H),2'(3'H)-pyran} and (2S,3'R,4'S,5'S,6'R)-6'-(Benzyloxyethyl)-4',5'-dihydro-3',4',5'-tribenzyloxy-spiro{benzo[b]furan-2(3H),2'(3'H)-pyran} 433](image)

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 %). Rf [SiO2, hexane-ethyl acetate (4:1)]: 0.51. vmax(Golden Gate)/cm⁻¹: 1454 (Ar), 1496 (Ar), 1598 (Ar), 2856 (CH), 2925 (CH). δH (400 MHz, CDCl3): 2.99 (1H8, d, J 16.3 Hz, CCH6 H8 Ar), 3.13 (1H5, d, J 16.4 Hz, CCH5 H5 Ar), 3.17 (1H8, d, J 16.3 Hz, CCH6 H8 Ar).
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Ar), 3.57 (1H, d, J 16.1 Hz, CCl\textsubscript{4} H\textsubscript{2} Ar), 3.57–4.26 (6H\textsuperscript{A&B}, m, sugar CH and CH\textsubscript{2}), 4.41–5.50 (8H\textsuperscript{A&B}, m, 4 × CH\textsubscript{2}Ph) 6.71–7.40 (24H\textsuperscript{A&B}, m, ArH). Assignment by COSY. m/z, (FAB\textsuperscript{+}): 629 [(M+H\textsuperscript{+}, 100 %)]. HRMS: 629.2824. C\textsubscript{4}H\textsubscript{4}O\textsubscript{6} requires M+H\textsuperscript{+} 629.2821.

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

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\textsuperscript{256}

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\textsubscript{aq} (4 × 100 mL), sat. NaCl\textsubscript{aq} (1 × 50 mL) and dried (MgSO\textsubscript{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**

![Structure of 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. v_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, (Cl⁻): 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**

![Structure of 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.
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. NaHCO₃. The layers were separated and the aqueous layer was extracted with DCM (3 ×). All organics were then combined, washed with water (3 ×) and then brine (1 ×). The organics were then dried (MgSO₄) 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 (MgSO₄) and concentrated under reduced pressure to give crude 111 as orange oil. Column chromatography [pet.ether/ DCM (2:1), SiO₂] 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, Rᵣ [SiO₂, pet.ether- DCM, (2:1)] 0.12. δH (400 MHz, CDCl₃): 1.42 (1H, s, NH), 1.75-1.82 (2H, m, CH₂CH₂N), 1.90-1.95 (2H, m, CH₂CH₂CH₂N), 2.10 (2H, t, J 6.5 Hz, CH₂N), 4.38 (1H, t, J 6.62 Hz, CH₂CH₂), 7.16-7.21 (3H, m, Ar-H), 7.24-7.33 (12H, m, Ar-H), 7.38-7.52 (10H, m, Ar-H).
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 Et₂O. The white ppt formed upon addition of Et₂O was removed by filtration and the filtrate washed with 10 % Na₂SO₄ and then water. The organics were then dried (MgSO₄) and concentrated under reduced pressure to yield 451 as white solid (13.6 g, 97%). δH (400 MHz, CDCl₃): 2.31 (2H, s, NH₂), 7.18-7.30 (15H, m, Ar-H).
REFERENCES


166 Data for the crystal structure appears in appendix B.


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


APPENDIX – A

Representative NMR spectra of selected products
N-Boc-2-Phenylethyl-5-(4'',5''-tetramethyl-1''',3''',2'''-dioxaborolan-2''-yl]-indole 338
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$\text{N-Boc-2-Phenylethyl-S-(para-toluyl)-indole 350}$
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).
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5-Bromoanthranil 290