THE UNIVERSITY OF SOUTHAMPTON

The Development of Novel Immobilised Reagents and Solid Phase Linkers

by

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Doctor of Philosophy

Department of Chemistry
Faculty of Science

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PREFACE

The research described in this thesis was carried out under the supervision of Dr. A. Ganesan at the University of Southampton between October 2000 and November 2003. No part of this thesis has been previously submitted at this or any other University.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

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Polymer-supported reagents have radically changed the way we perform modern chemistry. Most notably, the time from initial hit to lead in drug discovery has been dramatically reduced. A study into the use of polymer-supported alkylboranes as hydroborating reagents based upon 9-borabicyclononane (9-BBN) was made, and the potential of this reagent in relation to the solution-phase compound was evaluated.

An immobilised tetrafluoroarylsulfonyl chloride (TFAS) linker was developed, and reacted with a small number of phenolic substrates to give supported arylsulfonates. Four different palladium-mediated diversification protocols were investigated, allowing transfer hydrogenation and deuteration, and Suzuki and Heck cross-couplings. A solid-phase synthesis of the ACE II inhibitor Valsartan was developed using the TFAS linker, demonstrating the potential of this reagent for short linear syntheses.

An optimised preparation of the PDE5 inhibitor Cialis^{TM} was developed through the use of the *N*-Acyliminium Pictet-Spengler reaction.

The use of ionic liquids as a catalytic reaction medium for solid-phase Suzuki cross-coupling reactions was evaluated, and when used in conjunction with DMF was found to significantly accelerate the reaction, resulting in increased yields over a given period of time.

ACKNOWLEDGMENTS

I am most indebted to my supervisor Dr. Ganesan who showed me over 3 years of guidance and enthusiasm, along with eternal patience; for these virtues I wish to thank him sincerely. I would also like to thank the members of Dr. Ganesan's research group, with whom I shared a lab for 2 years; we shared some great times. During the final year of my PhD studies, I worked directly in the Combinatorial Centre of Excellence among a wonderfully diverse range of personalities, each of whom brought some kind of balance to the lab. I wish to thank all the people I met and worked with, you made my studies so much more enjoyable. To my family, my wonderful partner Christine, and all the other people who love and care for me, I dedicate this work to you; without your support and encouragement all those hurdles would have seemed insurmountable.

ABBREVIATIONS

AMP	Aminomethyl polystyrene
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bpoc	2-(4-Biphenylyl)isopropyloxycarbonyl
br	Broad
Bz	Benzoyl
cat.	Catalytic
CMS	4-Chloromethylstyrene
CMP	Chloromethylpolystyrene
d	Doublet
δ	Chemical shift (ppm)
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIAD	Diisopropyl azodicarboxylate
DIC	*N,N'*-Diisopropylcarbodiimide
DHP	3,4-Dihydro-2*H*-pyran
DMA	*N,N'*-Dimethylacetamide
DMAP	*N,N'*-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMS	Dimethylsulfide
dppf	Bis-(diphenylphosphino)ferrocene
dppp	Bis-(diphenylphosphino)propane
DVB	1,4-Divinylbenzene
ES	Electrospray (mass spectrometry)
Fmoc	9-Fluorenylmethoxycarbonyl
HMP	Hydroxymethyl polystyrene
HMPA	Hydroxymethylphenoxyacetyl
HMPT	Hexamethylphosphorous triamide
HOBt	1-Hydroxybenzotriazole

J	Scalar coupling constant (Hertz)
L.A.	Lewis acid
LAH	Lithium Aluminium Hydride
LDA	Lithium diisopropylamide
λ	Wavelength (nm)
m	Multiplet (NMR) or medium (IR)
Me	Methyl
Mes	Mesylate (methanesulfonyl)
OIL	Organic Ionic Liquid
p	*para*
PEG	Poly(ethylene) glycol
PMA	Phosphomolybdic acid
PPTS	Pyridinium-4-Toluene Sulfonate
PS	Poly(styrene)
q	Quartet
rt.	Room temperature
s	Singlet (NMR) or strong (IR)
SPOC	Solid-phase organic chemistry
SPOS	Solid-phase organic synthesis
SPPS	Solid-phase peptide synthesis
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TCA	Trichloroacetimidate
TFA	Trifluoroacetic acid
TMAO	Trimethylamine-N-Oxide
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMSOTf	Trimethylsilyl triflate
Trt	Trityl (Triphenylmethyl)
4-TSA	4-Toluene sulfonic acid
ν	Frequency (cm^{-1})
w	Weak

Introduction to Polymer-Assisted Chemistry

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The Development of a Solid-Phase Hydroborating Reagent

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The Development of a Tetrafluoroarylsulfonate Linker

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Introduction to Polymer-Assisted Chemistry

Chapter I Contents

1.1 Introduction to Polymer-assisted Chemistry

1.1.1 Solution-phase chemistry

Chemistry has been performed predominantly in the solution-phase. Since molecular interactions occur most readily when reactive substrates are solvated and allowed to come into direct contact with one another, the dissolution of reactants is the simplest way to facilitate their reaction in a controlled and predictable manner. The reaction solvent plays several important roles, including the transport of heat energy around reacting species, the delivery of reactive species into close proximity, and also the maintenance of homogeneity throughout the reacting mixture. Selective use of solvents also allows the thermodynamic stabilization of such highly reactive chemicals as butyl lithium and other organometallic reagents, and may be used to influence the overall outcome of the reaction process. Upon completion of any given reaction, the desired product must be isolated and can only be considered pure when it is free from all other substances such as unreacted starting materials, side products, catalysts and solvents etc. Clearly, the performing of chemistry in the solution-phase necessitates dedicated purification procedures, which not only requires skill on behalf of the experimentalist, but also specialized equipment, time and considerable effort. The preparation of selected chemicals for research purposes can of course be accomplished by hand, especially if the compounds desired are particularly unrelated or are required in large quantities. However, when large numbers of structurally similar compounds are desired solely for determination of biological activity and hence are required in only minute quantities, the task becomes repetitive and laborious.

1.1.2 Combinatorial chemistry

Within the last decade, more rapid preparation of organic molecules has become of paramount importance within the pharmaceutical industry, and many new techniques have been developed to aid the search for novel drug candidates. High-throughput screening methods developed by biologists for the assaying of small molecules as potential drug targets, has necessitated an acceleration of the synthesis of these candidates. Rapid screening of potential drugs has been pursued in this manner because the necessary structural characteristics of many desired biologically active compounds are often poorly understood. Now exists a technology which allows accurate screening of each of the potentially thousands of members of a library on an extremely minute scale and within a very short period of time.

Hence the current trend moves further towards larger numbers and smaller quantities of lead substances. In response, chemists have striven to satisfy the demand for molecules through the preparation of large chemical libraries by more streamlined parallel processes.[1,2] Of the many virtues brought to modern chemistry by this technique, perhaps the most impacting is the ability of the operator to produce very large numbers of structurally similar chemical compounds in a parallel manner known generally as combinatorial chemistry.[3,4] The term 'combinatorial chemistry' was defined by Czarnik as a subfield of chemistry, combining two or more series of chemical reactants in all possible combinations, such that large numbers of well defined products are formed in a manner which is amenable to screening for properties of interest.[5] Theoretically, 6 different amines may be reacted 6 times with each of 6 different acid chlorides to provide a chemical library of 36 unique and separate amides (scheme 1.1). In the preparation of large chemical libraries, large numbers of each type of starting material may be used such that arrays of many thousands of unique chemical compounds are produced.

6 different amine components

6 different acid chloride components	A1	A2	A3	A4	A5	A6
B1	A1B1	A2B1	A3B1	A4B1	A5B1	A6B1
B2	A1B2	A2B2	A3B2	A4B2	A5B2	A6B2
B3	A1B3	A2B3	A3B3	A4B3	A5B3	A6B3
B4	A1B4	A2B4	A3B4	A4B4	A5B4	A6B4
B5	A1B5	A2B5	A3B5	A4B5	A5B5	A6B5
B6	A1B6	A2B6	A3B6	A4B6	A5B6	A6B6

Scheme 1.1 Generation of an array of 36 unique compounds by combination of 6 x 6 different starting reactants

By virtue of the different combinations of starting materials present in each reaction vessel, each compound in the library is unique; however, the entire array will bear identical structural features inherited through the reaction operating overall. If the reaction in question builds into these molecules, a motif of biological significance, each member of the library will possess different biological properties dependent on the substitution of its precursors.

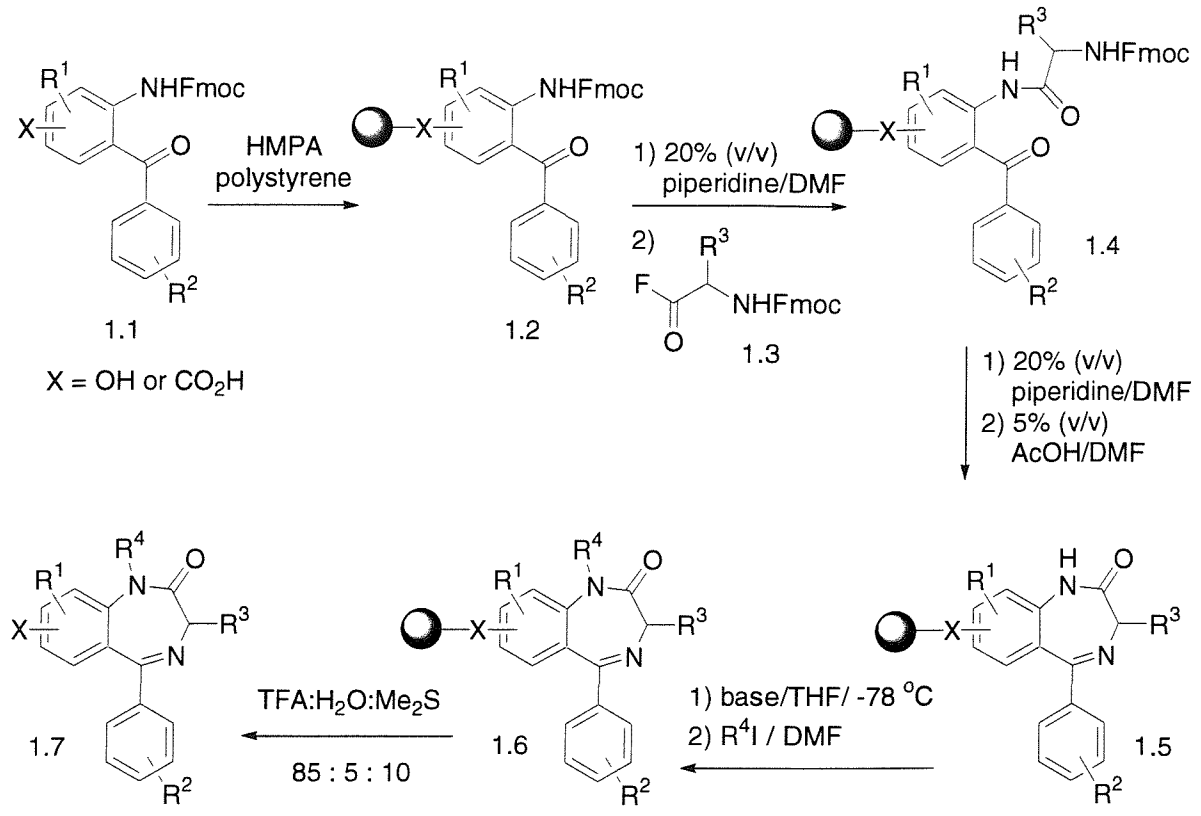
Furthermore, the combinatorial approach to organic synthesis may be divided into the two tactical domains of solution-phase and solid-phase chemistry. Both disciplines bring with them advantages and disadvantages, and neither represents a universal panacea. However, a combination of these techniques within a given research area most often relays significant advantage for such operations as the discovery and optimization of new protocols, screening of interesting physicochemical properties, and the genesis of new chemical libraries.

1.1.3 Polymer-supported chemistry

The radical idea that chemistry could be performed on tiny functionalised plastic beads was first realized by Robert Merrifield in 1963 with the synthesis of the tetrapeptide *L*-leucyl-*L*-alanylglycyl-*L*-valine via immobilisation of the intermediates on 2% cross linked chloromethyl polystyrene (CMP).[6] Merrifield's seminal report was soon to have an enormous impact on the modernisation of peptide synthesis, increasing dramatically the speed of the overall process. Merrifield had effectively embraced and solved the technical difficulties surrounding traditional solution-phase peptide synthesis such as protecting group manipulation, prohibitive solubility of amino acid derivatives and dedicated purification required at each synthetic stage.

Attachment of the first amino acid residue to the polystyrene support provided the requisite "*C*-terminal protecting group", allowing synthesis to be carried out on the "*N*-terminus". Further use of this "*C*-immobilisation, *N*-elongation" technique allowed Merrifield and Gutte to effect the total synthesis of the enzyme ribonuclease A in 1971, representing one of the most significant biochemical applications of this methodology today.[7] But the use of such synthetic techniques remained quite limited, given the harsh conditions of concentrated HF(aq) required to cleave the peptide from its benzylic support. However, the capability of such synthetic tools had in part been revealed, and significant efforts into more facile cleavage from polymer supports ensued.

Despite continued research efforts in the area of solid-phase chemistry, the technique remained exclusive to peptide synthesis until almost 30 years after its conception. Solid-phase chemistry was only brought into mainstream synthesis when Ellman and Bunin reported groundbreaking results of the high yielding (85-100% yield) synthesis of 10 different 1,4-benzodiazepines **1.7** (scheme 1.2).[8]



Scheme 1.2 Ellman's revolutionary solid-phase synthesis of benzodiazepines

1.1.4 Characteristics of polymer-assisted chemistry

Combinatorial chemistry has precipitated the development of new methods focused around improving the efficiency of performing chemical reactions and separations in both solid and solution-phases. Solid-phase chemistry brings great advantage at the separation stage, since the product is separated simply through filtration, either in the form of an immobilised product, or cleaved product in the filtrate. But, the same heterogeneity that is useful at the purification stage, can often be a liability at the reaction stage.

The true versatility of polymer-assisted techniques in modern synthesis was only properly revealed when the concept of automated chemical library synthesis was introduced to satisfy the continually increasing demands of drug discovery programs. Within these realms, supports of one kind or another have played a truly revolutionary role in the production of chemicals. Solid-phase techniques are particularly suitable for automation since the process of reagent addition, agitation, filtration and washing involve only the simplest of manipulations. Repetition of such processes presents no problem for robotic systems, and parallel processing of such laborious operations is best performed by automated machines. A correctly programmed robot synthesizer not only works continually without query, but also in a manner free from human error.

Today, the synthetic chemist is presented with a tremendously broad range of not only supported linkers for chemistry, but also supported reagents, scavengers, and catalysts. Nowadays upon designing a synthetic route, a continually increasing number of specifically designed supported reagents are available such that chemistry is no longer performed necessarily in the solution-phase alone.[9,10,11,12,13]

1.1.5 Support materials for solid-phase organic synthesis (SPOS)

Potentially, any solid material may be used for organic synthesis providing it can be chemically functionalised, and that it has sufficient structural integrity to withstand the conditions of the reactions for which it is intended. The use of several different physical supports for chemistry may be classified into several important categories:

1) **Hydrophobic supports:** which are insoluble in all solvents, e.g. crosslinked-polystyrene, functionalised silicas, aluminosilicates and controlled pore glass (CPG). (Macroporous polystyrene is by far the most common support material used for organic synthesis, and is generally inert to most reaction conditions.) 1% and 2% crosslinked-polystyrene supports are only readily swollen in organic solvents and are not suitable for synthesis with aqueous reaction media.

2) **Selectively soluble supports:** e.g. low molecular weight polyethylene glycol and linear polystyrene both of which are soluble in THF and CH_2Cl_2, but solidify upon addition of either hexanes or diethyl ether. Linear polystyrene of low molecular weight has been used for the microencapsulation of palladium catalysts, and also the volatile and highly toxic oxidant osmium tetroxide, used for the dihydroxylation of alkenes.[14]

3) **Hydrophilic supports:** which are insoluble in all solvents, e.g. poly(ethyleneglycol) (PEG) and Tentagel grafted resins (polystyene core, poly(ethyleneglycol) surface). Such supports are readily swollen in polar solvents such as water and DMF, facilitating synthesis in aqueous reaction media. However, these more costly supports commonly do not exhibit the structural integrity shown by the hydrophobic supports, and careful handling and solvation techniques must often be observed. Grafted supports are also usually very limited in terms of functional loading, which is often appreciably lower than that obtained using functionalised polystyrene.

4) **Miscellaneous supports:** including functionalised polymer pins, commonly used for immunological studies and the screening of peptides. Winks, consisting of porous disks of polyethylene are readily functionalised with carboxylic acid groups by oxidation with chromic acid. Winks are used mainly for peptide synthesis and surface screening of protein interactions. Functionalised laminated surfaces, including paper, cellulose, glass, polyethylene and polyacrylamide sheets, and hybrid combinations of these materials. Functionalised laminated surfaces are mainly used for 'very large scale immobilised peptide synthesis' (VLSIPS), where extremely minute quantities of peptides and oligonucleotides may be synthesized using ink-jet technology, and specifically when isolation of individual compounds is unnecessary. The functionalisation of flat surfaces in this way facilitates rapid screening through the use of fluorescent tags, located using appropriate optical scanning technologies.

1.1.6 Preparation of polystyrene supports

Of the many polymer supports available for synthesis, the most commonly used is 1-2% cross-linked polystyrene, prepared through suspension polymerization of styrene and divinylbenzene, in the presence of a radical initiator. Polymerisation is conducted using a biphasic mixture of organic and aqueous solvents, which are stirred together at a carefully controlled rate and temperature. The hydrophobic nature of styrene and divinylbenzene results in the formation of tiny polymerising droplets suspended in the aqueous-phase; the dimensions of which occupy a normal distribution dictated by the rate of stirring. A higher rate of stirring results in the formation of smaller organic droplets and hence a finer gauge polymerised resin. Present in the aqueous-phase of the reaction mixture is a surfactant (usually PVA), which acts to lower surface tension of the polymerising droplets, aiding emulsification of the two phases. Also necessary in the reaction mixture is the presence of a porogen component; an organic solvent such as toluene or heptane which is not polymerised, but which is present in the polymerising droplets in relatively high concentration. Following polymerization, the resin beads are isolated, and the porogen and other entrapped species are removed from the beads by thorough washing. Microscopic inspection of successfully polymerised beads reveals the presence of an enormous number of interstices within the structure of each bead. These 'pores' run randomly through the entire structure of the bead as a result of unpolymerised areas occupied in the reacting droplet by the porogen. This 'sponge-like' architecture, properly termed 'macroporous', is crucial to the overall use of cross-linked polystyrene as a chemical support.

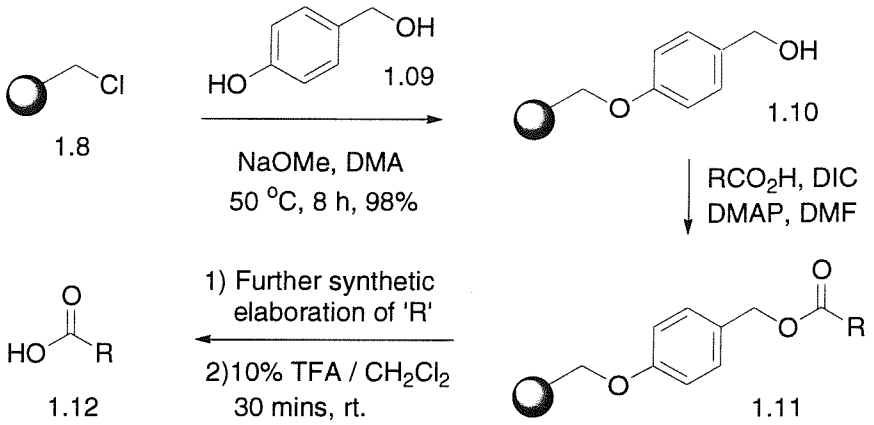
The absence of a porogen component results in the formation of totally intractable polymer beads which are brittle and devoid of pores; as a result of which, these beads do not facilitate permeation of solvated reactants, and hence are useless for synthetic applications. Macroporous polystyrene however, is readily swollen in an appropriate organic solvent to a gel-phase entity upon which chemistry can readily be conducted. Immobilised substrates resulting from the functionalisation of polystyrene resins are effectively solvated in this gel-phase environment, and essentially react as though fully solublised. Given the immobilised nature of reactive species, and the gel-like structure of common macroporous resins, the rate of reaction of these immobilised chemicals is heavily dependent upon the rate of delivery of reagents to the reactive sites within the support. The flux of material around reactive sites is then dependent upon the rate of diffusion of solutes in and out of each bead; which relates directly to the level of cross-linking and porosity of each bead, and indirectly to the solvent used to swell each bead to a gel-phase state. Generally however, the rate kinetics of reactions conducted on the gel-phase are dramatically slower than comparable solution-phase reactions. A 'pseudo-dilution' effect first described by Mazur and Jayalekshmy is inherently present as a result of the limiting rate of diffusion within a polymer support;[15] however, this has been utilised successfully for macrocyclisation via disulfide bond formation in peptide chemistry by Victor Hruby.[16]

The use of unfunctionalised polystyrene beads for synthesis is extremely limiting however, and although functionalisation may later be introduced to the beads, most synthesis resins are themselves produced from chloromethyl polystyrene **1.8** (CMP). Copolymerisation of 4-chloromethyl styrene with styrene and divinylbenzene allows for the preparation of CMP with a predictable chloride loading and excellent physical properties. This technique is the most commonly used for the preparation of CMP on bulk scale, which is further functionalised through reaction at the immobilised benzylic chloride site.

Aminomethyl polystyrene (AMP) for example is reliably prepared through reaction of potassium phthalimide with CMP in the presence of potassium hydroxide. The phthalimide substituted polystyrene resulting from this process is further reacted with hydrazine, releasing phthalhydrazide and giving an aminomethyl substituted polystyrene. These 'base' resins (CMP and AMP) are the most commonly used starting materials for further elaboration towards more exotic synthesis resins bearing specifically designed linkers.

1.1.7 Solid-phase linkers

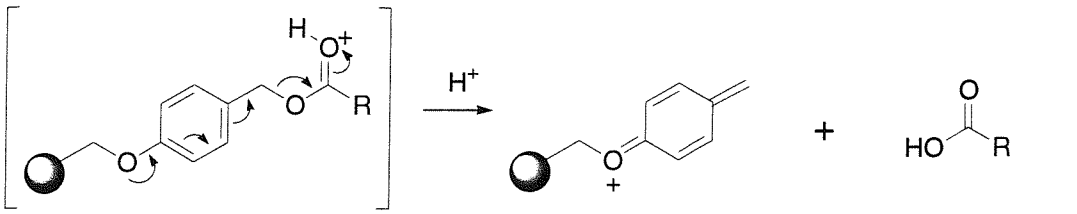
The area of solid-phase linkers was recently reviewed by Bradley *et al.*[17], and earlier by James.[18] Temporary immobilisation of reactive substrates on a supporting material is now most often achieved through the use of a selectively cleavable 'linker'; a tether which may be activated at the end of a synthetic sequence allowing total detachment of the substrate into the solution-phase prior to its isolation. This concept was first demonstrated in 1973 by Su-Sun Wang in the form of an acid-labile hydroxymethylphenoxyacetyl (HMPA) linker **1.10**. The linker was originally designed for the immobilisation of carboxylic acids, performed using a carbodiimide-activating agent (scheme 1.3). Other methods of acylation which have emerged through the use of the Wang linker include the use of mixed anhydrides with 2,6-dichlorobenzoyl chloride,[19] *N*-carboxyanhydrides,[20] and carboxylic acid activation using 1-(mesitylene-2-sulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT)[21] and 1-methylimidazole.



Scheme 1.3 Immobilisation of a carboxylic acid using the Wang linker

The strategic placement of an HMPA linkage between the polymer matrix and point of attachment of the desired substrate molecule allows far more user-friendly methods for compound cleavage, e.g. TFA rather than HF (in the case of Merrifield's original conditions).[22] When used for peptide synthesis, cleavage is normally achieved using 95% TFA, effecting also the global removal of acid-labile side-chain protecting groups. However, the electron releasing capacity of the 4-phenoxy substituent makes the Wang linker cleavable in solutions of TFA as dilute as 1%, which may be used when acid sensitive functionality is present in the immobilised substrate. Cleavage of the Wang linker results in the formation of an electrophilic 'quinone-methide' species **1.13**, which can react further with nucleophilic groups present in the cleaved substrate, resulting in loss of product (scheme 1.4).

As a remedy to this significant problem, the addition of nucleophilic scavengers may be made to the cleavage mixture in the form of several different chemical additives including: water, thioanisole or triethylsilane.

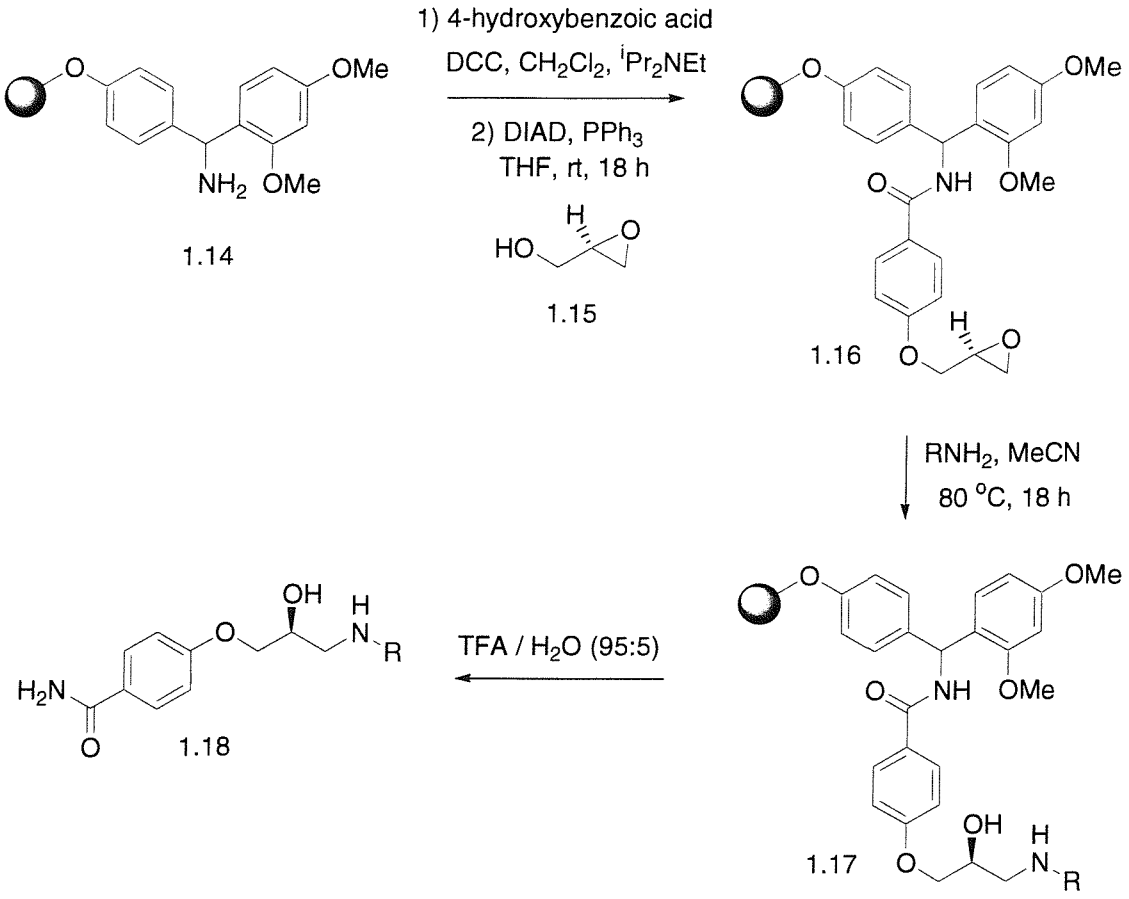


Wang linked carboxylate 1.11 — Quinone methide 1.13 — Carboxylate product 1.12

Scheme 1.4 Acid-mediated cleavage of the Wang linker

Additionally, the increased distance between the polymer matrix and point of attachment of the substrate may act beneficially with regard to the microenvironment surrounding the reactive substrate, and improved yields are generally reported through the use of linkers. Of the many solid-phase linkers which have become embedded into modern synthesis, there are several besides the Wang linker which are particularly noteworthy. One such example is the Rink linker **1.14**, developed around the recognized need for a more acid-labile system, which would allow direct cleavage to carboxamides, e.g. **1.18** (scheme 1.5.).[23]

In 2000, Bryan *et al.* demonstrated the preparation of a short series of phenoxypropanolamines **1.18** using Rink amide resin. Synthesis commenced with reaction of the Rink linker with 4-hydroxybenzoic acid resulting in formation of an immobilised aryl amide. The phenolic hydroxyl group was reacted with a chiral hydroxypropylene oxide under standard Mitsunobu conditions, followed by ring-opening of the epoxide using a series of primary amines to give good yields of immobilised phenoxypropanolamines **1.17**. Cleavage with concentrated TFA gave the desired carboxamides in good overall yields (scheme 1.5).[24]

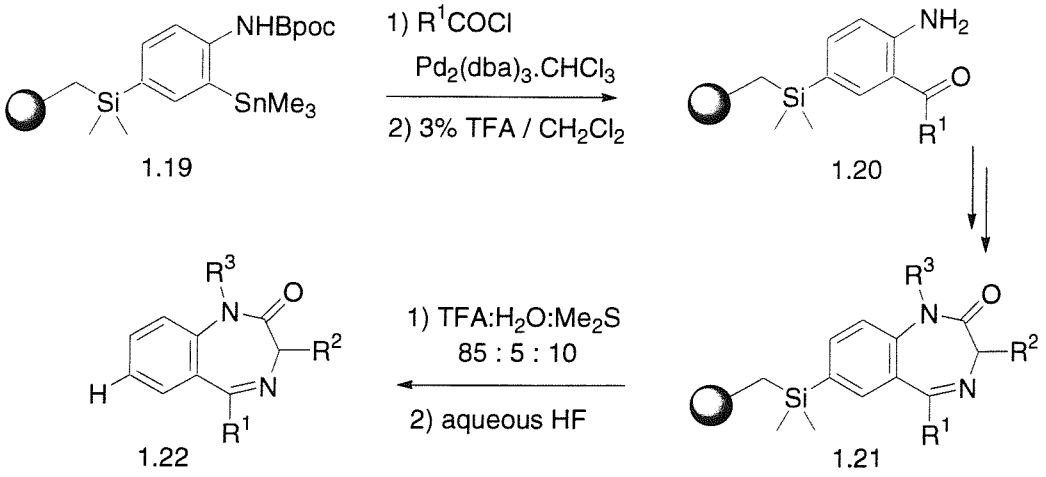


Scheme 1.5 Synthesis of phenoxypropanolamines using Rink amide resin

1.1.8 Linkers for traceless organic synthesis

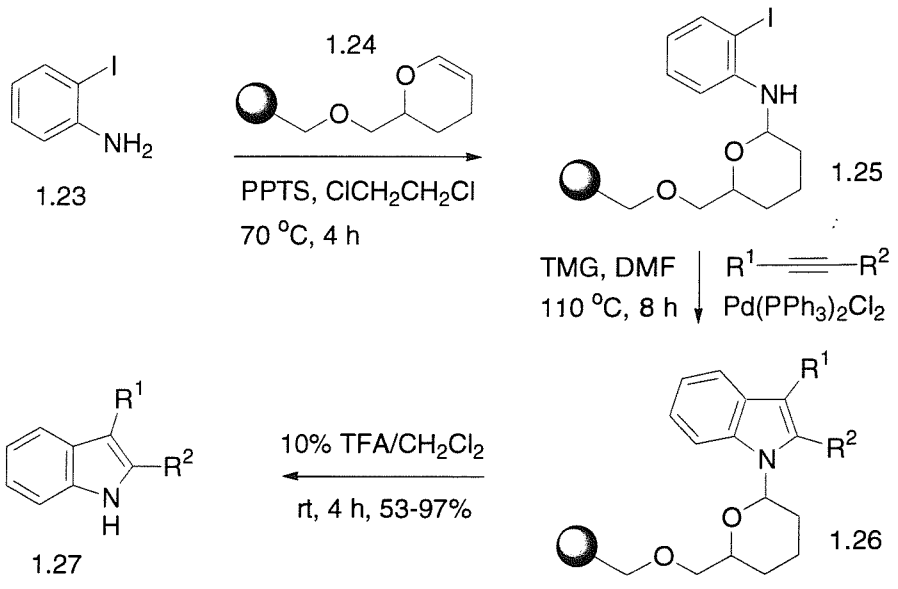
The linkers mentioned so far were all designed primarily around the efficient synthesis of peptides, and cleavage of all of these linkers results in the inclusion of specific functional groups deriving from attachment to the linker itself. Following reports of Ellman's solid-phase benzodiazepine synthesis (scheme 1.2), a surge of interest was created within the pharmaceutical industry upon realizing the capacity of solid-phase chemistry to generate not only peptides, but now also truly drug-like molecules. However, the linkers available at the time, all required of their substrates the presence of carboxylic or phenolic functions, and regenerated these same functions upon cleavage of immobilised substrates. The presence of such functional groups in final drug target molecules can exert a dramatic effect on the overall medicinal efficacy, and as such, are generally undesirable in many pharmaceutical compounds. With this in mind, organic chemists turned their attention to the development of new "traceless" linkers, which upon cleavage, leave no such undesirable functional groups in the product from their point of attachment. The subject of traceless linkers for organic synthesis was recently reviewed by Grigg *et al.*[25]

Jonathan Ellman was once again a pioneer in the development of the first traceless linker. Ellman's strategy involved the use of a silicon-based tether, which he promoted through the traceless synthesis of another library of 1,4-benzodiazepine derivatives **1.22** (scheme 1.6).[26, 27]



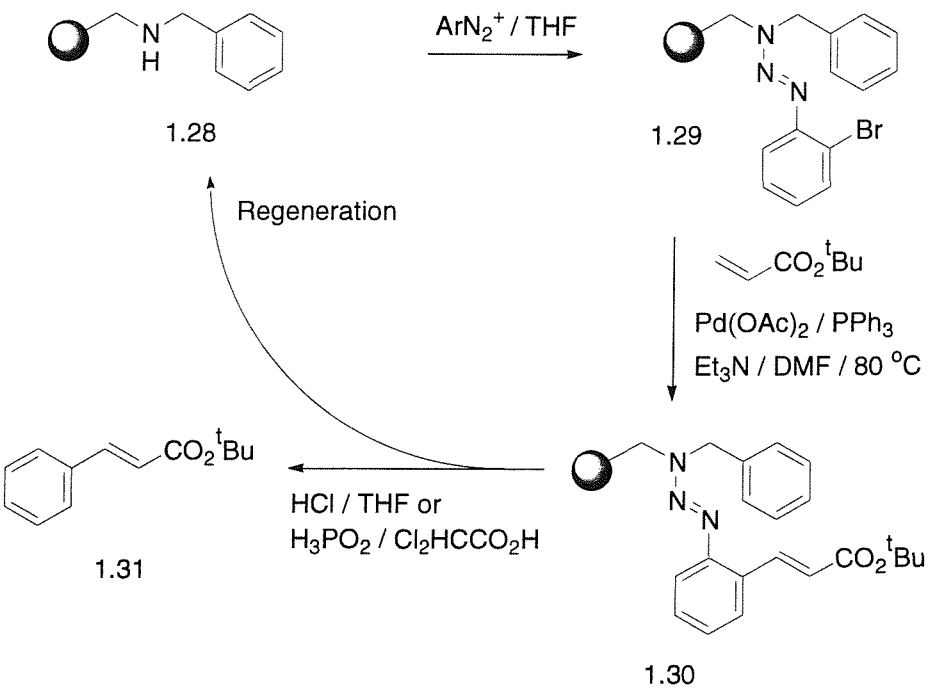
Scheme 1.6 Traceless synthesis of benzodiazepines using Ellman's silicon linker

In 1998, Smith, Stevenson, Swain and Castro reported the traceless solid-phase synthesis of a short series of 2,3-disubstituted indoles, using a linker based on the well known protecting group tetrahydropyran (THP). 2-Iodoaniline **1.23** was loaded onto the THP-polystyrene resin **1.24** to give the *N*-linked aryl iodide **1.25**. Palladium-catalysed cyclisation yielded the immobilised indoles **1.26**, which were cleaved from the support under acidic conditions to provide the indole derivatives **1.27** in 53-97% yield (scheme 1.7).[28]



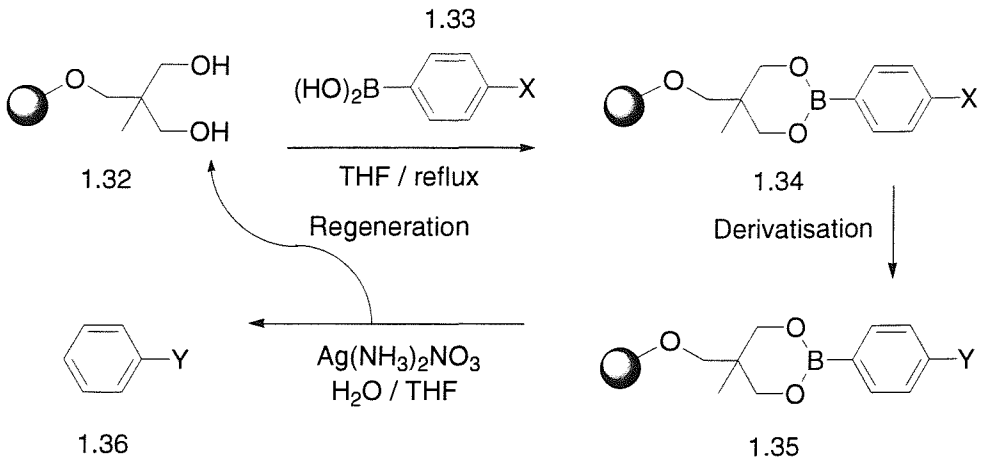
Scheme 1.7 A traceless linker based upon the common protecting-group tetrahydropyran (THP)

1998 saw the advent of a versatile nitrogen-based linker exploiting the well recognised chemistry of diazonium compounds. The T1-triazene traceless linker, developed by Bräse and Enders, is synthesized directly from Merrifield (CMP) resin through reaction with benzylamine, and further coupled with diazonium salts to give immobilised triazenes.[29] Scheme 1.8 shows reaction of the supported benzylamine **1.28**, with the diazonium salt of 2-bromoaniline, the halide substituent later providing a reactive site for the palladium-mediated Heck cross-coupling reaction with *tert*-butyl acrylate to give **1.30**. Traceless cleavage is induced protolytically with either HCl in THF, or through reductive deamination using H_3PO_2 in CH_2Cl_2, providing good to excellent yields of the desired α,β-unsaturated Heck products **1.31**.



Scheme 1.8 The 'T1' triazine-linker used here to perform Heck cross-coupling reactions

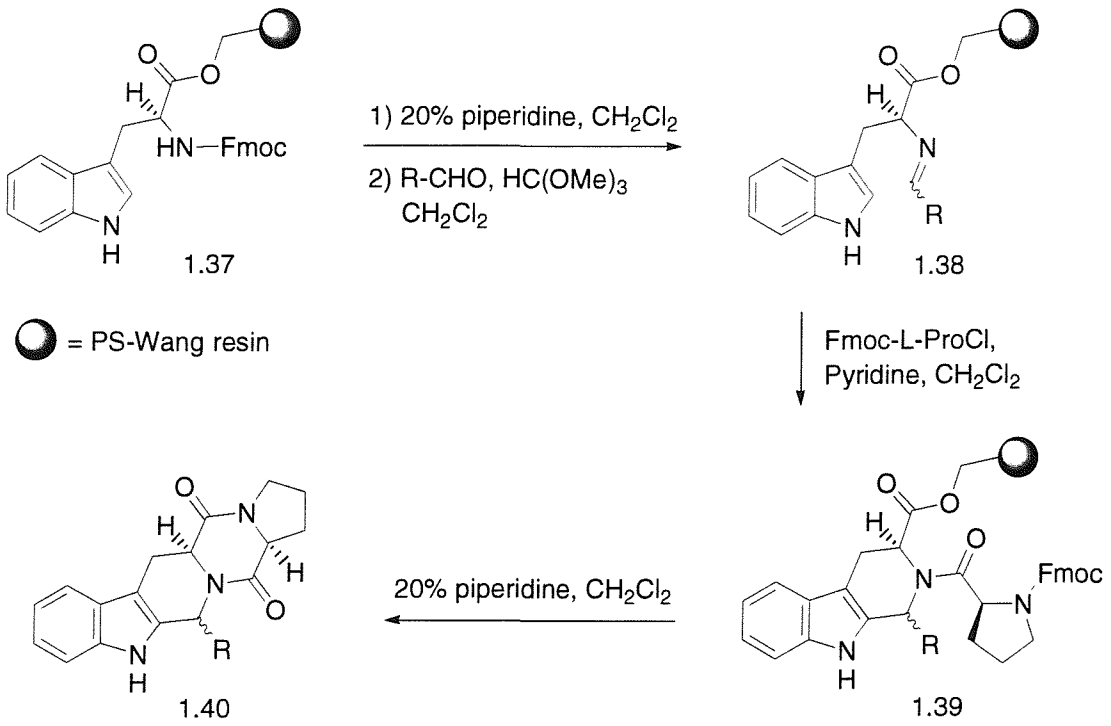
A boron linker used for traceless-type chemistry was reported by Pourbaix *et al.* in 2000, allowing the derivatisation of aromatic boronic acids as their cyclic boronates linked to the support through an ether tether **1.34**.[30] Although the demonstrated chemistry of this linker was limited to functional group transformations of aromatic substituents on the boronic acid, cleavage by mild protodeboronation allowed formation of the parent aromatic system, and regeneration of the linker **1.32** itself. Transformations of the aryl substituents including reductive amination, ester and amide formation, and Ugi four component condensation were shown, providing >45% overall yield, and >80% product yield respectively (scheme 1.9).



Scheme 1.9 The Pourbaix boronate linker for traceless synthesis

The properties of the linkers discussed so far for traceless synthesis have all exploited chemical features that are intrinsic to one specific element. However, numerous organic strategies have been devised for the synthesis of a multitude of chemical libraries in a traceless manner. One such example representing simplicity itself, involves immobilisation of *L*-tryptophan through its carboxyl function, providing an ester linkage, which may be cleaved through intramolecular substitution reactions. This strategy, adopted by Ganesan and Wang in 1999, permitted the solid-phase synthesis of the alkaloid cell cycle inhibitor series, the demethoxyfumitremorgins **1.40**.[31]

Schiff-base formation between the amine group of the tethered tryptophan and a short series of aromatic aldehydes, followed by *N*-Acyliminium Pictet-Spengler cyclisation with Fmoc-*L*-proline acid chloride provided the desired supported tetrahydro-β-carbolines **1.39**. Deprotection of proline Fmoc groups brought about cyclative cleavage from the support through proline-NH substitution into the carbonyl group of the ester tether. This cyclisation strategy permitted the synthesis of a series of demethoxyfumitremorgins **1.40** in very good yields and purities directly from the support (scheme 1.10). Although the cyclative cleavage methodology used here does not make use of a traceless linker, the overall synthetic strategy may be regarded as traceless.



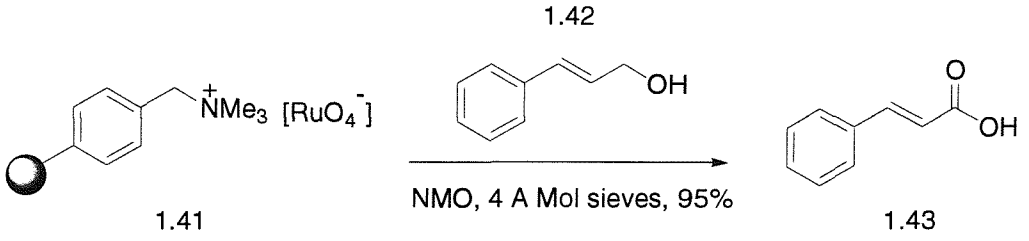
Scheme 1.10 Traceless synthesis of diketopiperazines by cyclative cleavage from hydroxymethyl polystyrene

1.1.9 Polymer-supported reagents for solution-phase chemistry

Ley defined supported reagents as being "reactive species associated with a support material".[32] The use of supported reactive species extends the application of functionalised polymers in a manner which is orthogonal to their use for solid-phase organic synthesis (SPOS), facilitating solution-phase chemistry in much the same way. Many reagents which might be used directly in solution, have now been immobilised on supports, enabling their removal by filtration after the reaction. Attachment of the reagent to the support may either be by covalent or ionic means, and as one of the fastest developing areas of solid-supported chemistry, there now exists a huge number of different supported reagents. Alongside the ease of removal of these immobilised chemicals, the use of supported reagents for solution-phase chemistry blesses the organic chemist with several welcome features. Whereas SPOS retains the compound of interest on a support, limiting analysis to a choice of FT-IR, microanalysis, or gel-phase MAS NMR; the use of supported reagents in the solution-phase allows analysis by all traditional techniques. However, in common with SPOS, the use of large excesses of reagents is not prohibitive since filtration allows total separation of products from reactants. Where the use of a supported reagent in vast excess is not limited by its cost, its overwhelming presence serves to drive even sluggish reactions to completion.

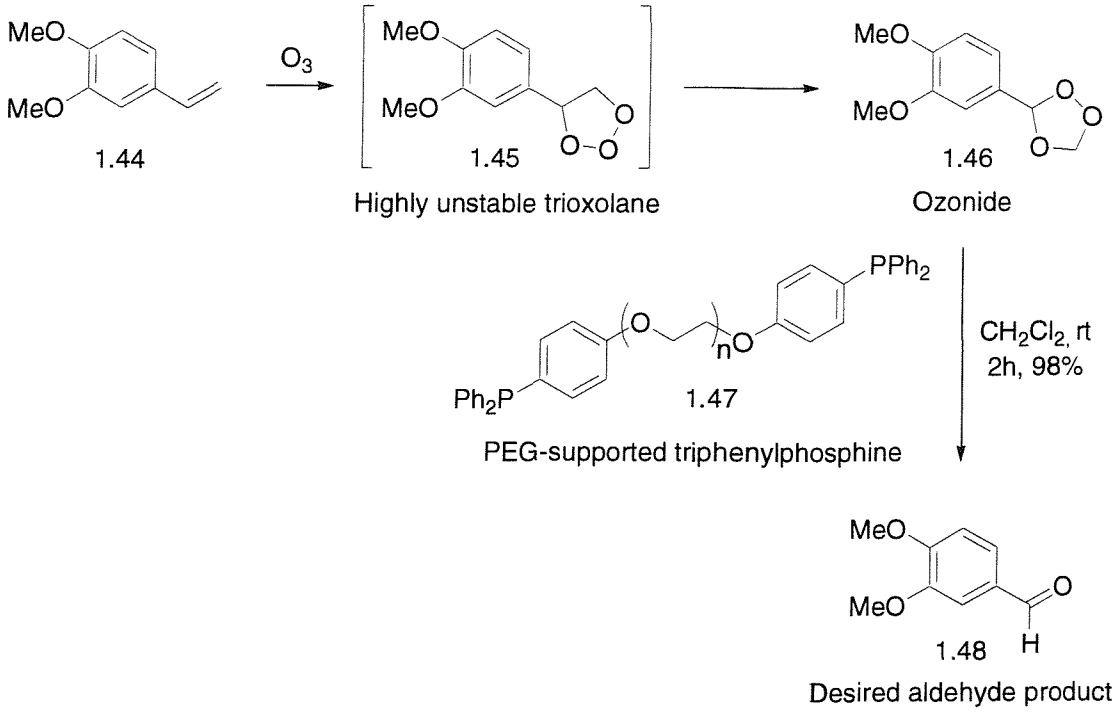
This exploitation of Le Chatelier's principle is used commonly to overcome reactivity gradients existing in large arrays of differently substituted starting materials, ensuring that rate kinetics does not affect overall yields of desired compounds. Noteworthy examples of supported reagents are far too many to discuss here, however, several very popular examples include the following supported chemicals.

In 1997, Ley and Hinzen reported a supported oxidant based around tetrapropylammonium perruthenate (TPAP), which could be used for the efficient oxidation of both primary alkyl and aryl alcohols.[33] Standing strongly in favour of this polymeric oxidant is the ease with which it is prepared through anion-exchange of commercially available Amberlyst IR 27 resin with an aqueous solution of potassium perruthenate. In general, oxidation is carried out using sub-stoichiometric quantities of the supported reagent **1.41** in combination with stoichiometric amounts of either the *N*-methylmorpholine *N*-oxide or trimethylamine *N*-oxide as co-oxidant. Reported yields of carboxylic acids e.g. **1.43** prepared by oxidation of alcohols e.g. **1.42** range from 50% to greater than 95% (scheme 1.11).



Scheme 1.11 Use of Ley's supported perruthenate for the oxidation of alcohols

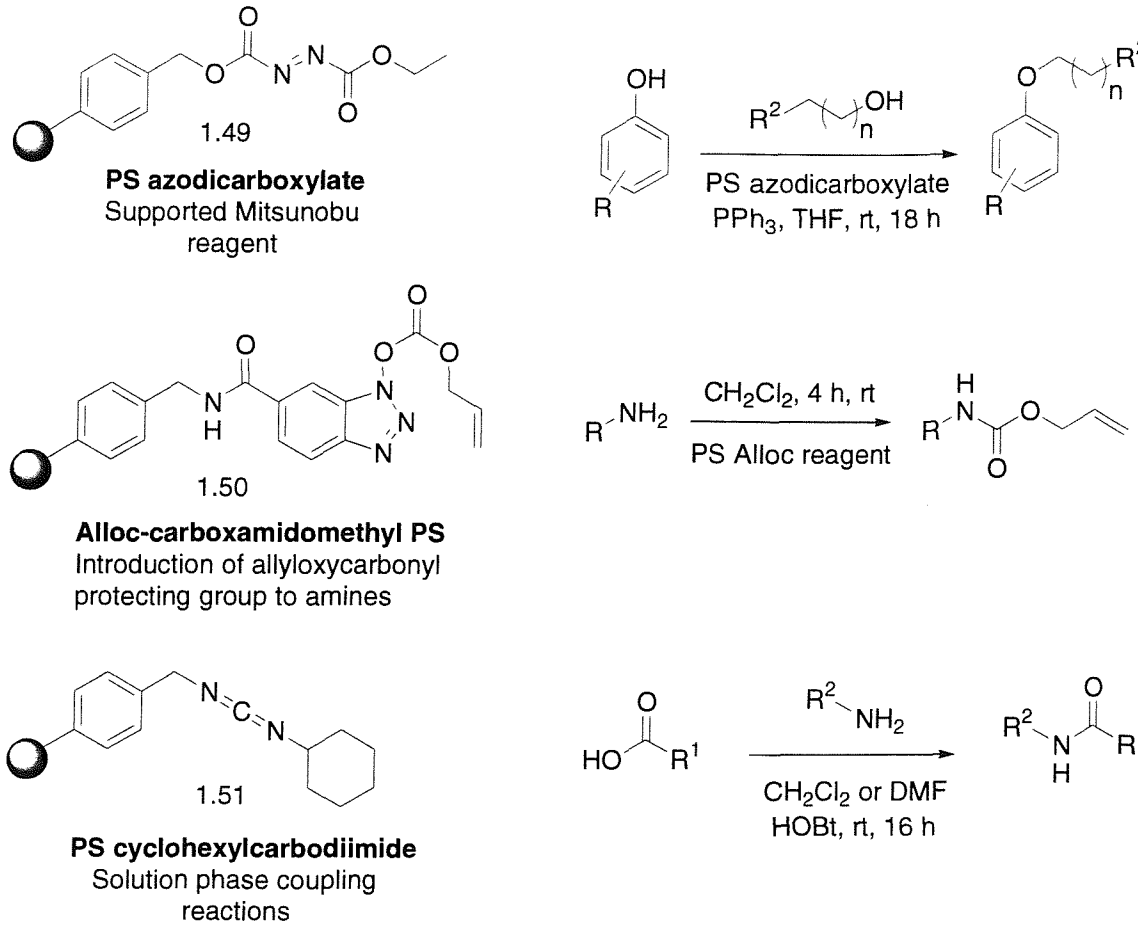
Although the oxidation of alkenes using ozone is well established as a synthetically useful transformation, the controlled decomposition of ozonides can be a hazardous process given the explosive nature of these highly unstable heterocycles, e.g **1.45**. Commonly employed reagents for the reductive decomposition of ozonides include dimethylsulfide and triphenylphosphine, which must be added to the ozonide cautiously and at low temperature. In 1999, Janda reported the safe and efficient decomposition of several ozonides in excellent yield using a new polyethylene glycol (PEG)-supported triphenylphosphine equivalent **1.47** (scheme 1.12).[34]



Scheme 1.12 Decomposition of an ozonide using Janda's supported triphenylphosphine

Janda proceeded to show the efficient regeneration of the spent linker, demonstrating the use of alane (AlH_3) to reduce the immobilised triphenylphosphine oxide byproduct in 100% yield and with 75% conversion.

Solid-phase reagents however, are not limited to supported oxidants and reductants, and there exists a large selection of reagents which allow the construction of new bonds. Supported reagents which permit useful transformations while retaining side-products on the support, are of particularly high synthetic value. For example, the Mitsunobu reaction is a well established method for bond construction between 2 nucleophiles, typically an alcohol, phenol, and a carboxylic acid (or another nucleophile with a pKa below 16).[35] The reaction is extremely robust and usually high yielding, however, the removal of reduced *N,N*-dialkylazodicarboxylate is often troublesome, requiring the use of chromatography in the solution-phase. The use of immobilised azodicarboxylate **1.49** serves to remedy this issue, since the reduced reagent remains attached to the support and is removed by filtration (scheme 1.13).[36] In an analogous manner, supported versions of reagents used to apply protecting groups such as Alloc-OBt-6-carboxamidomethyl polystyrene **1.50**, and coupling reagents such as *N,N'*-cyclohexylcarbodiimide **1.51** [37,38] have aided purification through minimizing the number of solution-phase reagents present in a reaction vessel (scheme 1.13).



Scheme 1.13 Three widely used supported reagents and respective application of each

1.1.10 Polymer-supported scavengers for solution-phase chemistry

Since very few chemical reactions are quantitative, purification of desired reaction products is usually inevitable. This time consuming problem is compounded when the operator has produced a large array of chemical compounds, which are contaminated by one or more excess reagents or side-products. In the solution-phase, this issue is considerably impeding to the high-throughput drive of combinatorial chemistry. However, when the same excess reagent or side-product is present throughout an array, immobilised scavengers can be used to effect global purification. The use of polymer-supported scavengers is in many ways complementary to the use of supported reagents, offering an attractive method for the removal of unwanted chemicals from reaction mixtures. Reaction of an undesired compound present in the solution-phase, with an excess of a specifically chosen functionalised polymer, results in the sequestration of the undesired compound either covalently or ionically. Total removal of the undesired compound may then be facilitated by filtration of the scavenger resin.[39] The choice of supported scavenger is obviously dependent upon the chemistry conducted.

The scavenger must first be chemically compatible with the desired reaction product so as not to exert deleterious effects on isolated yields. Secondly the operator must decide which solution-phase reagent will be used in excess, thereby ensuring total consumption of all other starting materials. The choice of excess reagent will then determine the choice of scavenger which will enable its removal at the end of the reaction.

In practice, the site separation of reactive species present between beads of functionalised supports means that within the same reaction mixture, 2 or more different scavengers (or reagents) each bearing mutually incompatible functions may be used together. As a result of this extremely powerful virtue of polymer-assisted chemistry, numerous reaction steps may potentially be effected in one pot, minimizing time, effort and overall expenditure encountered through separate purification steps (figure 1.1).

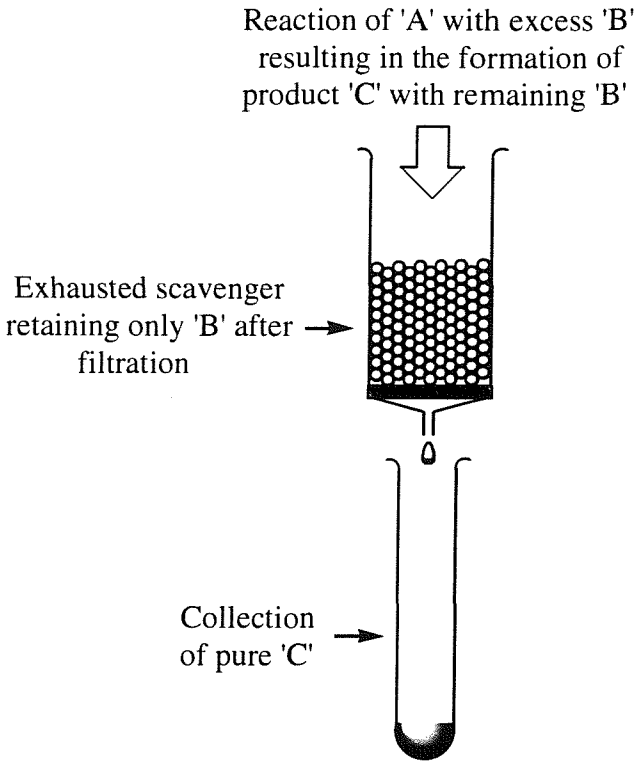
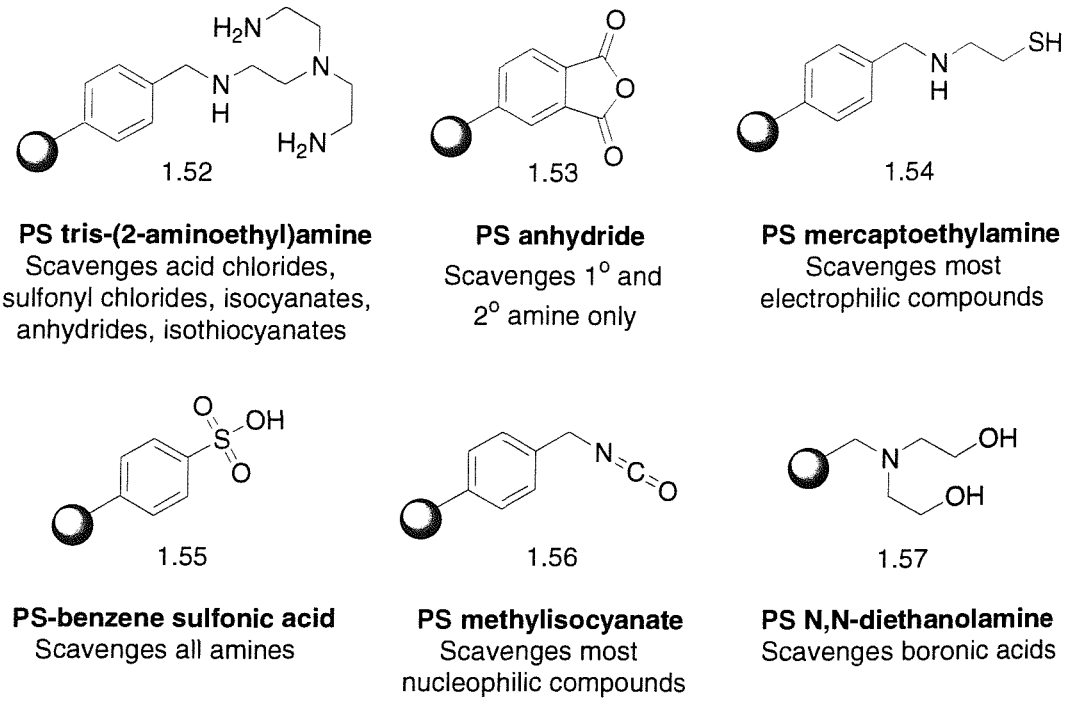


Figure 1.1 Use of scavenger resin to selectively remove excess solution-phase reagents

There now exists a multitude of available supported scavengers, custom produced with extremely high loadings, enabling efficient sequestration of chemicals bearing specific functionalities (figure 1.2).



PS tris-(2-aminoethyl)amine
Scavenges acid chlorides, sulfonyl chlorides, isocyanates, anhydrides, isothiocyanates

PS anhydride
Scavenges 1° and 2° amine only

PS mercaptoethylamine
Scavenges most electrophilic compounds

PS-benzene sulfonic acid
Scavenges all amines

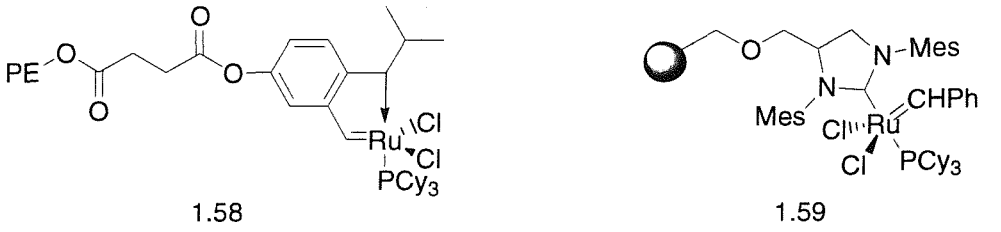
PS methylisocyanate
Scavenges most nucleophilic compounds

PS N,N-diethanolamine
Scavenges boronic acids

Figure 1.2 Various commonly used scavengers, immobilised on polystyrene (PS) supports

1.1.11 Polymer-supported catalysts for solution-phase chemistry

Polymer-supported catalysts may be used to promote the concept of atom economy in combinatorial chemistry, advocating the efficient use, recovery, and reuse of the catalyst entity. In particular, the use of immobilised ruthenium-carbene complexes developed by Grubbs (figure 1.3), have been used to expedite the ring-closing metathesis (RCM) reactions of numerous functionalised olefins (Table 1.1).[40]



Polyethylene glycol bound Ru complex

Polystyrene bound Ru complex

Figure 1.3 Two types of supported ruthenium catalysts for RCM reaction

The supported catalysts **1.58** and **1.59** are immobilised analogues of the well documented 2nd generation Grubbs ruthenium complex, which facilitates alkene metathesis, permitting the construction of small, medium and large ring systems.

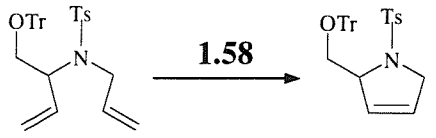
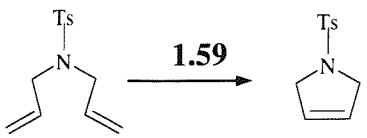
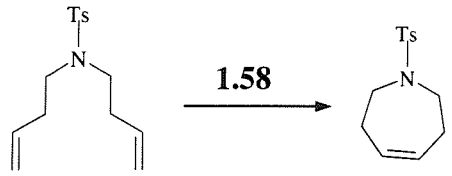
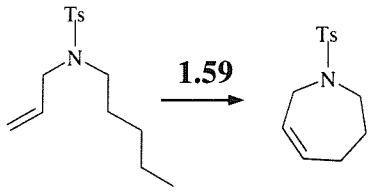
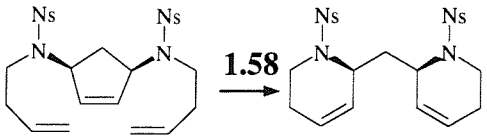
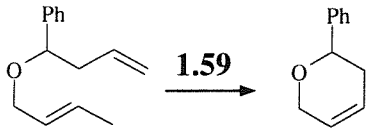
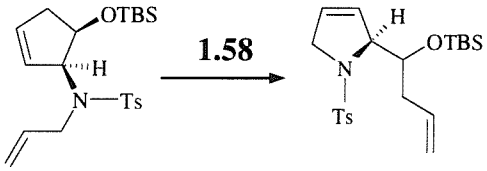
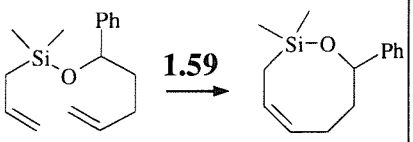
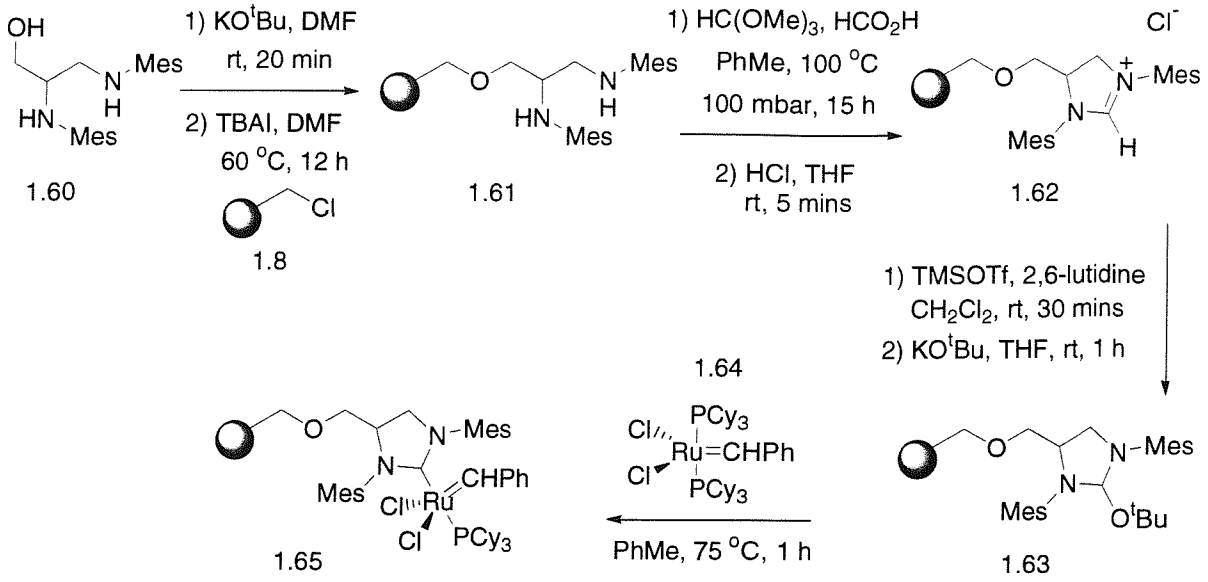
Substrate and Product	Yield [%]	Substrate and Product	Yield [%]
	90		92-99
	100		92-98
	100		96
	100		98

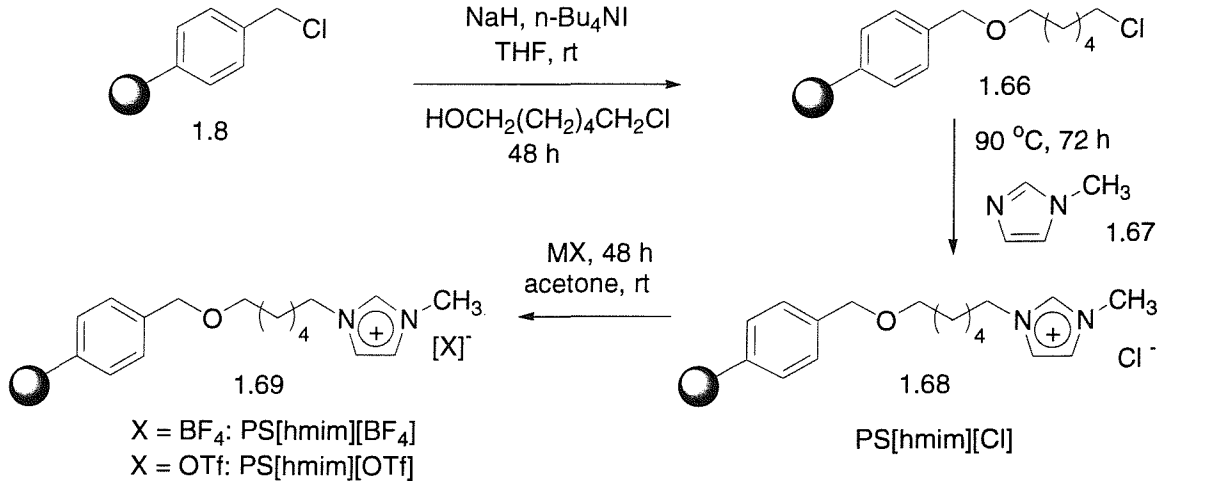
Table 1.1

The polystyrene-supported catalyst is prepared through reaction of mesyl-protected diamine **1.60** with CMP under basic conditions. Cyclisation of the protected immobilised diamine **1.61** using trimethyl orthoformate under acidic conditions, followed by anion exchange, yielded the support-bound 3,4-dimethyl-4,5-dihydroimidazolium chloride **1.62**. Further reaction with TMSOTf under basic conditions, followed by reaction with KO^{t}Bu in THF generates the immobilised precursor **1.63**, which was reacted with the ruthenium complex **1.64** to give directly the supported metathesis catalyst **1.65** (scheme 1.14).



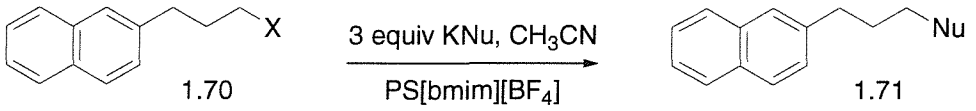
Scheme 1.14 Preparation of an immobilised metathesis catalyst developed by Grubbs

Ionic liquids that are fluid at room temperature are often salts of quaternary ammonium species with poorly coordinating ions. The resulting materials have recently attracted considerable attention as solvents and catalysts for a plethora of organic reactions.[41,42,43] The highly polar nature of organic liquids ensures immiscibility with many organic solvents, offering unique opportunities for recycling and phase switching techniques. Many reactions ranging from transition metal mediated processes to Friedel-Crafts reactions, C-C bond forming condensations and cycloadditions are dramatically accelerated in ionic liquids, hence these relatively new compounds have rapidly become established as catalysts for such processes. Recently, Kim and Chi demonstrated the catalytic activity of several imidazolium salts immobilised on a polystyrene support e.g **1.69**, retaining the useful accelerating properties of these materials (scheme 1.15).[44]



Scheme 1.15 Preparation of immobilised imidazolium salts as supported ionic liquids

The placement of a 6-carbon spacer between the resin matrix and imidazolium nucleus was found to be beneficial to the activity of the supported ionic liquid as a catalyst, and synthesis from CMP commences by reaction with 6-chlorohexanol. *N*-Alkylation of *N*-methylimidazole using the alkyl chloride terminal of the tether, provided the supported imidazolium chloride salt **1.68**. This was further subjected to ion-exchange using either methyl tetrafluoroborate, or methyl triflate to provide the corresponding counterion associated with the supported reagent. The supported ionic liquids **1.69** were shown to greatly facilitate nucleophilic substitution of alkyl mesylates and bromides, e.g. **1.70** with a variety of different potassium salts, giving in general excellent yields of the desired products, e.g. **1.71** (scheme 1.16). Furthermore, recycling of the immobilised catalysts was demonstrated with virtually no loss of catalytic activity.



1.70 1.71

2: X = OMs, **4:** X = Br Nu = Cl, Br, I, OAc, CN

Entry	Substrate	KNu	Temp °C	time h	Yield %
1	2	KCl	100	6	97
2	2	KBr	100	0.8	99
3	2	KI	100	0.5	99
4	4	KOAc	90	1	99
5	4	KCN	100	3	97

Scheme 1.16 Nucleophilic substitution reactions catalysed by supported ionic liquids

1.1.12 General Aims and Objectives

From its conception, the many virtues of solid-phase assisted chemistry have quickly become apparent. The purpose of this work is to further progress the development of solid-phase methods and general procedures, such that new immobilised reagents and linkers are better understood and may facilitate new chemistries.

The Development of a Hydroborating Agent on Solid-Phase

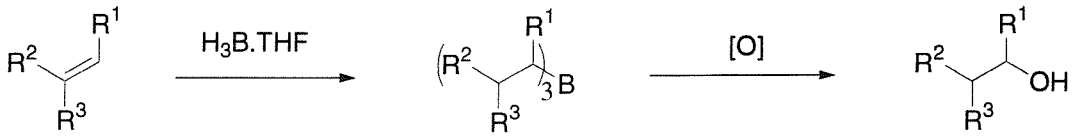
Chapter II Contents

2.1 The chemistry of organoboranes

2.1.1 The discovery of organoboranes

In 1862, Frankland reported the seminal preparation and characterisation of organoboranes;[45] however, this area of organometallic chemistry lay dormant until the attentions of Herbert Brown in 1936, during research for his Ph.D. thesis (published in 1939). From Brown's first report of the facile addition of diborane to alkenes and alkynes in ethereal solvents in 1956;[46] the research conducted by his group and that of his fellow researchers has proven the area of organoborane chemistry to be extremely lucrative and of high scientific value. Almost half a century has passed since the first applications of organoboranes came to light, and during this time, astonishing advances have been made in terms of applications and methodology. A multitude of new hydroborating reagents have since been born, many with extremely well evolved characteristics, the likes of which have proven themselves in exotic applications which are far reaching in almost all areas of organic chemistry. The efforts of Brown and his co-workers has made the chemistry of boranes universally integrated into modern organic synthesis and in 1979, Brown was awarded the Nobel Prize (shared with Georg Wittig). The chemistry of boron is now extremely well documented, yet every year additions are made to this hugely powerful methodology. Emerging from the plethora of its synthetic applications, Brown showed that hydroboration obeys certain rules.[47]

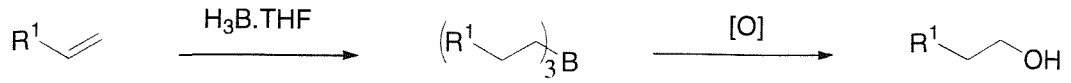
(1) Addition of borane across an unsaturated carbon-carbon bond is a spontaneous and usually quantitative process (scheme 2.1).



2.1 2.2 2.3

Scheme 2.1

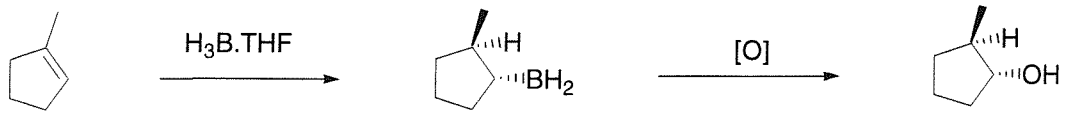
(2) Boron adds preferentially to the least hindered end of an unsymmetrical double bond, hence the overall addition takes place in an anti-Markovnikov manner (scheme 2.2).



2.4 2.5 2.6

Scheme 2.2

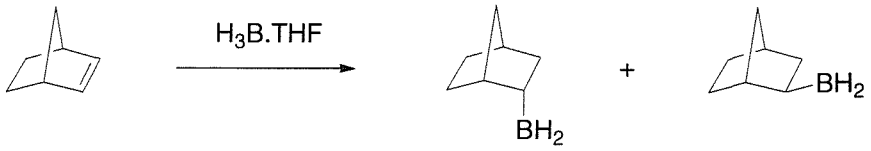
(3) Overall, addition of the B-H bond occurs to yield the *cis*-adduct; an observation that is consistent with the proposed concerted 4-centre transition-state (scheme 2.3).



2.7 2.8 2.9

Scheme 2.3

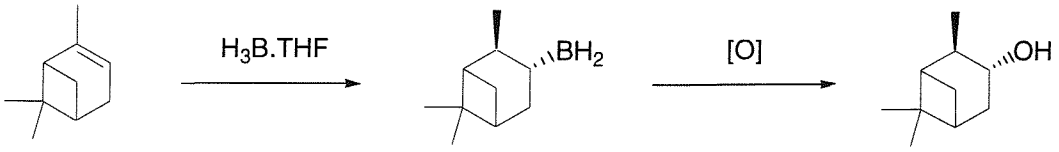
(4) Addition occurs over the less hindered face of the unsaturated bond (scheme 2.4).



2.10 0.4 % 2.11 99.6 % 2.12

Scheme 2.4

(5) Even during hydroboration of molecules as labile as α-pinene, skeletal rearrangements are not observed. Additionally, hydroboration is tolerant of a wide variety of functional groups (scheme 2.5).



2.13 2.14 2.15

Scheme 2.5

2.1.2 Borane complexes

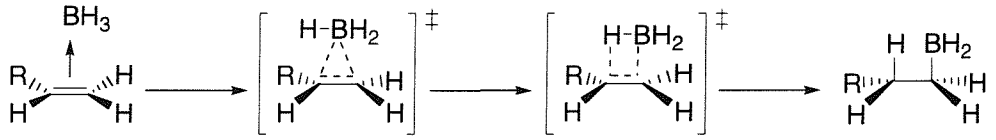
Borane may be prepared by *in situ* reaction of $NaBH_4$ with $AlCl_3$ or more commonly $BF_3.Et_2O$, however these reactions are now considered overly hazardous, given the highly flammable nature of borane, and with the wide commercial availability of borane complexes are mostly redundant on a laboratory scale.

Borane (BH_3) itself is a strong Lewis acid, and the most widely available boron hydride, supplied commercially as a complex with one of several different Lewis bases, e.g. THF,[48] DMS,[49] pyridine[50] and *N,N*-dialkylanilines.[51] Of these complexes, the most commonly used are those of THF or DMS since these are highly reactive and regularly used either as reducing or hydroborating agents.[52,53]

Borane complexes of pyridine and various *N,N*-dialkylanilines are generally more stable but as a tradeoff are also less reactive. However, borane-*N*-ethyl-*N*-isopropylaniline is commercially available as the neat complex and has been shown by Brown *et al.* to display reactivity similar to that of the THF and DMS complexes.[51]

2.1.3 The chemistry of boranes

The chemistry of BX_3 compounds is dominated by the electron deficient nature of boron, and hence the ready acceptance of an electron pair into its empty 2p orbital, resulting in the formation of a coordinate bond.[54] The boron-hydrogen bond is thermodynamically unstable with respect to the boron-carbon bond, and BH_3 adds rapidly across multiple carbon-carbon bonds, boron generally bonding with the carbon atom of least steric congestion and substitution (scheme 2.6).



2.16 2.17 2.18 2.19

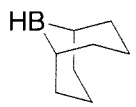
Scheme 2.6 Representative hydroboration of an alkene

The addition of borane across a carbon-carbon double bond is considered to involve initial coordination of BH_3 with the alkene **2.16**, through donation of π-electron density into the vacant 2*p* boron orbital prior to the formation of a four-centred cyclic transition state **2.18**. Fission of the boron-hydrogen bond then results in the formation of a new carbon-hydrogen (σ) bond **2.19**.

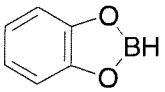
Given the trivalent nature of boron, the product of reaction of borane with many simple alkenes is a trialkylborane compound. Hydroboration of more sterically demanding alkenes, however, usually leads to the formation of an equilibrium mixture consisting of mono- and di-substituted products, the placement of which depends to a large extent on both the solvent and substrate employed. Given the reactivity of BH_3.complexes however, their reaction with either alkenes or alkynes often does not result in high and predictable

regioselectivity, and many more selective borane reagents have subsequently been developed. Of these more selective hydroborating reagents, the most commonly used are catecholborane,[55] pinacolborane,[56] dicyclohexylborane[57] and 9-borabicyclo[3.3.1]nonane (9-BBN).[58]

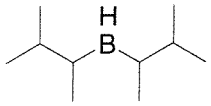
In contrast to borane complexes, these hydroborating reagents are all disubstituted with sterically hindered bulky groups, which have the effect of taming the reactivity and increasing the regioselectivity observed through their use.



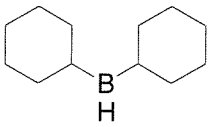
2.20
9-borabicyclo[3.3.1]nonane



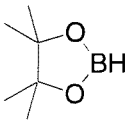
2.21
catecholborane



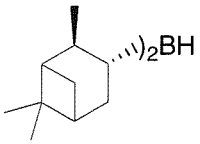
2.22
disiamylborane



2.23
dicyclohexylborane



2.24
pinacolborane



2.25 Ipc_2BH
diisopinocampheylborane

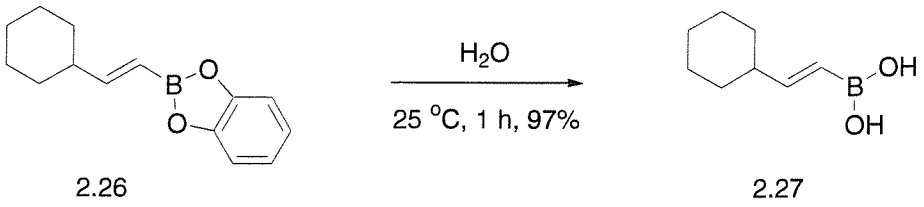
Figure 2.1 Commonly used hydroborating reagents formed from diborane

2.1.4 Catecholborane

Catecholborane (1,3,2-benzodioxaborane) **2.21** is readily prepared through the reaction of borane and catechol, and is stable if stored at 4 °C under an inert atmosphere. At room temperature, the reaction of catecholborane with alkenes and alkynes is sluggish, however, at elevated temperatures the reaction proceeds smoothly to give exclusively the monohydroboration product with high regioselectivity.[59]

Alkylcatecholboranes and alkenylcatecholboranes are usually isolated by crystallisation or low-pressure distillation, and are often insensitive to air, though they must be protected from moisture on prolonged storage. Catechol boronate esters are readily hydrolysed in the presence of water to give the corresponding boronic acid and catechol, and must be protected through transesterification with a diol (often as the pinacol ester) if the functionality is to be preserved through transformations involving protic sources.

Brown and Gupta reported the synthesis of alkenylboronic acids by hydrolysis of the precursor B-alkenylcatecholborane species; the acids were easily isolated in high yields and purities by filtration as crystalline solids of low water solubility, which are usually easily handled in air without significant decomposition.[60]



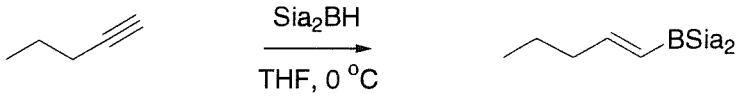
2.26 2.27

Scheme 2.7 Preparation of alkenylboronic acids via hydrolysis of alkenylcatecholboronates

This facile hydrolysis does however provide a convenient and high yielding route to boronic acids[61] which in their own right are extremely useful synthetic precursors, most notably in the palladium-mediated Suzuki-Miyaura cross-coupling reaction (See chapter 3 for further detail).[62]

2.1.5 Disiamylborane

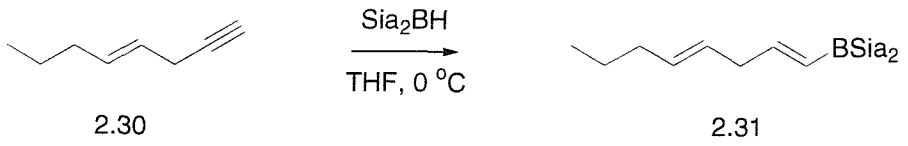
Both terminal and internal alkynes react rapidly at 0 °C with disiamylborane to give alkenyldisiamylboranes, and competing dihydroboration is insignificant even when an excess of the borane is used, since the steric demands of the disiamyl-group prohibit further reaction of the alkenylborane.[63]



2.28 2.29

Scheme 2.8 Monohydroboration of a terminal alkyne using disiamylborane

In contrast to a solution of diborane in THF, which is quite non-discriminating between unsaturated substrates, disiamylborane is a far more selective reagent, allowing the hydroboration of both terminal and internal alkynes in the presence of all but totally unhindered terminal alkenes.[64] This useful feature has made disiamylborane a choice reagent for such hydroboration reactions.

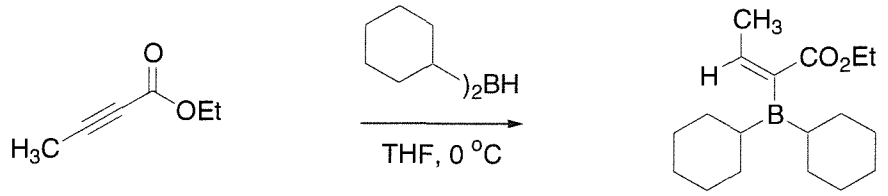


2.30 2.31

Scheme 2.9 Chemoselective hydroboration of a terminal alkyne in the presence of an internal alkene

2.1.6 Dicyclohexylborane

Dicyclohexylborane may in many cases be used in place of disiamylborane, however, its slightly lower steric bulk often permits dihydroboration of alkynes in better yield than disiamylborane. Close control of reaction stoichiometry does usually allow isolation of the alkenyldicyclohexylborane products in excellent yield.[65]

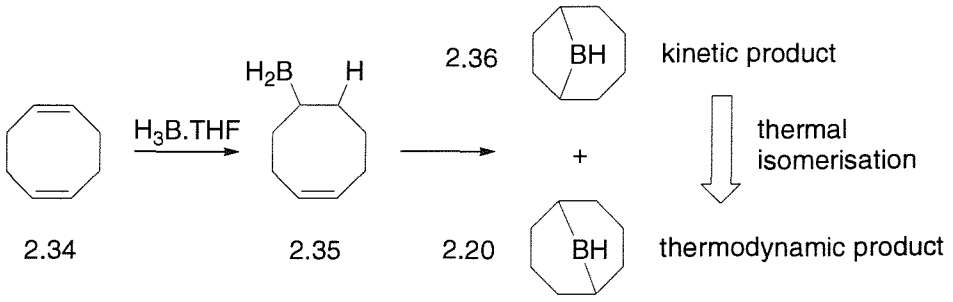


2.32 2.33

Scheme 2.10 Monohydroboration of an internal alkyne using dicyclohexylborane

2.1.7 9-Borabicyclo[3.3.1]nonane (9-BBN)

9-BBN is a bulky dialkylborane, first prepared by Köster in 1960 by hydroboration of 1,5-cyclooctadiene.[58] 9-BBN is isolated as a highly crystalline solid dimer which in contrast to most other dialkylboranes is readily handled under standard conditions given its relatively high stablity to air.[66,67]



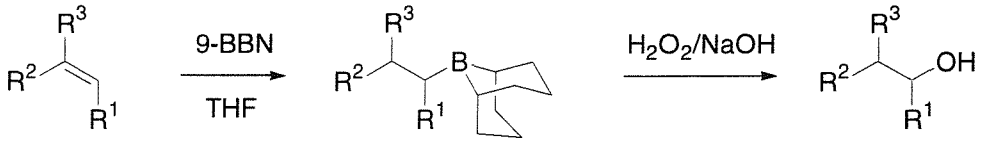
2.34 2.35

Scheme 2.11 Preparation of 9-BBN by hydroboration of 1,5-cyclooctadiene with borane

The hydroboration of 1,5-COD **2.34**, yields the [4.2.1] **2.36** and [3.3.1] **2.20** adducts as major and minor products respectively, with the former being the kinetically favoured product of the reaction. Thermal isomerisation is effected at 100 °C to give quantitatively the thermodynamically favoured [3.3.1] product, which is commercially available. The popularity of 9-BBN as a dialkylborane reducing agent stems from its ease of use due to its crystallinity and relative insensitivity to air and heat. However, reactions involving 9-BBN are most commonly carried out in dry THF and under an inert atmosphere.

In common with most other dialkylboranes, 9-BBN exists as the dimer, although when solvated, it reacts as the monomer. 9-BBN exists as the boat-boat conformer in order to minimise transannular interactions, hence the 9-BBN adduct has imposed upon it considerable steric constraints. As a result of the steric hinderance around the boron centre, 9-BBN displays far greater regioselectivity in further hydroboration reactions, relative to the simple $H_3B.THF$ and $H_3B.SMe_2$ reagents, and is influenced to a large extent by the electronic properties of the substrate.

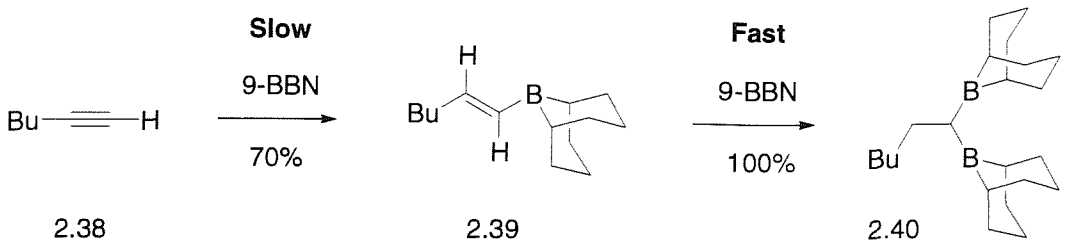
In common with catecholborane, 9-BBN is an extremely versatile reagent, allowing a wide range of chemical transformations to be carried out. Of the many synthetic elaborations possible using 9-BBN, the most common use is for selective hydroboration prior to oxidation, to yield the corresponding alcohol, aldehyde or ketone depending upon the hydroboration substrate. Alkenes are hydroborated and oxidised to the corresponding alcohol.



2.1 2.37 2.3

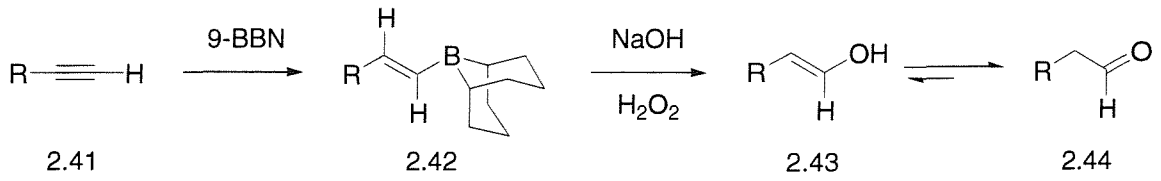
Scheme 2.12 Regioselective hydroboration of a trisubstituted alkene

In contrast with other dialkylboranes, 9-BBN hydroborates alkenes much faster than corresponding alkynes. The hydroboration of terminal alkynes with an equimolar quantity of 9-BBN thus leads to competitive formation of 1,1-diboryl adducts.[68]



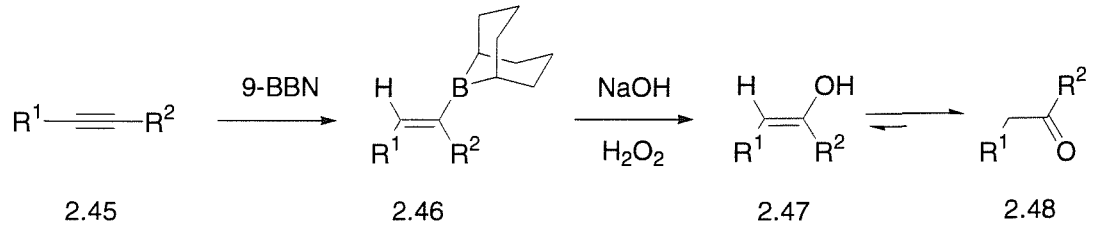
Scheme 2.13 Competing reactions in the hydroboration of alkynes

Where the steric or electronic properties of a terminal alkyne do permit monohydroboration at the terminus, oxidation of the so-formed vinylborane intermediate leads to the formation of the corresponding aldehyde species.



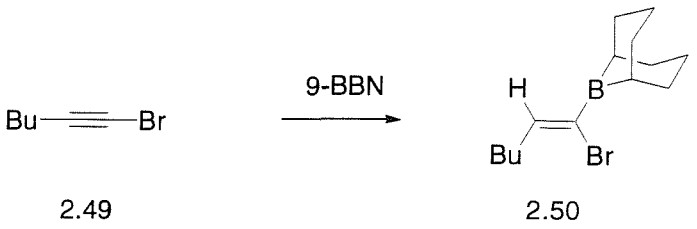
Scheme 2.14 Hydroboration/oxidation of a terminal alkyne to give the corresponding aldehyde

In contrast, 9-BBN is an efficient reagent for the monohydroboration of internal alkynes resulting in the formation of the corresponding vinylborane, usually in very high yields.[69] Oxidation of the vinylborane product results in the formation of the corresponding ketone usually also in very respectable yields.



Scheme 2.15 Hydroboration/oxidation of an internal alkyne to give the corresponding ketone

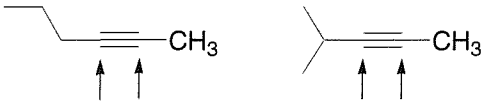
The hydroboration of 1-halo-1-alkynes with 9-BBN results exclusively in the formation of (Z)-1-halovinylboranes, which may be protonolysed to give the *cis*-vinyl halides.[70]



2.49 2.50

Scheme 2.16 Hydroboration of an internal 1-bromoalkyne

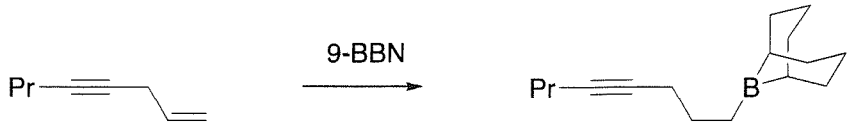
The regioselectivity of several hydroborating agents in reaction with substituted alkynes was compared in order to assess the difference in directing properties of the substrates (figure 2.2).



Diborane.THF	40 : 60	25 : 75
Disiamylborane	39 : 61	7 : 93
Dicyclohexylborane	33 : 67	8 : 92
9-Borabicyclononane	22 : 78	4 : 96

Figure 2.2 Relative regioselectivities of various hydroborating reagents

From these results it is apparent that 9-BBN is indeed the most selective of these hydroborating reagents, and although regioselectivity is not totally exclusive in the cases of the substrates chosen, the steric differences at either alkyne carbon are extremely subtle. The different rates at which 9-BBN hydroborates alkenes and alkynes has been exploited synthetically in the selective manipulation of molecules containing both functions.[71]

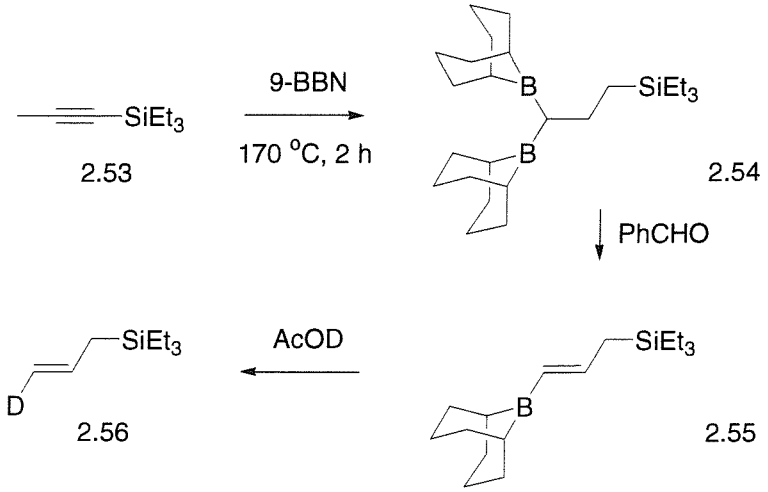


2.51 2.52

Scheme 2.17 Chemoselective hydroboration of an alkene in the presence of an alkyne

Protonolysis and deuterolysis of B-substituted-9-BBN compounds

The protonolysis of B-alkyl-9-BBN derivatives using carboxylic acids takes place at a useful rate only at elevated temperatures. However, protonolysis of B-vinyl-9-BBN derivatives occurs at 0 °C with total retention of configuration around carbon. If deuterated acetic acid is used, a useful method for the generation of deuterium labelled trans-alkenes arises, as demonstrated by Soderquist *et al.*[72]



Scheme 2.18 Deuterolysis of a B-alkenyl-9-BBN derivative

Regioselective hydroboration

9-BBN exhibits remarkable steric- and electronic-based regioselectivities which distinguish it from many other hydroborating reagents. For example, the alkene substrate series shown below, give the relative selectivities for boron placement upon hydroboration using either BH_3.THF or 9-BBN in THF.[73] It is obvious that with each of these substrates 9-BBN shows a far greater regioselectivity, which is not bettered through the use of any other single hydroborating reagent.

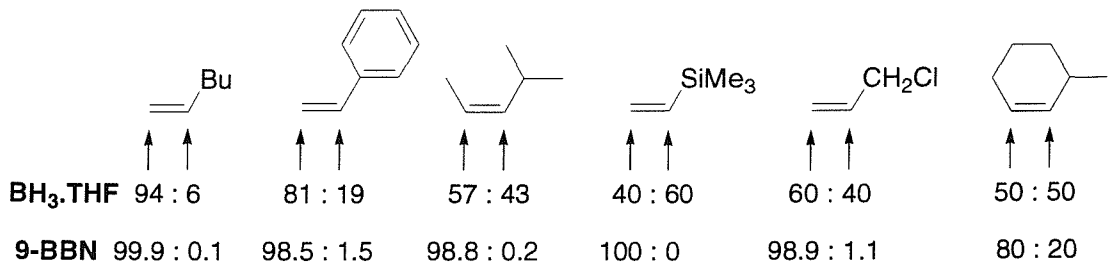
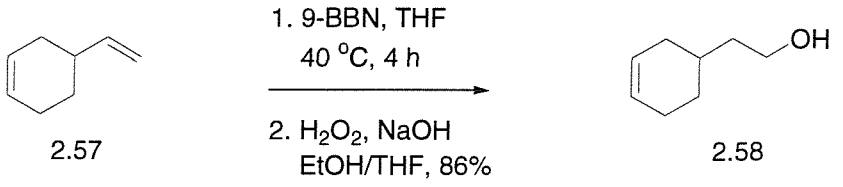


Figure 2.3 Relative regioselectivities observed during hydroboration of substituted alkenes

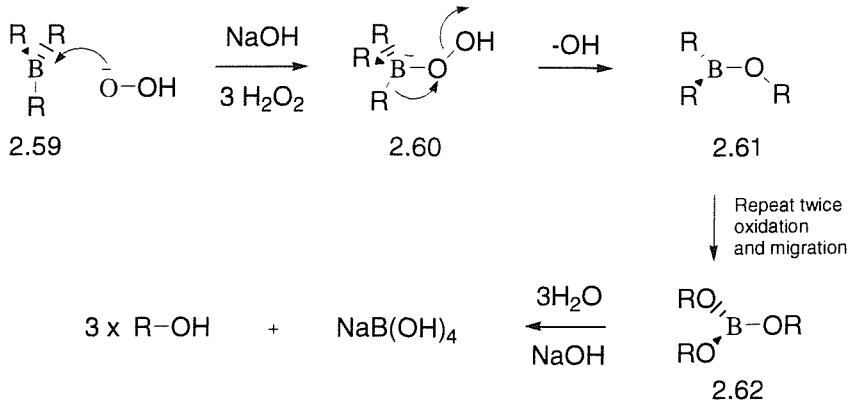
The monohydroboration of symmetrical non-conjugated dienes using 9-BBN or other bulky borane derivatives is not usually possible, even by controlled addition of the hydroborating reagent, since the 2 alkenes essentially react independently of one another. However, in compounds containing alkene functions which are non-equivalent, 9-BBN may be used to chemoselectively hydroborate the more reactive group. For example 9-BBN may be used to selectively hydroborate only the terminal alkene function of 4-(vinyl)cyclohexene, leaving the less reactive internal alkene unaffected upon oxidation of the trialkylborane intermediate.[74]



Scheme 2.19 Chemoselective hydroboration of 4-vinylcyclohexene

Oxidation of organoboranes

The oxidation of alkylboranes to alcohols, and alkenylboranes to aldehydes and ketones are reactions of fundamental importance with regard to organoborane chemistry.[75] Many different oxidising conditions have been employed depending upon the substrate, however the original conditions as reported by Brown involve the use of alkaline hydrogen peroxide. A mixture of 3 molar equivalents of both sodium hydroxide and hydrogen peroxide relative to the alkylborane were found to produce virtually quantitative oxidation, and these conditions remain the most commonly employed today where substrate sensitivity is not an issue. Of principal importance, Brown noted that the stereochemistry of the carbon-boron bond is totally maintained through its conversion to a carbon-oxygen bond, a feature which heavily promotes the use of borane reagents in asymmetric synthesis. The combination of sodium hydroxide and hydrogen peroxide generates the powerful α-effect nucleophile sodium hydroperoxide. Given the electophilicity of the vacant boron 2p orbital in the alkylborane, attack of a hydroperoxide anion on the trigonal planar metal centre is facile, generating a tetrahedral borate anion. Migration of an alkyl group from boron to oxygen liberates a hydroxide anion, resulting in the formation of a new and stable carbon-oxygen bond. Repetition of this process occurs with the remaining carbon-boron bonds resulting overall in the formation of a trialkoxyborane, hydrolysis of which produces three moles of the corresponding alcohol and one mole of sodium borate.



Scheme 2.20 Mechanism of oxidation of trialkylboranes using alkaline peroxide

Many different reagents have been reported for the oxidation of alkylboranes to the corresponding alcohols, each bearing their own advantages and disadvantages. Kabalka and Slayden reported the use of a slight excess of trimethylamine-*N*-oxide dihydrate (TMANO) to effect oxidation in either hydrocarbon or ethereal solvents over a wide range of temperatures.[76] The rate of oxidation was determined to decrease in the order: tertiary > cyclic secondary > acyclic secondary > n-primary > branched primary > vinyl.[77,78]

Given the reaction conditions under which peroxide oxidation is performed, TMANO offers distinct advantages where base sensitive functionalities exist in either the substrate or product. The compatibility of TMANO with a wide variety of different solvents makes this reagent more suitable for oxidation of immobilised organoboranes, where the predominantly aqueous reaction conditions of traditional alkaline peroxide would not allow efficient swelling of a polymer support.

In 1989, Kabalka *et al.* reported the use of sodium perborate as another efficient agent suitable for oxidation of organoboranes. Standing in favour of the use of sodium perborate is its very wide commercial availability and very low cost (comparable to H_2O_2), however, on a laboratory scale usage, these factors are not especially important. The reagent is soluble only in largely aqueous solvent mixtures, although in its action it has been shown to be exceptionally mild and hence tolerant of sensitive functionalities.[79]

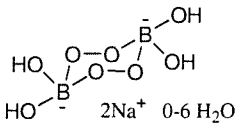
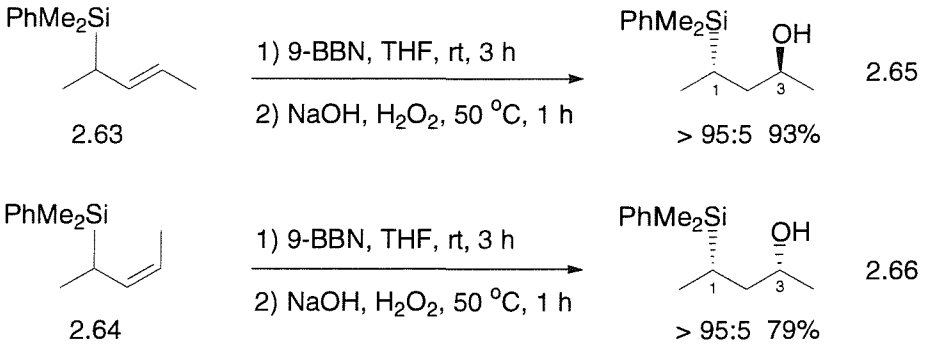


Figure 2.4 Sodium Perborate

The phase transfer base tetramethylammonium hydroxide has been shown to be an especially effective reagent in conjunction with hydrogen peroxide for the oxidation of organoboranes on solid-phase given its solubility in common organic solvents, e.g. THF and DME. The reagent is commercially available as a standard solution in MeOH.

Asymmetric hydroxylation using 9-BBN

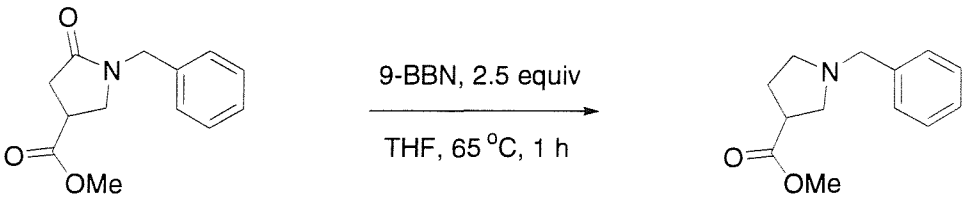
Fleming *et al.* described the diastereoselective hydroboration/oxidation of phenyldimethylsilyl substituted alkenes, noting that almost total 1,3-control was possible through hydroboration/oxidation of either the *cis* or *trans*-alkene.[80] This simple methodology then allows useful hydroxyl-containing 'building-blocks' to be prepared in a predictable stereodefined manner, and subsequently used in such applications as total synthesis of complex natural products.



Scheme 2.21 1,3-diastereoselectivity of hydroboration/oxidation of silylalkenes with 9-BBN

Selective reduction

9-BBN may also be used to effect the selective reduction of carbonyl-containing groups in the presence of other reducible functionalities. For example, Collins *et al.* used 9-BBN to reduce the 5-membered lactam to the cyclic tertiary amine in the presence of an alkyl methyl ester.[81] Krishnamurthy *et al.* showed that the reduction of common functions such as nitriles and epoxides by 9-BBN is slow, and alkyl and aryl halides and nitro groups are not reduced.[82]



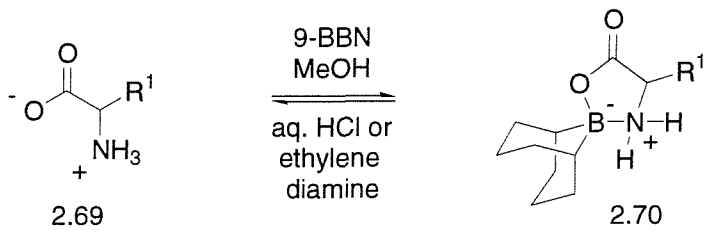
2.67 2.68

Scheme 2.22 Chemoselective reduction using 9-BBN

Protection of amino acids

Fields *et al.* demonstrated the use of 9-BBN as an effective protecting group for functionalised amino acids allowing masked derivatives to be chemically manipulated prior to deprotection under either acidic or basic conditions.[83] The amino acid is derivatised with 9-BBN to give the thermodynamically stable 5-membered boroxazolidinone, while the side-chain remains free for further functionalisation.

The lipophilic properties of the 9-BBN carbocycle impart a high degree of organic solubility to these derivatives which may readily be manipulated as relatively concentrated solutions in THF and other commonly employed solvents. Given the sparingly soluble nature of most natural amino acids in organic solvents, the ability to manipulate masked derivatives represents a significant improvement in ease of handling.



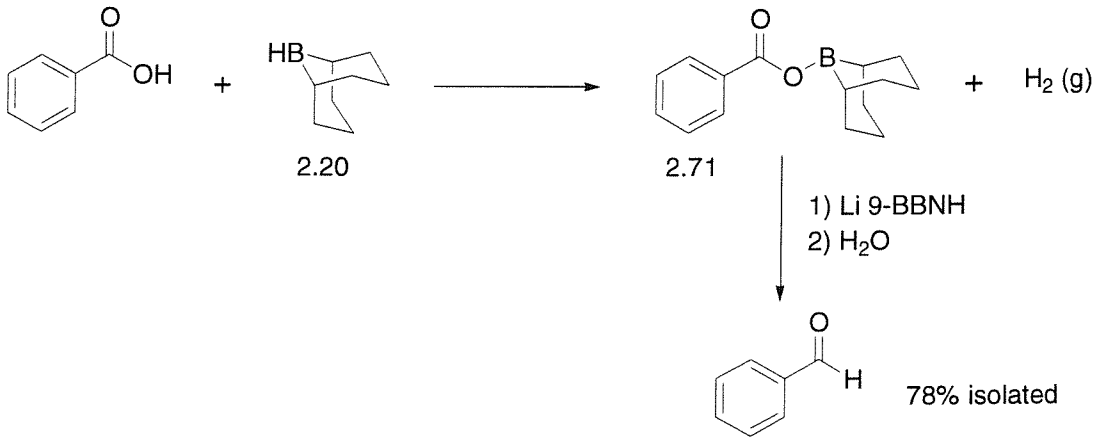
2.69 2.70

Scheme 2.23 Boroxazolidinone protection of amino-acids using 9-BBN

Through the course of their studies, Fields *et al.* found that masking of amino acids with 9-BBN offers a protecting group which is remarkably tolerant to the reaction conditions employed for many common functional group transformations, including oxidation using *m*CPBA, alkylation and acylation with alkyl and acyl halides respectively.

Conversion of carboxylic acids to aldehydes

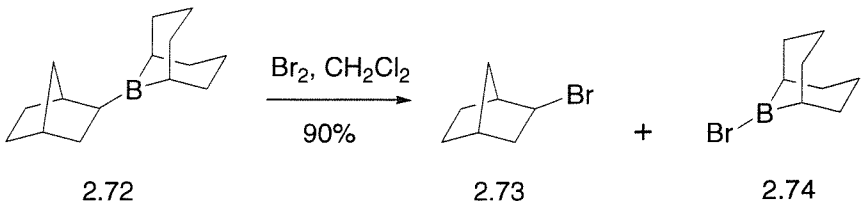
Cha *et al.* demonstrated that acyloxy-9-BBN compounds formed through the reaction of 9-BBN with aryl or alkyl carboxylic acids are readily reduced to the aldehyde oxidation level using lithium 9-boratabicyclo[3.3.1]nonane (Li 9-BBN), which itself is readily prepared through the reaction of 9-BBN with LiH in THF.[84] Reduction in this manner offers advantage over conventional reagents such as $LiAlH_4$, since functions such as methyl esters and nitro groups, which are not derivatised by 9-BBN are not subsequently reduced by Li 9-BBN.



Scheme 2.24 Conversion of carboxylic acids to aldehydes

Conversion of alkenes to alkyl bromides

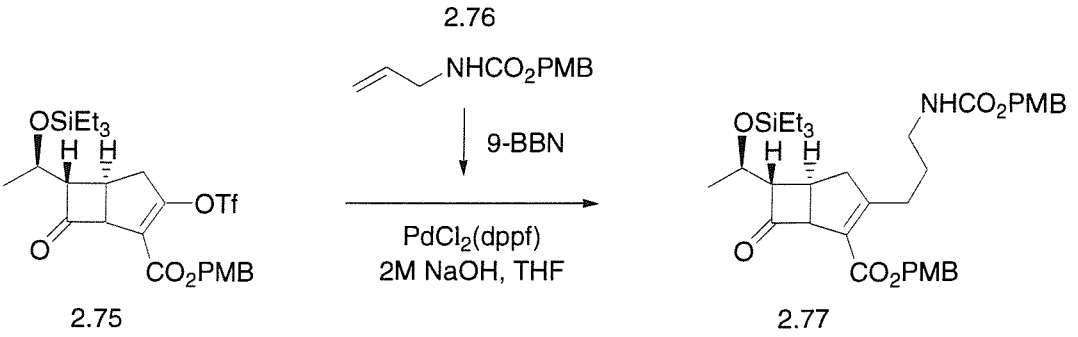
Reaction of elemental bromine or iodine with *sec*-alkyl-9-BBN derivatives in the absence of light, results in the formation of 2° alkyl bromides or iodides in excellent yield. In most cases, hydroboration/halogenation is carried out as a 'one-pot' synthesis employing a slight excess of 9-BBN at the first stage. This reaction represents an extremely facile method for the formation of alkyl bromides and iodides, which would otherwise be more difficult to accomplish directly by other means. For example, Brown *et al.* described the hydroboration and bromination of norbornene derivatives in very impressive isolated yields.[85]



Scheme 2.25 Halogenation of trialkylboranes using 9-BBN and elemental Br_2

Palladium-mediated cross-coupling reactions

Of perhaps the most powerful synthetic transformation on offer within the wide range of the 9-BBN 'toolbox' is the capability of palladium-catalysed carbon-carbon bond formation. This reaction has been exploited by Narukawa *et al.* in the synthesis of 2-alkyl substituted carbapenems by the hydroboration of alkenyl fragments using 9-BBN, prior to the palladium-catalysed cross-coupling of the so formed trialkylborane derivatives with carbapenem-2-yl triflates.[86]

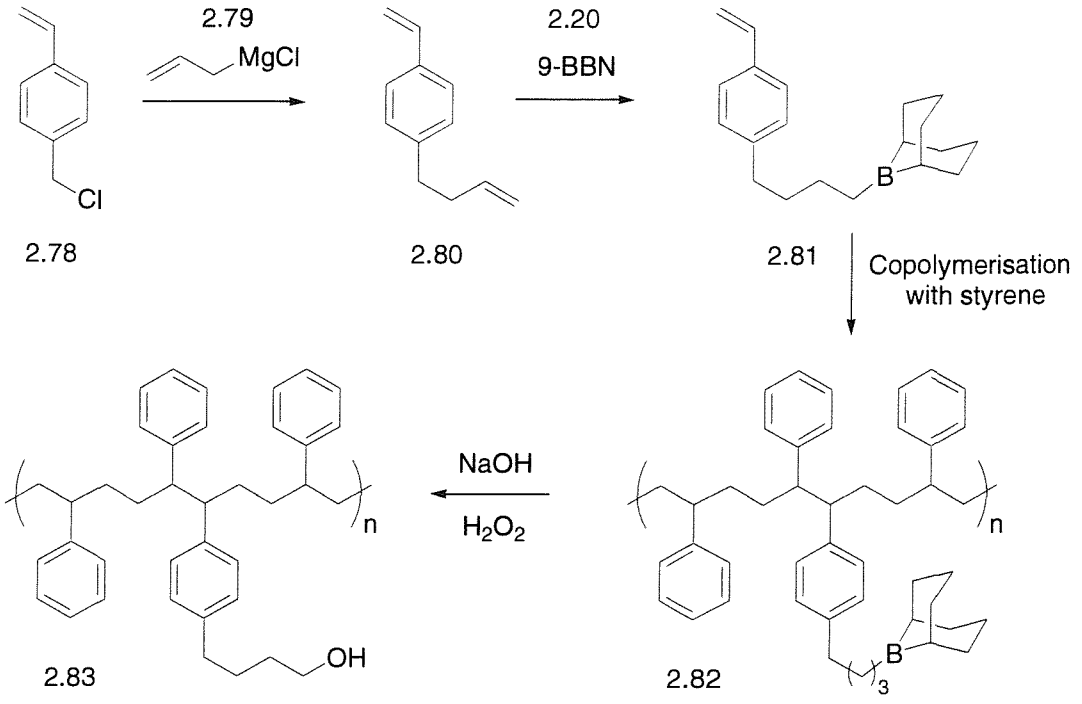


Scheme 2.26 Palladium-catalysed cross-coupling of 9-BBN derivatives with vinyl triflates

Coupling is effected in an analogous manner to the original Suzuki-Miyaura coupling, and reaction conditions are identical. Again, the transformation is conducted as a 'one-pot' procedure, using only a slight excess of 9-BBN to ensure total consumption of the alkenyl precursor. Over a short series of coupling reactions performed using 5 mol% $PdCl_2(dppf)$, yields ranged from 64-85% isolated, highlighting this transformation as both highly efficient and of wide synthetic utility.

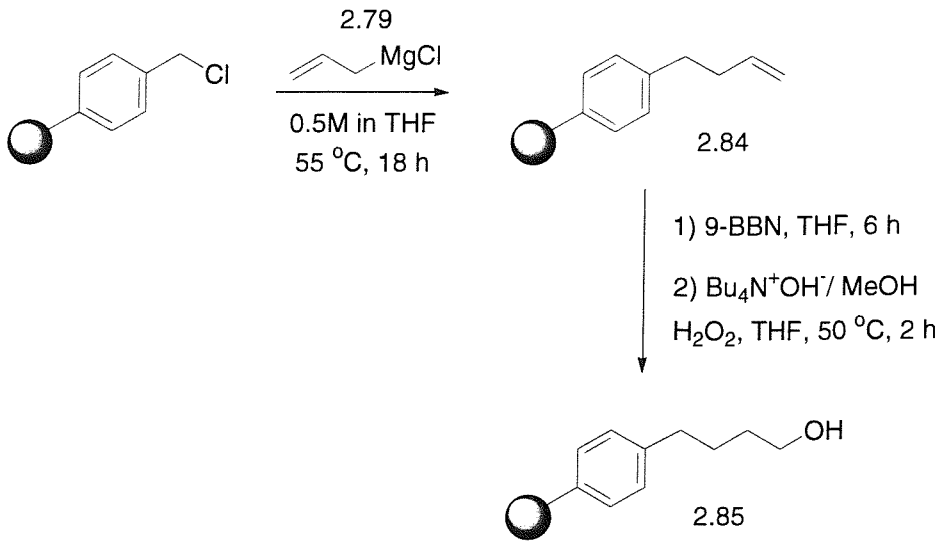
2.1.8 The development of solid-phase 9-BBN

There are very few reports of hydroboration with regard to Polymer-supported chemistry, however Chung *et al.* have described the synthesis of functionalised syndiotactic polystyrene polymers through the polymerisation of borane containing monomers.[87] 4-[B-(n-butylene)-9-BBN]styrene was prepared in 2 steps, starting with the Wurtz coupling between allylmagnesium chloride and 4-chloromethylstyrene to form 4-(3-butenyl)styrene. Selective monohydroboration by 9-BBN at the α-alkene position in an anti-Markovnikov manner then afforded the 4-[B-(n-butylene)-9-BBN]styrene which could be copolymerised with styrene using a metallocene catalyst (scheme 2.27).



Scheme 2.27 Polymerisation of a borane-containing monomer to give functionalised polystyrenes

Oxidation of the borane containing polymers was achieved using $NaOH/H_2O_2$ at 40 °C for 3 hours to give the desired hydroxy-containing polymers. The borane copolymers were found to be rather sensitive to atmospheric oxygen, which gave rise to premature oxidation. However they were found to be stable over long periods by storage under dry argon at room temperature. Other reports of the use of 9-BBN within the realms of solid-phase chemistry involve direct hydroboration of immobilised alkenes, resulting in the formation of the corresponding trialkylborane. Harikrishnan *et al.* used this procedure for the preparation of hydroxybutylpolystyrene following oxidation of the supported trialkylborane.[88]



Scheme 2.28 Preparation of hydroxybutyl polystyrene from chloromethyl polystyrene

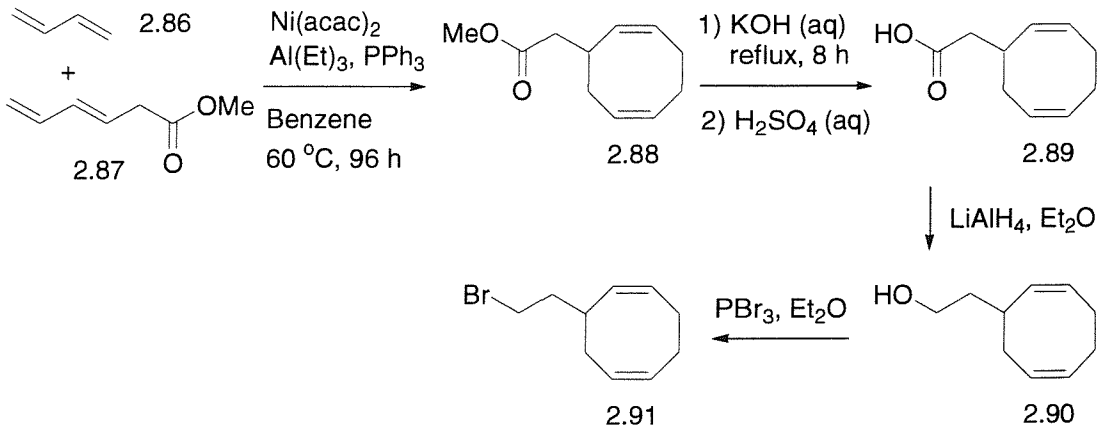
2.1.9 Project objectives

Given the very high synthetic utility of 9-BBN in the solution-phase, coupled with the distinct lack of immobilised hydroborating agents in the literature, we saw an opportunity for the development of such a reagent. However, we envisioned immobilisation of 9-BBN, not through boron linkage, but via a bond made to the carbocyclic structure of the reagent. Immobilisation of a 1,5-cyclooctadiene derivative followed by on-bead hydroboration of the 9-BBN precursor, was expected to allow the formation of a solid-phase hydroborating agent based upon 9-BBN. However, in light of the commercial unavailability of suitably functionalised cyclooctadiene systems, a synthetic strategy was investigated in the first instance.

2.2 The development of a hydroborating agent on solid-phase

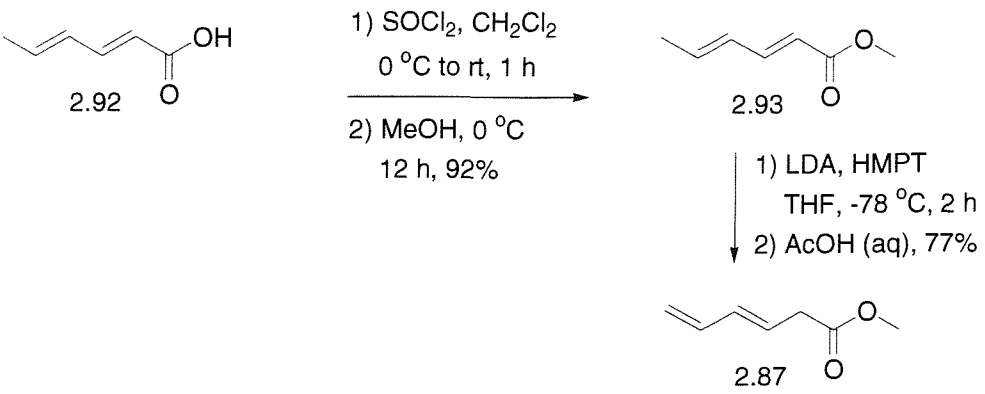
2.2.1 Intermolecular Nickel(0) catalysed [4+4] cycloaddition

The synthesis of eight-membered ring systems presents a challenge for the organic chemist due to the ring strain and transannular interactions incurred upon substitution.[89] Scientific interest in eight membered carbocycles has therefore given rise to numerous synthetic strategies towards such systems. Several interesting publications involving intermolecular nickel(0) catalysed [4+4] cycloaddition reactions have been reported.[90,91] Brun, Tenaglia and Waegell, demonstrated examples of intermolecular cycloadditions, in which several substituted butadiene derivatives were reacted with 1,3-butadiene.[91] However, the reaction does not show high chemical selectivity, and the reported yield of these reactions are generally low (<40% in most cases).[92] Scheme 2.29 shows a proposed reaction plan for the formation of a cyclooctadiene derivative considered appropriate for solid phase immobilisation. The nickel(0) catalysed cyclisation is reported to proceed only in 37% yield. However, since the overall route involves only 3 synthetic steps, this procedure was investigated.



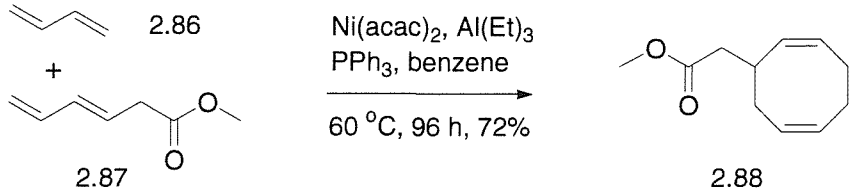
Scheme 2.29

Upon formation of ester **2.88**, access to a wide range of functionally diverse derivatives is possible as shown. In our primary studies however it is important that the loading of the immobilised cyclooctadiene can be assessed via chemical cleavage. The Wang linker (HMPA) is suitable for our purposes, and is cleavable in dilute trifluoroacetic acid (1-10% v/v in CH_2Cl_2). Synthesis of the ester starting material methyl hexa-3,5-dienoate **2.87** is documented,[93] and was carried out as detailed (scheme 2.30).



Scheme 2.30

The nickel(0) catalysed cyclisation of **2.87** was successful, however the reaction gave a mixture of products which were subsequently inseparable by column chromatography or fractional distillation (scheme 2.31).

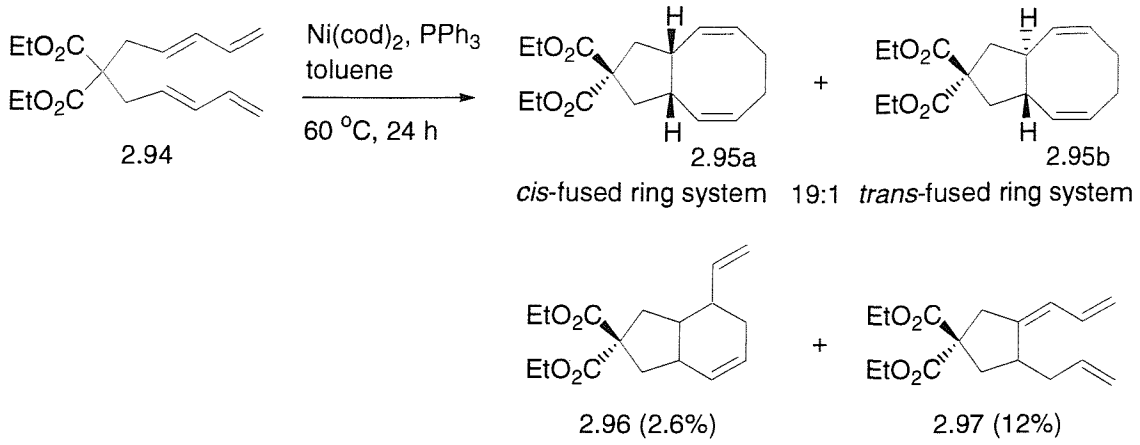


Scheme 2.31

Given these problems our attention was directed towards the intramolecular cyclisation of similar dienyl precursors as an alternative.

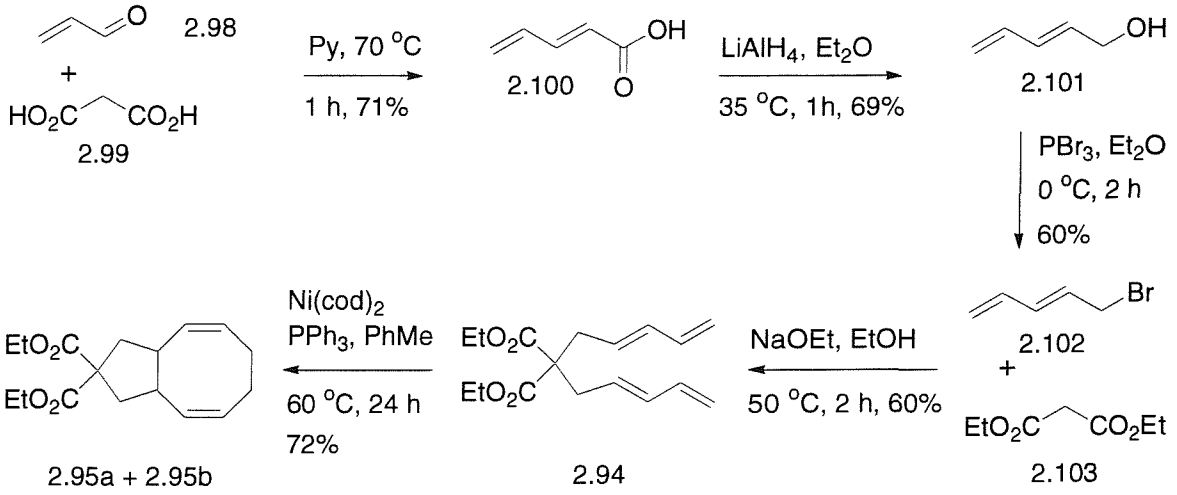
2.2.2 Intramolecular Nickel(0)-catalysed [4+4] cycloaddition

Although extensive studies have been made of nickel-catalysed intermolecular cycloaddition reactions of 1,3-butadienes, the first intramolecular version was reported by Wender and Ihle in 1986,[94,95] who describe cycloaddition reactions of bis-dienes separated by either a 3 or 4 carbon atom linker. The catalyst/ligand ratio was found to exert a major influence on the relative yield of side products obtained, which were reported to be separable by flash chromatography. Scheme 2.32 shows the outcome of a reaction conducted by Wender and Ihle, which was anticipated to be more suitable for our purposes.



Scheme 2.32

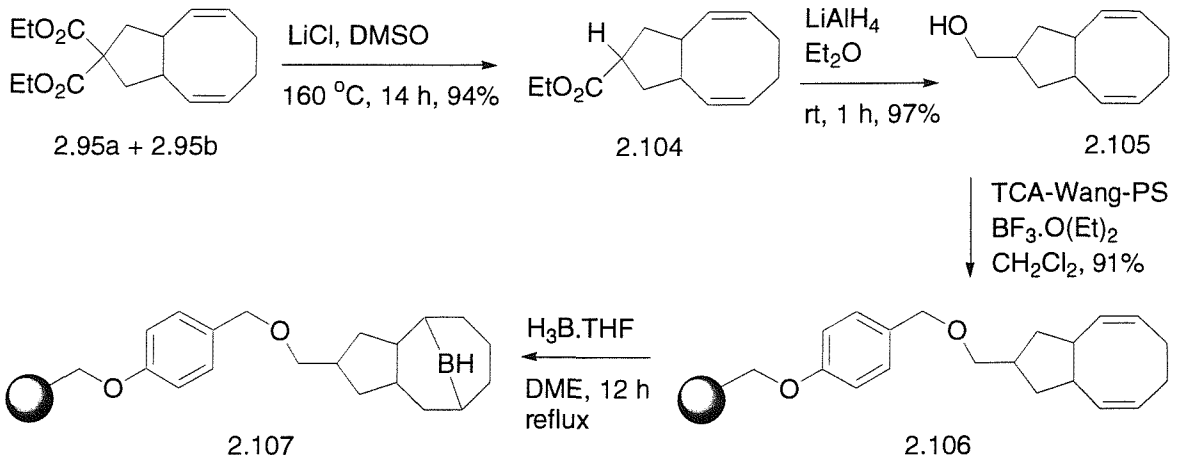
Formation of the *cis*-fused cyclooctadiene **2.95a** is greatly favoured over that of the *trans*-isomer **2.95b** (19:1). This route towards a functionalised cyclooctadiene was investigated experimentally since reported yields are high (70%) and literature procedures are available for the synthesis of tetraene **2.94**. Wender and Ihle prepared the tetraene diester **2.94** (scheme 2.33). The synthesis commences with a Doebner modification of the Knoevenagel reaction between malonic acid and acrolein (propenal).[96] Reduction of the (*E*)-dienoic acid **2.100** with LAH affords alcohol **2.101**.[97] Bromination of **2.101** produces the dienyl bromide **2.102**,[98] which is reacted with diethyl malonate to afford tetraene **2.94**.[99]



Scheme 2.33

In practice, it was found that the literature procedure[96] for drying (*E*)-Penta-2,4-dienoic acid **2.100** at 50 °C under high vacuum, resulted in the formation of a completely insoluble polymeric material.

Dissolution of **2.100** in diethyl ether prior to drying ($MgSO_4$) and removal of solvent *in vacuo* was found more appropriate. The preparation of (*E*)-Penta-2,4-dienol **2.101** also proved problematic, since impurities were found to persist even after repeated vacuum distillation. Alcohol **2.101** was found to be chemically unstable on silica gel, and attempted column chromatography resulted in the formation of brown/black decomposition products. Distillation of bromide **2.102** afforded a product of good spectroscopic purity, albeit in rather poor yield initially (34%, 44%, 53%). Tetraene **2.94** was also rather unstable and unsuitable for column chromatography. Vacuum distillation of this compound gave rise to a significant quantity of polymeric by-product and poor recovery yields (45%).



Scheme 2.34

Nickel(0) catalysed cyclisation of 2,2-bis(Penta-2,4-dienyl)1,3-dicarboxylic acid diethyl ester (tetraene **2.94**) was accomplished to yield a mixture of *cis*- and *trans*-fused cyclooctadiene ring systems **2.95a** and **2.95b,** along with side products which not only proved difficult to characterise, but also time-consuming to purify and isolate.[94] It was reasoned that both the *cis*- and *trans*-fused cyclooctadiene ring systems would allow formation of the desired 9-borabicyclo[3.3.1]nonane moiety, and given the 19:1 ratio of *cis:trans* isomers described in the literature, separation of these compounds was not attempted. However, based upon the literature yields of side-products formed by β-hydride elimination (**2.97**, 12%) and 6-membered ring formation (**2.96**, 2.5%) it was considered important that these materials be completely removed, to prevent complications at later stages. TLC (9:1, hexane / EtOAc) indicated a rather broad spot (Rf = 0.3-0.4), which was isolated by column chromatography. However, reverse-phase HPLC indicated the presence

of 4 different components within the isolated material, each with separation in the order of only several seconds.

Preparative-HPLC (normal-phase) was conducted, eluting with 25:1 (hexane/EtOAc), however no resolution between sample components was observed. Thin-layer chromatography using silver nitrate doped plates and $KMnO_4$ (aq) visualisation, indicated 4 distinct components, albeit with poor separation from one another, and several attempts were made at silver nitrate doped silica column chromatography.[100] However, using flash silica doped in the normal manner with 1%, 5% and 10% $AgNO_3$ (w/w) failed to give the required resolution between components, and at best only milligram quantities of clean diester **2.95a** + **2.95b** were obtained.

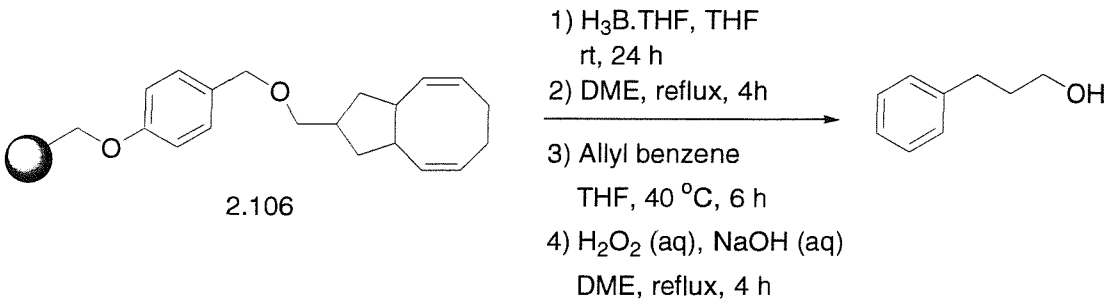
We decided to use the difference in chemical reactivity towards hydroboration by the regio-selective reagent 9-BBN (0.5M in THF) in order to derivatise the more reactive terminal alkene groups in the side products **2.96** and **2.97** over the less reactive internal alkenes of the desired cyclooctadienes **2.95a** and **2.95b**.[101] Hydroboration of the product mixture using a substoichiometric quantity of 9-BBN (0.3 mol equivalents based on literature distribution) was performed. Upon oxidative workup, the product was shown chromatographically to contain new highly polar components, corresponding to the expected alcohols. Column chromatography of the mixture allowed isolation of a material which was again run on silver nitrate doped TLC plates, and shown now to consist only of one main band which was taken to be the *cis* and *trans* mixture of unreacted cyclooctadiene diesters **2.95a** and **2.95b**. Following isolation of these diesters, Krapcho dealkoxycarbonylation[102,103] was performed in the normal manner using a mixture of lithium chloride and dimethyl sulfoxide at 160 °C to give the mono-ester **2.104** in good yield (94%, scheme 2.34).

LAH reduction of the ester function[97] afforded alcohol **2.105** in 97% yield, which was shown by LCMS (EI) to consist of two major products separated by just 2 seconds. Both components gave the correct mass ion and a fragmentation pattern consistent with the desired alcohol. **2.105** was subsequently immobilised on polystyrene resin by means of a trichloroacetimidate-activated Wang linker (scheme 2.34). Cleavage of alcohol **2.105** from a sample of the loaded resin **2.106** was performed[104] using standard conditions (5% TFA/CH_2Cl_2) to recover the alcohol in 91% yield, indicating that loading had proceeded with high efficiency. Following immobilisation, **2.106** was hydroborated using a large excess of $H_3B.THF$. Thermal isomerisation was performed to yield the [3.3.1] bridged ring system by reflux in DME at 85 °C for 1 hour. The resin was washed with THF, in order to remove adventitious borane residues, and dried under high vacuum before subsequent use.

At each stage of the synthesis following Ni (0) cyclisation, spectroscopic analysis was performed, however the interpretation of ^{1}H and ^{13}C NMR has been particularly difficult.

^{13}C NMR spectra show the presence of at least two different components each displaying different signal intensities, probably arising from differences in the stereochemical configuration of the *cis* and *trans* isomers at each stage. Variable temperature ^{1}H and ^{13}C NMR did not provide any useful further information.

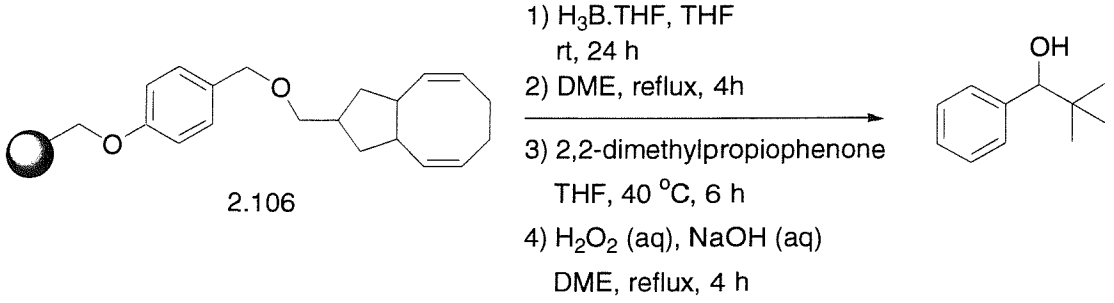
2.2.3 Solid-phase hydroboration of allyl benzene



Scheme 2.35

The hydroboration and subsequent oxidation of allyl benzene (scheme 2.35) was carried out on small scale (106 mg resin). However, due to the poor recovery of product material after oxidation (2 mg, impure), purification and characterisation proved difficult. By capillary-GC analysis, the product appeared identical to a dihydrocinnamyl alcohol standard. However, we have been unable to reproduce this result on a large scale.

2.2.4 Solid-phase reduction of 2,2-dimethylpropiophenone



Scheme 2.36

The reaction of the solid-phase hydroborating reagent with 2,2-dimethylpropiophenone was also investigated (scheme 2.36), and the impure product of oxidation was spectroscopically examined by NMR. The resulting spectra showed appropriate chemical shift values for the aromatic and aliphatic regions in comparison to a standard sample produced by the reduction of the ketone starting material using $NaBH_4$, but attempts to produce larger quantities of material were unsuccessful.

2.2.5 Conclusions

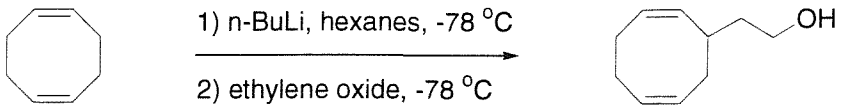
Synthesis of a functionalised cyclooctadiene derivative bearing suitable functionality to allow immobilisation on HMPA resin was accomplished, despite the lengthy and low-yielding route required. However, hydroboration of the immobilised COD derivative did not product an active hydroborating agent in its own right. The stereochemical complexity of the fused [5.8] carbocycle served only to hamper any attempts made to understand the reasons for these continually disappointing results. Hence, a far more refined and direct strategy was required.

2.3 Direct functionalisation of 1,5-cyclooctadiene (1,5-COD)

The nickel-catalysed synthesis of cyclooctadiene derivatives proved to be problematic at every stage. Given the rather involved routes initially undertaken, it is obvious that the time and cost incurred in preparing an immobilised 9-BBN analogue would be prohibitive. Part of the popularity of the solution-phase reagent stems from the ease of its preparation from readily available 1,5-COD **2.34**. In designing a supported alternative, our ideal precursor should be as synthetically simple and cost effective as possible to help ensure widespread acceptance of the new reagent. With these issues in mind, we pursued a more direct procedure for the preparation of functionalised CODs, however there have been remarkably few cyclooctadiene derivatives prepared to date.

2.3.1 Attempted synthesis of cycloocta-2,6-dienyl ethanol (2.90)

In 1986, Winkler and Sridar[105] reported the seemingly straightforward synthesis of cycloocta-2,6-dienyl ethanol **2.90**, albeit in rather poor isolated yield (35%), through reaction of ethylene oxide with the preformed anion of 1,5-cyclooctadiene (scheme 2.37).



2.34 2.90

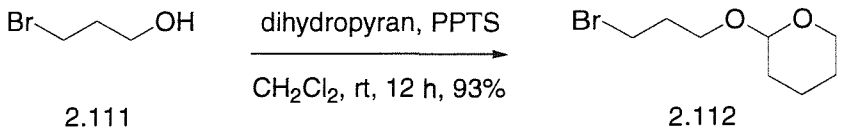
Scheme 2.37 Winkler's synthesis of cycloocta-2,6-dienyl ethanol

The literature supplementary information was obtained, and the reaction performed as described, however even at low temperature (-78 °C throughout) none of the desired compound was obtained at all. The only isolated materials resulting from the reaction were shown to be the polymerisation product, polyethylene glycol, with minimal incorporation of the cyclooctadiene moiety, and high return of 1,5-cyclooctadiene upon workup.

Despite the initially discouraging results obtained by the attempted alkylation of the 1,5-cyclooctadiene anion, it was decided that this approach was to be investigated more thoroughly, since the reaction could potentially generate cyclooctadiene derivatives directly without the need for lengthy synthesis. Given that the reaction of the cyclooctadiene anion with an epoxide produced mainly polymeric products, it was anticipated that more fruitful results be obtained through the use of a non-polymerisable electrophile. In the first instance we chose THP-protected halohydrins as suitable trapping electophiles given the stability of the tetrahydropyranyl group under highly basic conditions, and its facile acid-catalysed hydrolysis to the hydroxyl precursors.

2.3.2 Synthesis of THP-protected alkyl cyclooctadienes

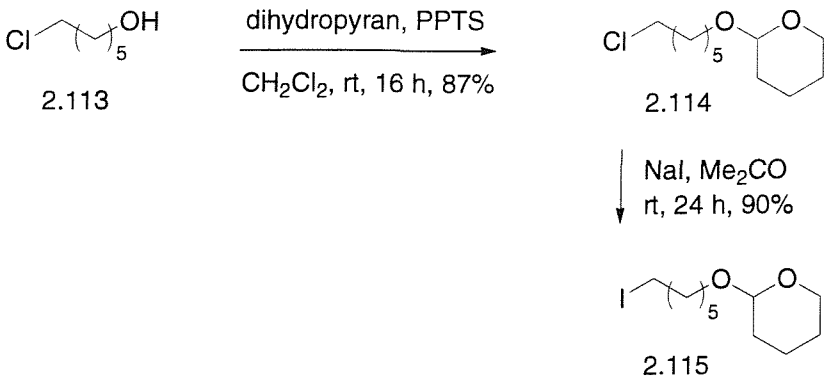
3-bromopropan-1-ol **2.111**, and 6-chlorohexan-1-ol **2.113** were chosen as suitable halohydrin substrates, since both are commercially available and relatively inexpensive, and nucleophilic displacement of the leaving group would give COD derivatives bearing 3 and 6 carbon tethers respectively. The synthetically useful hydroxyl terminal functions were protected through formation of the tetrahydropyranyl derivatives (scheme 2.38 and 2.39).[106]



2.111 2.112

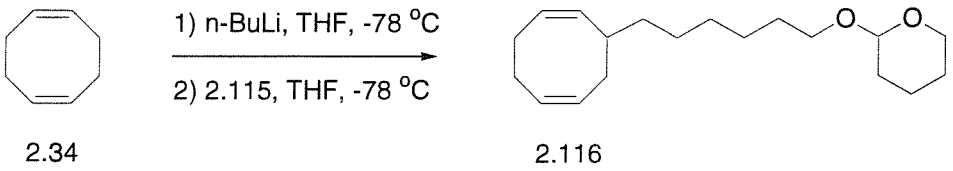
Scheme 2.38 THP-protection of 3-bromopropan-1-ol

The protected chloro-compound **2.114,** was rendered more reactive towards nucleophilic displacement through Finkelstein halogen exchange using sodium iodide to produce the iodo-derivative **2.115** (scheme 2.39).



Scheme 2.39 THP-protection of 6-chlorohexan-1-ol

The alkylation reaction of 2-(6-iodo-hexyloxy)-tetrahydropyran **2.115** with the preformed cycloocta-1,5-dienyl anion was performed (scheme 2.40). Following aqueous work-up, the reaction was found to have given rise to two compounds as shown by gas chromatography. However these have not proven at all possible to separate by conventional column chromatographic methods.



2.34 2.116

Scheme 2.40 Alkylation of 1,5-COD

The mass-spectrum of the reaction products shows the incorporation of a tetrahydropyranyl moiety in both compounds produced, however the thermal instability of the products was such that even under low temperature chemical ionisation conditions, a molecular ion was not observed. The ^{13}C NMR spectrum indicates favourably that substitution of the cyclooctadienyl ring had occurred, and would suggest the formation of the desired mono-substituted allylic product alongside a very small quantity of the symmetrical disubstituted compound.

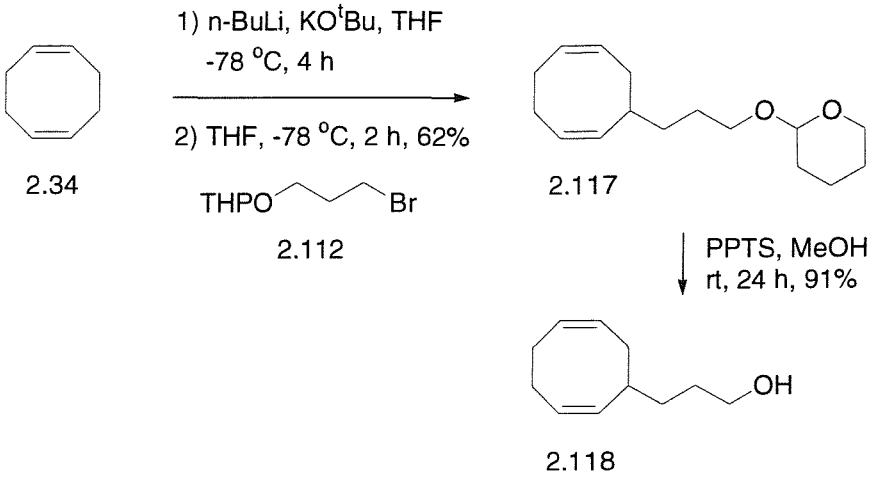
2.3.3 Optimisation of conditions for metallation and functionalisation

Since the use of n-butyl lithium results in a large return of the starting materials, we considered alternative bases with which to form the required 1,5-cyclooctadienyl lithium species. The addition of the tertiary diamine TMEDA to metallation reactions, frequently

improves yields through disaggregation of coordinated lithium species; in effect, producing a more reactive 'naked anion'. However, even the addition of 1 equivalent of TMEDA to our otherwise identical deprotonation reaction of 1,5-cyclooctadiene, was not found to increase significantly the yield after reaction with THP-protected 3-bromopropan-1-ol (42% yield increased to 45%).

In particular we were interested in using the so called "superbase" or "LIKOR" Lithium-Potassium Alkoxide base, which may be formed *in situ* from equimolar quantities of tert- or n-butyllithium and potassium t-butoxide in THF. Such reagents are described in detail for the deprotonation of many cyclic and non-cyclic allylic compounds, although they do not appear to have been used in conjunction with cyclooctadiene.[107] Scheme 2.41 shows the alkylation reaction conducted using the Schlosser base mixture at low temperature. We were very pleased to observe success of the reaction in 62 % isolated yield, producing **2.117** very cleanly, with only a trace of the inseparable vinylic substituted product.

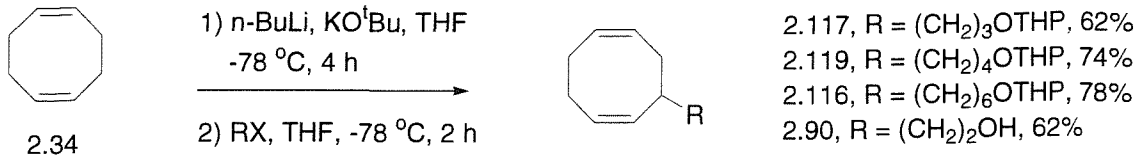
Initial reactions were conducted at –95 °C, however, more recent results show that product yield and purity is unaffected when the reaction is conducted at –78 °C. Deprotection of the THP group[106] of **2.117** was conducted cleanly using PPTS in methanol to afford the alcohol **2.118** in excellent yield.



Scheme 2.41 Schlosser base deprotonation of 1,5-COD

This encouraging result prompted us to consider further examples of this chemistry with the intention of diversifying the novel reaction products to other synthetically useful materials. We can now report successful reaction of the preformed cyclooctadienyl anion with THP-protected halohydrins of 3, 4 and 6 carbon atom chain lengths. Of these electrophiles, the iodobutyl and iodohexyl derivatives gave superior yields of the desired products with

smaller quantities of the undesired isomeric impurity, relative to the bromopropyl electrophile. These results are summarised below (scheme 2.42).



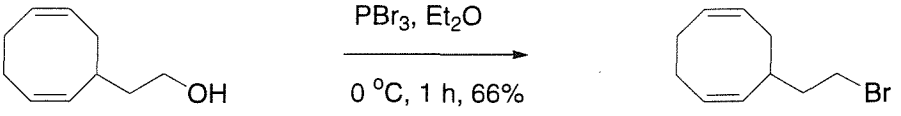
2.34

Scheme 2.42 Reaction of electrophiles with cyclooctadienyl lithium

The success of these reactions in general caused us to reconsider our initial goal, which was to repeat Winkler's synthesis of cyclooctadienyl ethanol **2.90** now using our modified Schlosser base conditions. Reaction of ethylene oxide with cyclooctadiene lithiated under the super base conditions, gave rise to an isolated yield of 62% of the desired compound, which was remarkably clean and free from positional isomers.

2.3.4 Diversification of cyclooctadienyl derivatives

Access to cyclooctadienyl bromide from cyclooctadienyl ethanol, was attempted by two different routes, both of which were successful. The initial method employing triphenylphosphine and carbon tetrabromide in acetonitrile, generating *in situ* the reactive "pentavalent" species Ph_3PBr_2, caused difficulties with isolation of the product bromide free from phosphine impurities. However, the use of phosphorus tribromide in anhydrous diethyl ether, enabled isolation of the desired bromide **2.91** in 66% yield (scheme 2.43). The bromide is however quite unstable, and darkens rapidly upon exposure to air and light. Purification was best performed by rapid passage through a short plug of chromatographic silica, eluting with neat hexanes as described in the experimental section.

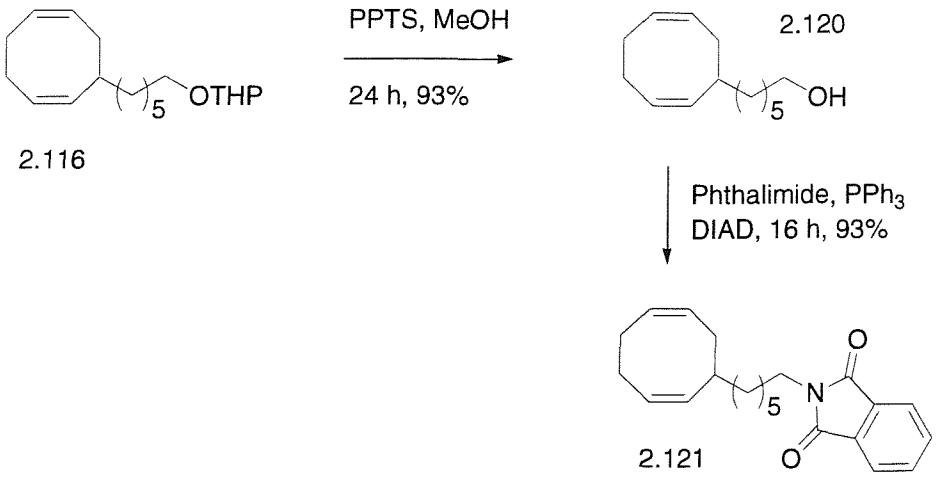


2.90 2.91

Scheme 2.43 Bromination of cyclooctadienyl ethanol using phosphorus tribromide

Reaction of cyclooctadienylhexan-1-ol **2.120** under Mitsunobu[108] conditions employing phthalimide as the displacing nucleophile afforded cleanly the phthalimido derivative **2.121** (scheme 2.44).

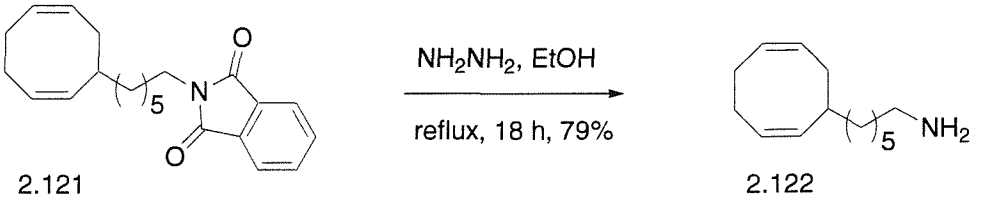
Purification of this compound was straightforward using column chromatography, and the clean material was obtained in 93% yield without problems.



Scheme 2.44 Phthalimide functionalisation under Mitsunobu conditions

From **2.121** was prepared in 79% yield, the parent amine **2.122** via deprotection of the phthalimido moiety using hydrazine hydrate in refluxing ethanol (scheme 2.45). Purification of the crude amine was not straightforward however, and although chromatographic methods were explored, the amine was not obtained in analytical purity.

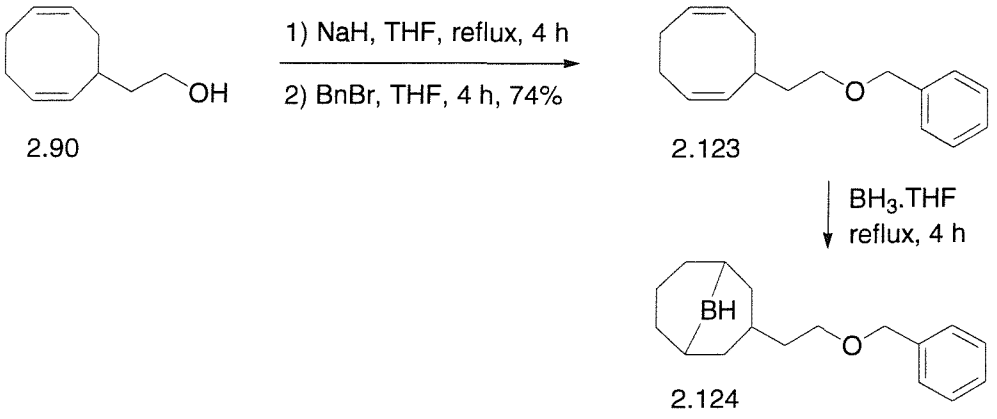
The impurities, which by NMR appear to constitute approximately 5-8% are not identified, but indicate certain duplication of the main signals in the aliphatic region. However, GC reveals only 1 main signal, and the amine is still suitable for immobilisation onto an appropriate support, and therefore still offers an important precursor for our preliminary studies into solid-phase alkylboranes.



Scheme 2.45 Phthalimide deprotection using hydrazine hydrate

2.3.5 Development of a solution-phase hydroborating model of 9-BBN

Reaction of cyclooctadienyl ethanol **2.90** with sodium hydride, generated *in situ* the alkoxide species which was reacted with benzyl bromide in THF at reflux over 4 hours, affording the benzyl ether in 74% yield. Hydroboration of the cyclooctadienyl moiety of the ether using H_3B.THF complex also at reflux in THF gave the boron-containing adduct **2.124** (scheme 2.46). Anticipating the instability of the hydroborated species, purification was not attempted. However, residual solvent and adventitious borane was carefully removed under high vacuum in an attempt to allow isolation of the desired dialkylborane ether **2.124**.

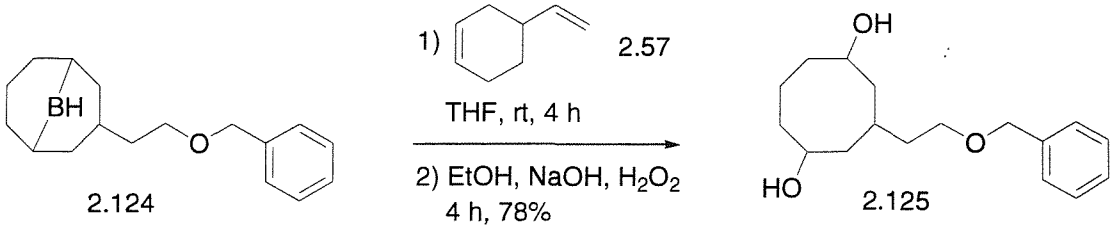


2.90 2.123 2.124

Scheme 2.46 Preparation and hydroboration of ethyl cyclooctadiene benzyl ether

Addition of fresh THF, followed by 1 equivalent of freshly distilled 4-vinylcyclohexene was made, and the reaction was allowed to proceed at room temperature over 4 hours.

To the reaction mixture was added an equal volume of ethanol, and oxidation of alkylboranes in the reaction mixture was performed by addition of aqueous NaOH and H_2O_2 dropwise, giving rise to an exothermic reaction (scheme 2.47).

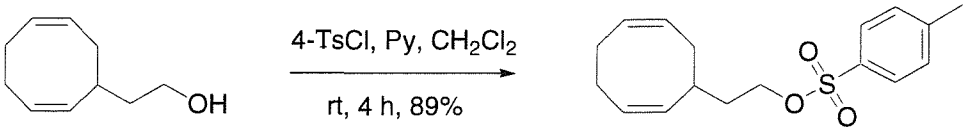


2.124 2.125

Scheme 2.47 Hydroboration of 4-vinylcyclohexane using immobilised 9-BBN model

Aqueous workup and extraction of the reaction mixture led to the isolation of a new major product. Chromatographic isolation and analysis by NMR confirmed the new substance to be the product of hydroborated/oxidation of the cyclooctadienyl benzyl ether **2.125** in 78%. However, very disapointingly, only traces of the oxidation product of 4-vinylcyclohexene were obtained. We were led to conclude that hydroboration of the cyclooctadienyl ether was successful, although the dialkylborane **2.124** so formed was not itself a hydroborating species. In an attempt to understand the issues surrounding the unreactivity of our benzyl ether model system, we were prompted to simplify our COD derivative still further in order to more closely model 9-BBN itself.

Commencing from cyclooctadienyl ethanol **2.90** once again, we envisaged the preparation of 3-ethyl-1,5-cyclooctadiene **2.127** through reduction of the tosylated compound **2.126**. Cyclooctadienyl ethanol **2.90** was readily tosylated using TsCl and pyridine in CH_2Cl_2 at room temperature (scheme 2.48). Interestingly we found that the tosylation reaction was complete in under 4 hours at room temperature, and subsequent reaction time gave rise to diminishing yields of the desired sulfonate **2.126**. Over long periods of time (48 hours) large quantities of a side-product were found to be produced, later elucidated as chloroethyl cyclooctadiene, the product of tosylate elimination by a chloride ion source (pyridinium hydrochloride).

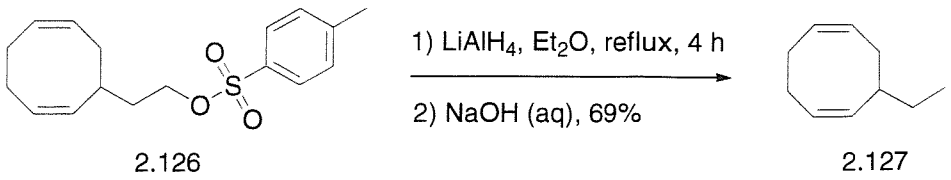


2.90 2.126

Scheme 2.48 Tosylation of cyclooctadienyl ethanol

While the observed side-reaction was not of immediate utility, we were pleased to recognise this substitution reaction as a convenient method by which cyclooctadienyl alkyl halides could be prepared from the parent alcohol **2.90**.

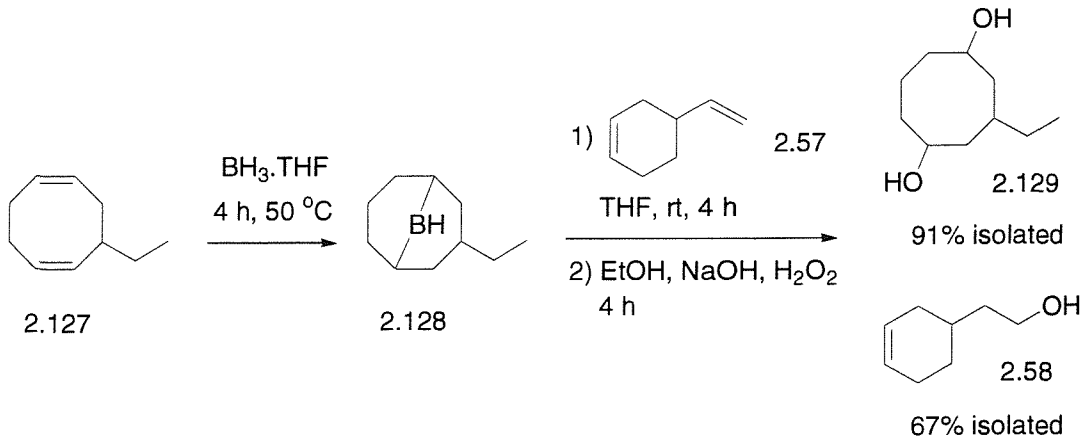
With the tosylated cyclooctadienyl ethanol **2.126** derivative in hand, reduction to ethyl cyclooctadiene **2.127** was performed in good yield using LAH in diethyl ether at reflux temperature. Excess reducing agent was quenched and lithium salts were precipitated by the addition of aqueous NaOH to the reaction mixture, and the crude ethyl COD was isolated by filtration. Short-path vacuum distillation of the crude alkene provided the pure desired compound **2.127** in 69% isolated yield (scheme 2.49).



2.126 2.127

Scheme 2.49 Reduction of tosylated cyclooctadienyl ethanol

Hydroboration of the ethyl COD derivative 2.127 in a manner analogous to that used for the hydroboration of the benzyl COD ether was conducted. Once again, volatile species were removed under high vacuum to afford a colourless glass. The postulated dialkylborane 2.128 was immediately reacted with 4-vinylcyclohexene 2.57 as before, and oxidation of the reaction mixture was performed. To our relief we were soon to observe two new products of oxidation by TLC; these were isolated by chromatography and determined as the expected ethyl cyclooctanediol 2.129 in 91% yield, and the more gratefully received 4-(1-hydroxyethyl)-cyclohexene 2.58 in 67% yield. Even more impressively, only the product of terminal oxidation of 4-vinylcyclohexene 2.57 was isolated, as would be expected from hydroboration using 9-BBN in solution. The more sterically hindered internal alkene was completely unaffected in the isolated product, indicating regioselective hydroborating action from our functionalised 9-BBN analogue (scheme 2.50).

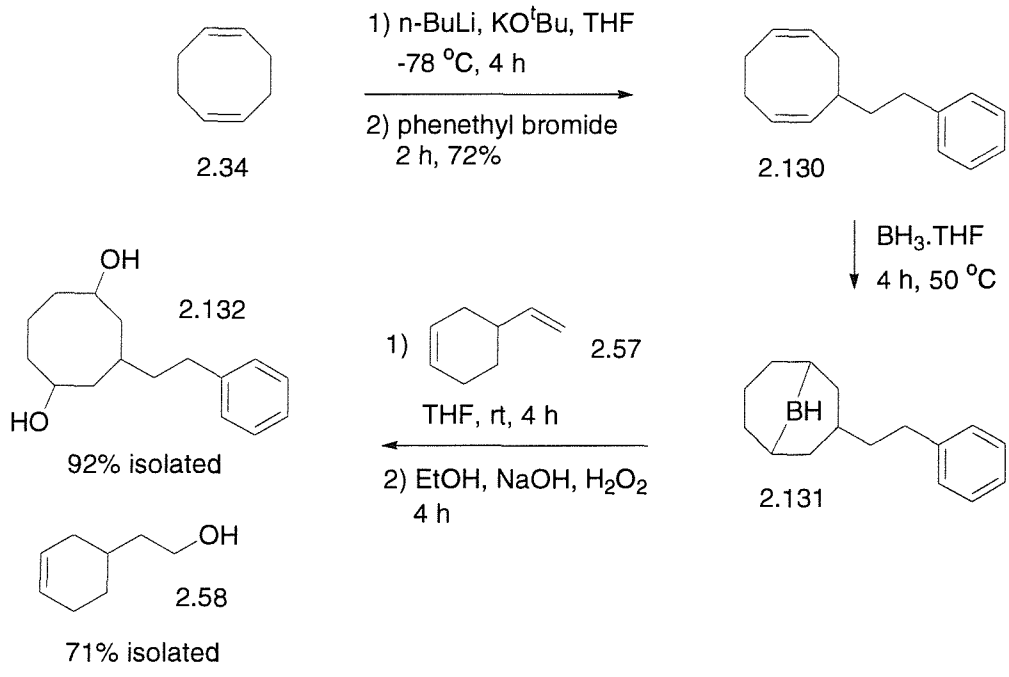


2.127 2.128

Scheme 2.50 Hydroboration/oxiation of 4-vinylcyclohexene

With renewed hope for the successful development of a supported 9-BBN analogue, we desired to more closely approximate our model system on the functionalised COD derivative as it would be immobilised on a polystyrene support. Given that hydroboration of our previous benzyl COD ether **2.123** had failed to produce an active hydroborating species, we chose to persist with another benzyl-type model, omitting the oxygen ether atom from the COD tether.

Reaction of phenethyl bromide with lithiated cyclooctadiene, formed by *in situ* reaction of 1,5-COD **2.34** under the standard Schlosser base conditions, gave after chromatographic purification, phenethyl cyclooctadiene **2.130** in 72% yield. Hydroboration of the phenethyl cyclooctadiene was performed in the manner previously described for both the benzyl ether **2.123**, and ethyl COD **2.127** derivatives, and removal of volatile species was performed under high vacuum. Addition of 4-vinylcyclohexene **2.57** in THF was made to the freshly formed dialkylborane **2.131**, and the reaction was stirred over 4 hours at room temperature. Subsequent oxidation in the normal manner was performed with alkaline hydrogen peroxide, and following aqueous extraction and purification of the oxidation products, we were once again delighted to isolate the desired 4-(1-hydroxyethyl)cyclohexene **2.58** in 71% yield (scheme 2.51).



Scheme 2.51 Preparation and evaluation of phenethyl cyclooctadiene as a hydroborating agent

2.3.6 Conclusions

We have demonstrated the use of the LIKOR superbase reagent in allowing formation of the highly reactive cyclooctadienyl anion, and the subsequent reaction of this species with various electrophiles. Of the electrophilic species chosen, it is unsurprising that the iodo-derivatives give the highest yields and most selective reaction with the pre-formed anion. We have also modified the reaction conditions set out by Winkler,[105] regarding synthesis of cyclooctadienylethanol **2.90**, such that a respectable yield (62%) can now be reported, and full characterisation data published.

We have also produced a small variety of 1,5-cyclooctadienyl derivatives bearing pendant functions, in order to further demonstrate the utility of the Schlosser base alkylation strategy. Although the initial reaction offers access only to the THP-analogues (with the exception of reaction with ethylene oxide), these are easily converted to the parent hydroxyl derivatives. Using well-established functional group interconversions, a host of other compounds is therefore immediately accessible. These results have now been published by ourselves.[109]

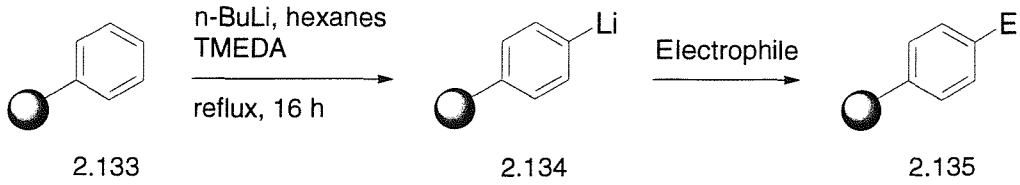
From the successful use of our hydroborated ethyl- and phenethyl-model systems as efficient hydroborating agents themselves, we can speculate that the presence of the ether oxygen heteroatom in the first benzyl ether model, prohibits its action as a hydroborating agent.

This may be a consequence of intramolecular coordination of the oxygen atom with the oxophilic boron atom of the carbocyclic ring system. However, coordination in this manner would not be expected to totally retard further hydroboration reactions.

Having established active hydroborating 9-BBN derivatives in the solution-phase, our next objective was to translate our results to the solid-phase, given that we now have access to a variety of different cyclooctadiene derivatives bearing useful functionalities.

2.4 Alkylation of polystyrene by lithiation of the support

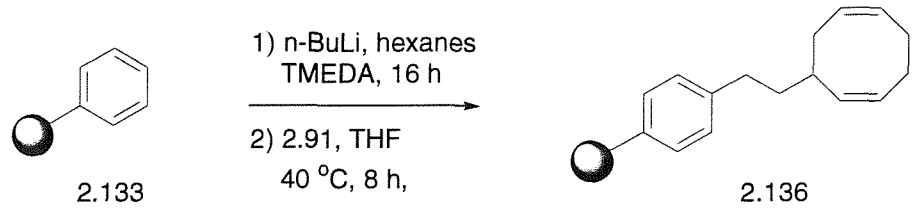
Attempts to functionalise polystyrene supports by way of a Wang linker did not produced the results we desired. Our attention was turned to the use of direct alkylation methods for resin functionalisation, with particular interest in the polystyrene lithiation chemistry developed by Leznoff and Fyles.[110] Functionalisation in this manner circumvents the use of a linker, and has been shown to allow substitution of the support to a high loading level.



Scheme 2.52 Leznoff's procedure for polystyrene lithiation

2.4.1 Reaction of supported phenyl lithium with COD derivatives

Reports by Leznoff *et al.* showed that various polystyrene resins were successfully metallated using a refluxing mixture of n-BuLi and TMEDA in hexane (scheme 2.52). The highly reactive supported phenyl lithium species **2.134** was subsequently quenched by reaction with a variety of electrophiles, including alkyl and acyl halides and even carbon dioxide, to give the appropriately substituted polymers. Our intention was to prepare supported phenyl lithium from regular unfunctionalised polystyrene resin (2% crosslinked with DVB), followed by reaction of the metallated species with cyclooctadienylethyl bromide **2.91** in the hope that nucleophilic displacement of the halide would yield a supported cyclooctadiene, linked to the resin matrix through a 2-carbon tether. Preparation of lithiated polystyrene as detailed by Leznoff, proved successful in yielding a bright red polymer, which was immediately reacted with cyclooctadienylethyl bromide **2.91** in THF at room temperature (scheme 2.53).

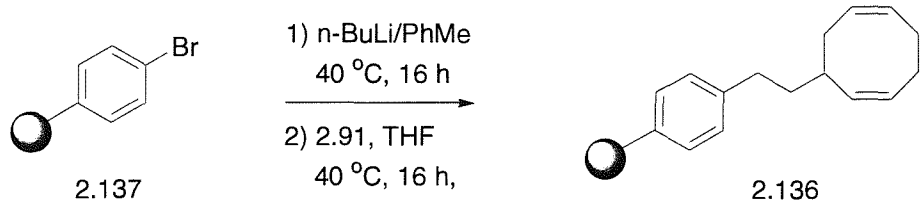


Scheme 2.53 Reaction of lithiated polystyrene with cyclooctadienyl ethyl bromide **2.91**

In our hands however, functionalisation was subsequently shown to have proceeded in very low yield, and hydroboration of the support followed by reaction with allyl benzene provided only 12% of the desired 1-hydroxy-3-phenylpropane after oxidation. We were led to conclude that incomplete lithiation of the polystyrene had occured in our hands, perhaps due to poor swelling of the resin in the hexane based reaction mixture. We speculated that only surface functionalisation of the support had occured, which was responsible for the subsequently poor yields at the hydroboration/oxidation stage. However, we had succeeded in demonstrating that the immobilised COD derivative functioned as intended, providing the desired hydroboration/oxidation product, albeit in poor yield.

2.4.2 Halogen-metal exchange using 4-bromopolystyrene

Further attempts at using lithiation methodology were conducted using 4-bromopolystyrene **2.137** (0.83 mmol/g). Lithium halogen exchange of this resin was conducted using a solution of n-BuLi supplied in toluene, in the hope that greater swelling of the resin in this medium would lead to more efficient substitution of the resin upon reaction with the bromide **2.91** (scheme 2.54).



2.137 2.136

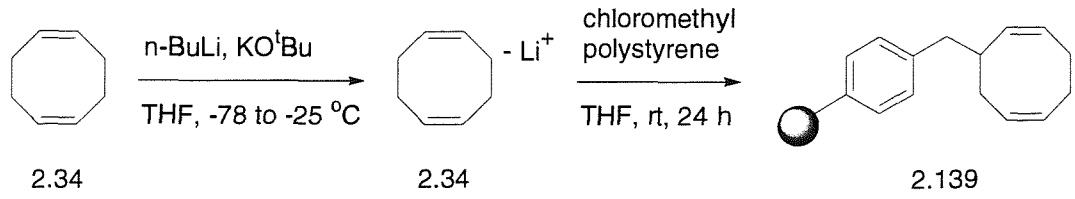
Scheme 2.54 Halogen/metal exchange with 4-bromopolystyrene

However upon reaction of the presumed resin bound phenyl lithium sample with cyclooctadienylethyl iodide, elemental analysis revealed 4.1% remaining bromide corresponding to 0.51 mmol/g. Therefore substitution of the cyclooctadienylethane species had taken place in very low yield if at all, and we were unsurprised to find that hydroboration of this resin and subsequent reaction with allyl benzene produced none of the desired 3-phenyl propan-1-ol upon oxidation with alkaline peroxide.

2.4.3 Reverse alkylation of chloromethyl polystyrene

At this stage of the project, we had already developed a versatile procedure for the functionalisation of 1,5-cyclooctadiene, and using this strategy, we were successful at developing model systems, which could be hydroborated and used as hydroborating agents themselves.

Given that our procedure for the preparation of functionalised COD derivatives centred about the *in situ* generation of lithium cyclooctadiene prior to its reaction with a series of alkyl halide electrophiles; we supposed that reaction directly with chloromethyl polystyrene might also prove fruitful. Indeed, the most encouraging results were obtained through direct alkylation of chloromethyl polystyrene with pre-formed cyclooctadienyl lithium (scheme 2.55). Our initial preparations were made using a very high loading chloromethyl polystyrene supplied by Nova-Biochem^{AG} with a chloride loading of 4.55 mmol/g, confirmed by elemental analysis.



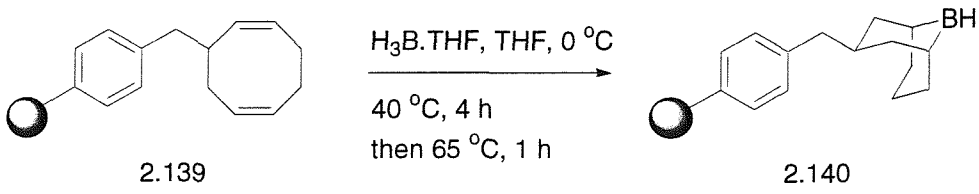
Scheme 2.55 Direct alkylation of CMP with cyclooctadienyl lithium

The chloromethyl polystyrene was washed thoroughly with anhydrous THF, however the resin was not dried after the last wash, rather it was maintained as a mobile slurry in THF and added directly as such from a dropping funnel into a fresh preparation of cyclooctadienyl lithium held at –78 °C. Following total addition of the polymer, the reaction was stirred vigorously, maintaining the low temperature over 4 hours. The reaction was allowed to warm to ambient temperature and proceed for a further 24 hours, when the dark purple resin beads were filtered on a glass sinter and washed. Exposure to atmospheric moisture and addition of wet THF immediately rendered the reactive purple beads colourless once again, and washing was carried out using a solution of 1 M HCl (aq) in THF (50:50 v/v) to ensure the removal of residual butoxide base and lithium salts.

To our delight, the dried resin **2.139** was found to have dramatically increased in mass, and extensive functionalisation was later confirmed by microanalysis; revealing a residual chloride loading of only 0.45 mmol/g corresponding to a substitution of 86% taking into account the mass change of the resin. The new resin loading was calculated as 3.85 mmol g^{-1} COD.

2.4.4 Hydroboration/oxidation using cyclooctadienylmethyl polystyrene

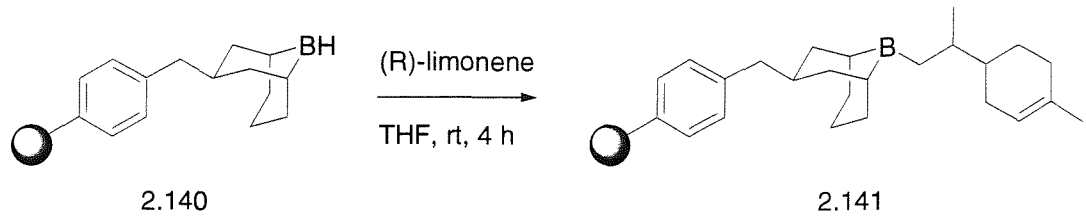
Hydroboration of the cyclooctadienylmethyl polystyrene **2.139** was performed by reaction of the resin (pre-swollen in anhydrous THF) with commercially available $H_3B.THF$ complex (1 mol dm^{-3} in THF). In order to ensure complete reaction of the immobilised cyclooctadienyl moiety with the borane, 10 molar equivalents of borane were used. The reaction was stirred at 40 °C for 4 hours, followed by 1 hour at reflux (65 °C) to allow for rearrangement of the expected [4.2.1] bridge system to the desired [3.3.1] system (scheme 2.56).



Scheme 2.56 Hydroboration of cyclooctadienylmethyl polystyrene

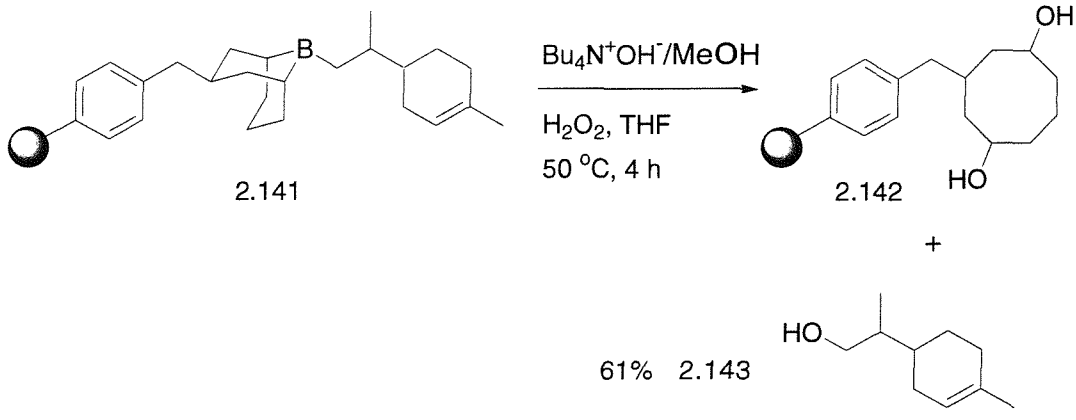
Following hydroboration, the resin was washed using only freshly distilled THF and hexanes, in order to minimise decomposition of immobilised borane species by hydrolysis. Through the course of our studies, it became apparent that the hydroborated resin is highly reactive and that handling must be carried out in a dry and inert atmosphere, as the fresh resin is rapidly rendered inactive through prolonged exposure to air. Atmospheric decomposition is such that a glass reaction vessel containing the exposed resin becomes noticeably warm to the touch, indicating disappointingly that our reagent has not inherited the insensitivity towards moisture and oxygen associated with unfunctionalised 9-BBN. We consider the highly reactive nature of our immobilised borane to have arisen as a consequence of the lack of dimerisation available on the support.

Elemental analysis for total boron content of the hydroborated resin **2.140** revealed a loading of 3.24 mmol g^{-1}, and this loading was used to determine subsequent reaction yields from hydroboration/oxidation experiments. In our initial studies, limonene was chosen to demonstrate the hydroborating selectivity of the resin bound reagent, regarding discrimination between the relatively unreactive internal and reactive terminal olefin functions respectively (scheme 2.57). The freshly hydroborated resin **2.140** was slurried in dry THF, to which was added an excess of (*R*)-limonene, and the reaction vessel was purged with argon and agitated at room temperature for 4 hours.



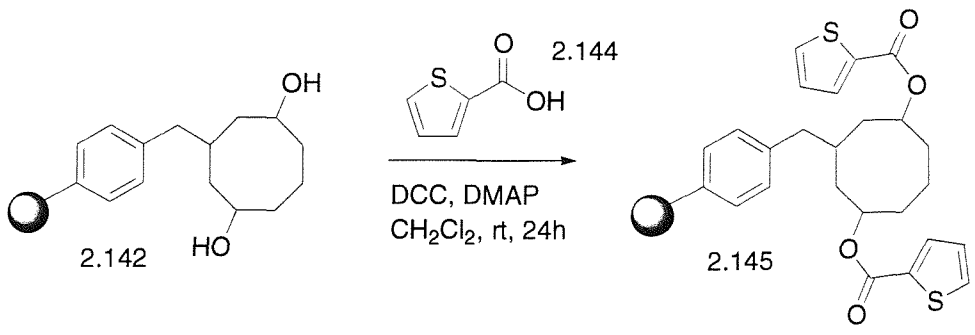
Scheme 2.57 Reaction of immobilised 9-BBN analogue with (*R*)-limonene

The resulting trialkylborane resin **2.141** was thoroughly washed with anhydrous THF and hexanes to remove unreacted limonene, then dried under high vacuum overnight (scheme 2.57). The resin **2.141**, slurried in THF/methanol was oxidised by addition of hydrogen peroxide and the basic phase-transfer reagent (tetra-n-butylammonium hydroxide), giving rise to a highly exothermic reaction. Following filtration of the oxidised resin **2.142**, the supernatant and resin washings were collected and extracted with ethyl acetate/hexanes, and the extracts were combined and concentrated. After elution of the supernatant reaction mixture through a thin pad of silica, the desired product **2.143** was obtained in 61% isolated yield, corresponding to an active boron loading of 1.97 mmol/g (scheme 2.58).



Scheme 2.58 Oxidation of immobilised trialkylboranes

Oxidation of the supported limonene trialkylborane **2.141** provided the desired mono-oxidised alcohol **2.143**, and the cyclooctanediol by-product, which remains immobilised on the resin, thereby facilitating purification. In order to check the efficiency of the oxidation stage, derivatisation of the immobilised diol **2.142** was made using 2-thiophene carboxylic acid **2.144** and the coupling reagents DCC and DMAP, to afford sulfur-containing resin **2.145** (scheme 2.59).



Scheme 2.59 Derivatisation of the oxidised support

Elemental analysis of **2.145** for sulfur reported a substitution of 4.05 mmol/g (total sulfur for both substitutions) indicating that oxidation of the trialkylboranes on the resin had occured efficiently.

To more thoroughly evaluate the use of the resin as a hydroborating reagent, a short series of readily available olefins was chosen (table 2.1). The reaction with solution-phase 9-BBN is reported for all substrates, hence allowing direct comparison of reaction products and yields with reported data. In addition, all alcohols produced by the hydroboration/oxidation of these olefins are available commercially and were obtained to provide chromatographic references and minimise time spent on novel compound characterisation.

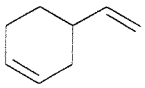
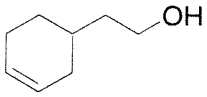
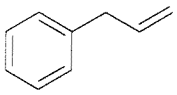
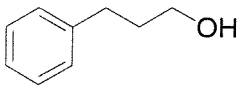
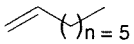
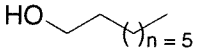
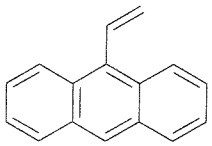
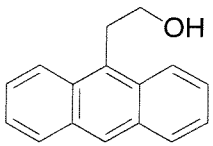
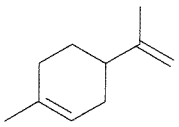
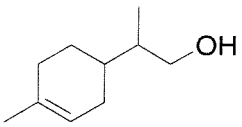
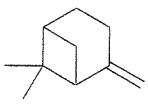
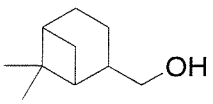
Entry	Alkene Substrate of hydroboration	Product Alcohol from oxidation	Isolated Yield (%)	Literature [ref] Yield (%)
1			60	89
2			53	91
3			56	86
4			35	45
5			61	69
6			59	78

Table 2.1 Alkene substrates hydroborated using solid-phase 9-BBN

Table 2.1 shows the substrates chosen, the alcohols produced upon hydroboration/oxidation, and the calculated reaction yields (based on 3.25 mmol/g boron). Following oxidation of the trialkylboranes formed in each case, simple purification was performed by passage of the concentrated supernatant and washings through a short silica plug, eluting with ethyl acetate/hexanes (1:9 v/v). Oxidants were efficiently removed, and concentration of eluted alcohols was made *in vacuo* to determine product mass. No further purification was performed, and in all cases product purity by NMR analysis was shown to be excellent.

2.4.5 Evaluation of loading effect on supported hydroboration

In order to determine the most suitable loading level of cyclooctadiene on the resin, further research was made using a CMP resin of 1.82 mmol/g Cl. Alkylation resin was performed identically as for the initial batch prepared from 4.55 mmol/g CMP. Experiments were performed using the lower loading resin, and limonene as our standard test alkene. The COD resin prepared from 1.82 mmol/g CMP was hydroborated using 10 molar equivalents of H_3B.THF complex in a procedure identical to that for the very high loading resin **2.139**, and washed as before using anhydrous THF and hexanes.

Due to concerns regarding the stability of the dried resin bound reagent, drying overnight under high vacuum was omitted, and the resin wash washed with anhydrous THF. The drained resin cake was immediately transferred under argon to a dry flask equipped with overhead stirring, and a solution of 5 molar equivalents of limonene (based on total conversion of CMP to immobilised COD, and complete hydroboration) in excess dry THF was added. The reaction mixture was stirred at 40 °C for 40 hours under argon, then filtered and washed as before using dry THF and hexanes. The trialkylborane resin was then split into 4 equal portions and oxidation of each was made using different oxidant mixtures (table 2.2).

Oxidant mixture	Isolated yield *
Bu_4NOH in MeOH / H_2O_2	66%
Trimethylamine N-Oxide	66%
H_2O_2 / NaOH aq in THF	59%
Sodium perborate aq / THF	0%

Table 2.2 *The yields reported are based upon a maximum boron loading of 1.5 mmol/g confirmed by boron elemental analysis

When either tetra-n-butylammonium hydroxide/H_2O_2, or trimethylamine-*N*-oxide was used as the oxidant, we can see from table 2.2, that the overall yields of hydroborated/oxidised limonene were identical to that given by the very high loading COD resin **2.139**. These results serve to illustrate that the performance of the hydroborated COD resin is independent of the level of substitution. However, table 2.2 also shows that in comparison to the aforementioned oxidants, the use of aqueous alkaline peroxide is not as efficient, resulting in a lower yield of oxidation (59%). Aqueous sodium perborate in THF was totally inadequate as an oxidant for the immobilised trialkylboranes, and did not afford any of the desired product.

2.4.6 Gel-phase ^{11}boron NMR Studies

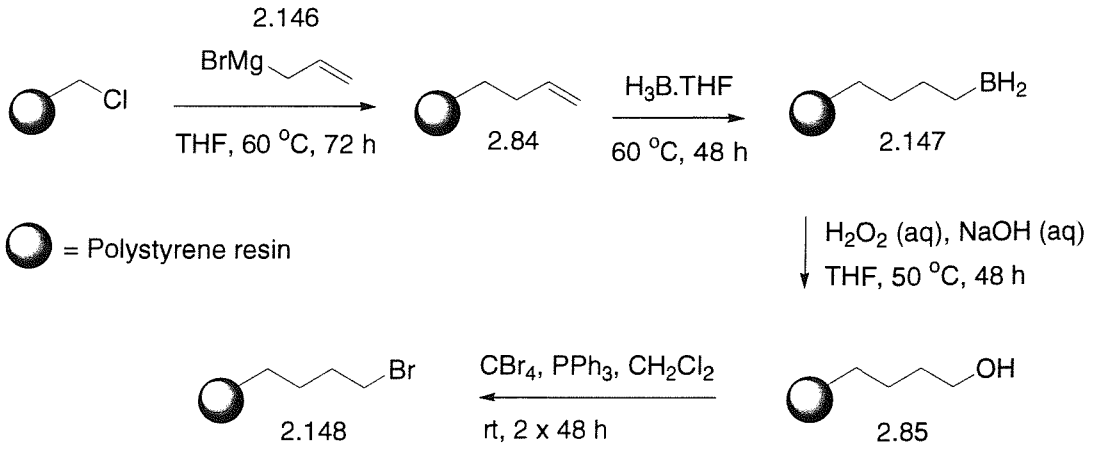
From the yields obtained, we can see that there is still a significant difference in the total loading of boron on the resin, and the yield arising after hydroboration/oxidation. We attempted to address this discrepancy by gel-phase ^{11}B NMR studies. Through these experiments we have shown the presence of two immobilised boron species. The inconclusive nature of the ^{11}Boron NMR spectra recorded from our hydroborated resins clearly requires further attention in order to properly understand the nature of the borane species immobilised on these resins. Only one of the observed two resonances in the ^{11}Boron spectra, corresponds to the chemical shift assignable to commercially available 9-BBN at 28 ppm relative to $BF_3.OEt_2$. The other resonance at 19.8 ppm, integrates to over an order of magnitude greater than the first, and remains unassigned, but is thought to arise from the monomeric dialkylborane species.

The relative air/moisture stability of 9-BBN, particularly in the solid isolated compound is attributed to its tendency to dimerise. Solutions of 9-BBN in ethereal solvents such as diethyl ether and THF are also remarkably inert because of the stabilising Lewis acid/base interaction of the ether oxygen atom and the highly oxophilic boron atom. However in the solid phase, it is anticipated that no such dimerisation could be possible, thereby rendering a dry sample of the hydroborated resin extremely reactive. The stability of many alkyl boranes may however be greatly increased through complexation of the boron atom with a suitable Lewis base. Indeed many otherwise unstable boranes are commercially available as tertiary amine or phosphine complexes, which readily dissociate in solution. We anticipated that complexation of our highly reactive resin bound 9-BBN with a suitable ligand could improve the handling and storage requirements of the reagent. However, addition of a solution of triphenylphosphine in THF to the freshly prepared hydroborated resin acted only to reduce the reactivity of the reagent, and did not give greater stability to air or moisture.

2.4.7 Increasing the tether length of the support

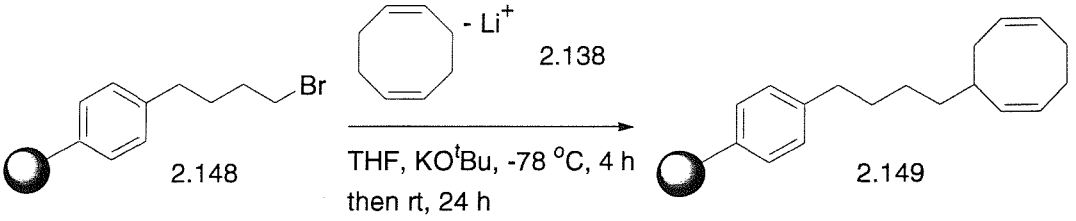
The regioselective hydroborating properties of solution phase 9-BBN derive from the steric bulk of the cyclooctane carbocycle, restricting reactivity to only one face of the molecule. The addition of further substituents might be expected to add considerably to this steric restriction, perhaps to the detriment of the overall reactivity of the reagent. The reaction of CMP and cyclooctadienyl lithium provides only a single methylene spacer between the cyclooctadienyl ring system and the resin matrix. Hence to determine the constraints of such a short tether, it was decided that studies should also be made using 4-bromobutyl polystyrene **2.148** in place of CMP, providing in this instance, a four-carbon spacer.

We anticipated that the use of a 4-carbon tether between the resin matrix and cyclooctadiene moiety should highlight any restricting effects of a single carbon spacer through observed differences in reactivity, stability to air or moisture, and total overall yields obtained in subsequent chemistries. 4-Bromobutyl polystyrene **2.148** is not commercially available, and although its preparation is unpublished, experimental protocols were available through NovaBiochem^{AG}. Synthesis of the resin was carried out starting from very high loading CMP (4.55 mmol/g) (scheme 2.60).



Scheme 2.60 Preparation of 4-bromobutyl polystyrene

The very high loading CMP was swollen in dry THF to which was added dropwise at 60 °C, allylmagnesium bromide **2.146**. The reaction was stirred over three days at 60 °C, and the butenyl resin **2.84** was washed and dried thoroughly. Hydroboration of the supported alkene was achieved over 2 days at 60 °C using a large excess of borane in THF. Oxidation of the resulting immobilised borane **2.147** was conducted using alkaline peroxide in THF at 50 °C for 2 days, resulting after washing and drying in the formation of the desired 1-hydroxybutyl polystyrene **2.85**. Bromination of the hydroxyl function of resin **2.85** was performed using carbon tetrabromide and triphenylphosphine in CH_2Cl_2 at room temperature over 4 days. Elemental analysis of the 4-bromobutyl polystyrene **2.148** gave a total bromide loading of 2.83 mmol/g, and this resin was subsequently alkylated in the same way as the CMP resins of different loading (scheme 2.61).



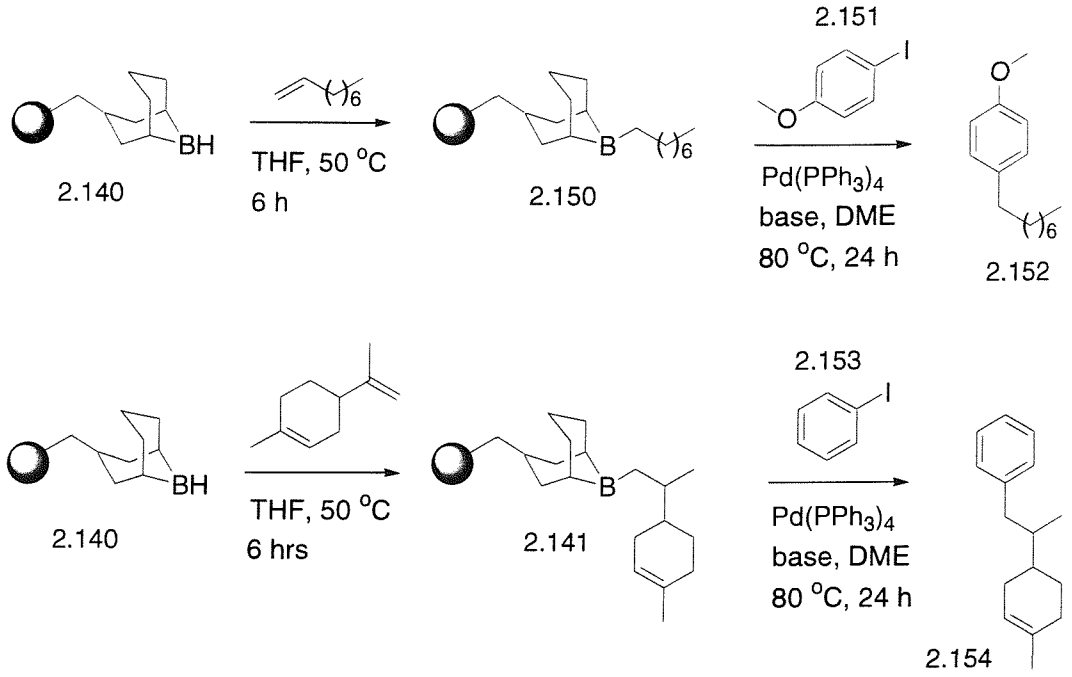
Scheme 2.61 Direct alkylation of 4-bromobutyl polystyrene

Elemental analysis for bromide revealed a residual level of only 0.39 mmol/g Br, indicating that substitution was highly successful. Hydroboration of resin **2.149** was conducted in the same way as for COD resin **2.139**, and the dialkylborane resin reacted with limonene in THF as before. Oxidation of the supported trialkylboranes using TBAH/H_2O_2 was performed, and the hydroxylated limonene isolated by chromatography. The yield of hydroxylated limonene following purification was calculated as 67%, based upon quantitative hydroboration and oxidation. This result indicates that while there is little to be gained through the use of an extended tether between the reaction site and the resin matrix, the reagent still functions in the desired manner. Upon handling of the hydroborated resin, it was apparent that the extended chain length did not improve the stability of the reagent, and manipulation under dry and inert conditions remained necessary.

2.4.8 Suzuki-Miyaura palladium-mediated cross-coupling reactions

Carbon-carbon bond forming reactions have always been of particular importance to organic chemists. Of several strategies available, one of the most versatile methods is the Suzuki-Miyaura cross-coupling reaction.[111] A great deal of research interest has been made into this very facile method for carbon-carbon bond formation between aryl halides and either boronic acids or *B*-alkyl 9-BBN derivatives, both reactions being catalysed by a palladium(0) species and an inorganic base.[86,112,113] Of interest now is the use of our immobilised 9-BBN analogue **2.140** for the initial hydroboration of suitable alkenes, followed by palladium-mediated cross coupling with different aryl and vinyl halides.

Our limited studies were conducted using hydroborated COD resin **2.140**, derived from high loading CMP (3.25 mmol/g in boron), and hydroboration of 1-octene and of (*R*)-limonene was carried out in the normal manner, providing two batches of trialkylborane substituted resins. Variation of the aryl iodide and base was made, however tetrakistriphenylphosphine palladium(0) was used as the catalyst in both cases (scheme 2.62).



Scheme 2.62 Suzuki-Miyaura coupling reactions with immobilised 9-BBN

Since tetrabutylammonium hydroxide (TBAH) was used with success as the base for our hydroboration/oxidation chemistry, we decided to use this reagent as a base for our Suzuki-Miyaura coupling reactions.

Entry Number	Aryl Iodide	Alkene Substrate	Base Used	Isolated Yield (%)
1	4-Iodoanisole	1-Octene	Bu_4NOH in MeOH	0
2	4-Iodoanisole	1-Octene	NaOH 2M in H_2O	30
3	4-Iodobenzene	(*R*)-Limonene	Bu_4NOH in MeOH	0
4	4-Iodobenzene	(*R*)-Limonene	NaOH 2M in H_2O	26

Table 2.4

We can see from the results in table 2.4 that TBAH is an unsuitable base for these reactions, and although the yields for entries 2 and 4 are low, the desired compound was isolated in both cases when an aqueous solution of sodium hydroxide was used as the base.

These results are encouraging, although the chemistry obviously requires optimisation, which could be investigated through the use of different palladium catalysts, reaction solvents, and reaction bases.

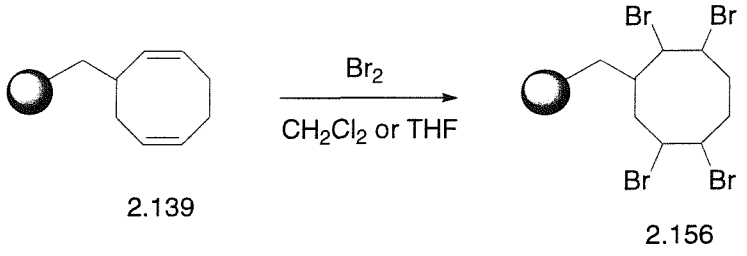
2.5 Further uses of immobilised cyclooctadiene

2.5.1 Immobilised cyclooctadiene as a halogen scavenger

1,5-cyclooctadiene **2.34** is a volatile compound with an extremely penetrating smell, and has been shown to exhibit carcinogenic and mutagenic properties. These factors make handling of this liquid awkward, but disposal of 1,5-COD residues on a large scale can be particularly problematic. Through the course of our research using cyclooctadiene, we found that its addition reaction with elemental bromine resulted in the quantitative consumption of the diene to give the relatively odourless cyclooctane-1,2,5,6-tetrabromide **2.161**. Of particular note, is the extremely high rate of reaction between COD and Br_2, prompting us towards the use of immobilised cyclooctadiene **2.139** for the removal of halogen residues from solution-phase reaction mixtures. Given the simple and direct approach developed by us for the preparation of immobilised COD, we saw potential for this application. Such a reagent could be expected to aid significantly the purification and isolation of desired halogenated products without the need for lengthy chromatography, distillation or recrystallisation. Additionally, the only functionality present in such a supported reagent are the alkenes, which would not be expected to interfere with the course of most other common reactions, or sequester any other species from a reaction mixture.

2.5.2 Scavenging of bromine and iodine from solution

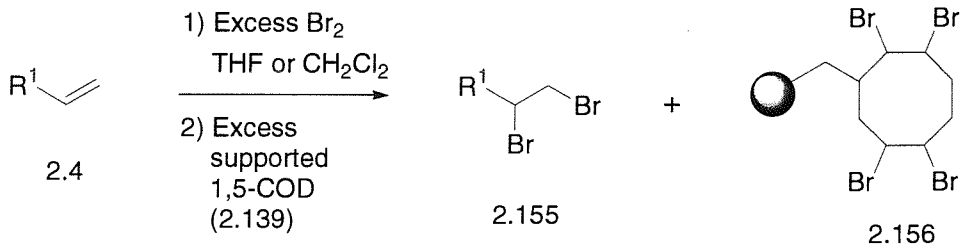
Investigation of the halogen scavenging properties of immobilised cyclooctadiene **2.139** were conducted initially by reaction of the supported diene with standard solutions of bromine and iodine in both CH_2Cl_2 and THF. 0.1 Mol dm^{-3} solutions of the halogens in each solvent were prepared, and a known mass of the supported COD corresponding to 2 molar equivalents with respect to the total halogen present, was added in the dry form. Almost instantaneous decoloration of bromine was observed from the CH_2Cl_2 solution, resulting in a colourless slurry in under 1 minute. Scavenging from the THF solution was slightly slower, however, the bromine was removed completely in under 5 minutes.



2.139 2.156

Scheme 2.63 Bromination of supported cyclooctadiene

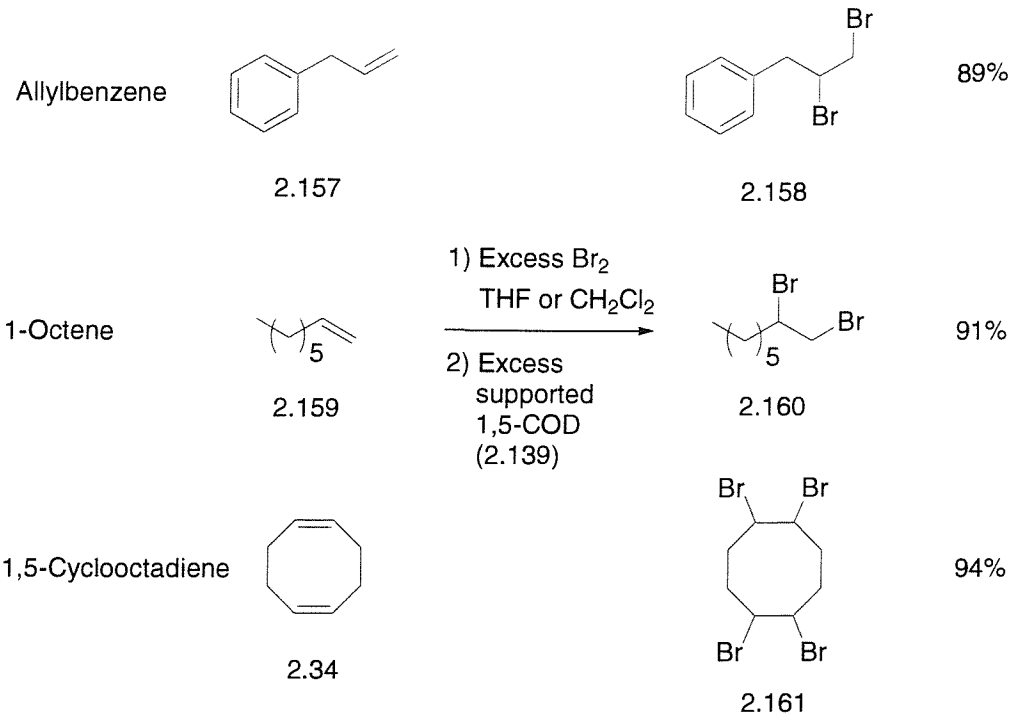
Interestingly, the rate of reaction between iodine and the scavenger resin was noticeably slower than for bromine, indicating a less facile addition of iodine to the alkene moieties of the scavenger. Nevertheless, complete decolouration of the iodine standards was achieved in 4 hours at room temperature, which still provides utility for the scavenger used to remove elemental iodine. The use of the scavenger may be broadly summarised as in scheme 2.64 below, if for example, we intended to simplify isolation of brominated alkenes from excess bromine. The use of excess bromine relative to the alkene, expedites the reaction and ensures total consumption of the alkene starting materials. In this way, the ability to scavenge one of the starting materials has allowed the use of an unequal stoichiometry of reagents in order that the limiting reagent is exhausted quickly and quantitatively (scheme 2.64).



Scheme 2.64 Intended use of supported COD to scavenge excess bromine from the reaction

2.5.3 Bromination of alkenes in solution

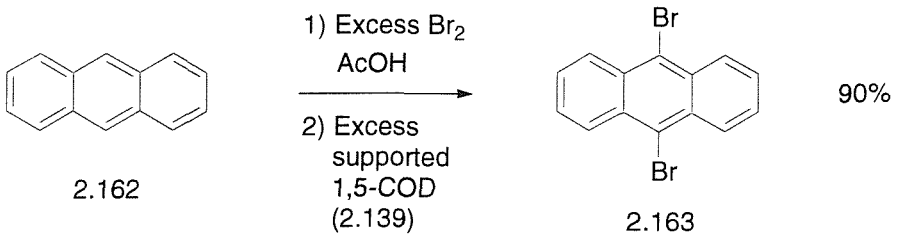
In order to evaluate the performance of our immobilised halogen scavenger, we chose to react several readily available alkenes with a slight excess of bromine in CH_2Cl_2. Following completion of the reactions, which were all allowed to proceed for only one hour at room temperature, a 2-fold excess of the COD resin was added to remove excess bromine. Each bromine containing reaction mixture was exposed to the COD resin for 1 hour, then rapidly filtered, and the resins washed with CH_2Cl_2. The reaction filtrate and washings were combined and concentrated *in vacuo* to give the desired halogenated compounds, which were analysed without further purification (scheme 2.65). We were happy to find that in each case, isolated yields of halogenated products was extremely high. However, more pleasing was the very good purity of each product, none of which received any conventional purification.



Scheme 2.65 Dibromination of a selection of readily available alkenes

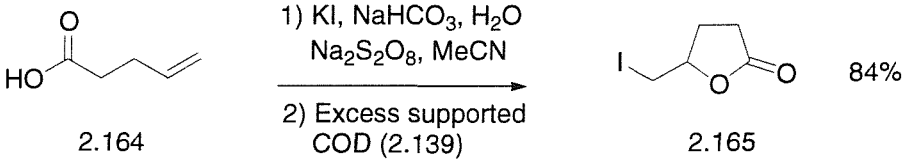
2.5.4 Scavenging of bromine from other solvents

So far we have only used either CH_2Cl_2 or THF as reaction solvents in which to apply our halogen scavenger resin **2.139**. We chose to investigate the ability of the scavenger in a different solvent system, to evaluate the performance as before. The reaction of anthracene **2.162** with elemental bromine is conducted in neat acetic acid resulting in the formation of 9,10-dibromoanthracene **2.163**.[114] The reaction was performed at 0 °C using an excess of bromine, and after 1 hour, a 2-fold excess of the COD resin **2.139** (based upon initial bromine present) was added. However, scavenging of bromine present was noticably slower in AcOH than in CH_2Cl_2 or THF. This was attributed to the poor swelling of the polymer bound reagent in AcOH alone, and was rectified by the addition of THF to the crude reaction mixture. The dilution of the crude reaction with THF was observed to aid the scavenging rate of the resin, and within 1 hour, the reaction was decolourised completely leaving only the bright yellow colour of the desired dibromide product **2.163**. Filtration, washing and concentration *in vacuo* of the reaction mixture, yielded the desired product in 90%, which was confirmed by NMR to be of excellent purity (scheme 2.66).



Scheme 2.66 9,10-dibromination of anthracene using excess Br_2 in acetic acid

Also of interest is the removal of residual iodine from crude halogenation mixtures, and we turned our attention to the iodolactonisation of 4-pentenoic acid **2.164** using KI, $NaHCO_3$ and $Na_2S_2O_8$ in aqueous conditions.[115] Again, the reaction was performed using an excess of the halide (I^+), formed by the *in situ* reaction of KI and $Na_2S_2O_8$. The reaction was allowed to proceed for 2 hours, and was then extracted into a small volume of CH_2Cl_2. Excess supported COD **2.139** was added to the yellow/brown reaction mixture, and scavenging of residual iodine was complete within 4 hours. Filtration and *in vacuo* concentration allowed isolation of the desired product **2.165** in 84% yield (scheme 2.67).



Scheme 2.67 Iodolactonisation of 4-pentenoic acid

2.5.5 Conclusions

In summary, we have developed a novel immobilised hydroborating reagent which is prepared through a very direct alkylation/hydroboration strategy commencing with chloromethyl polystyrene. The supported reagent was shown to retain the useful chemoselective yet highly reactive properties of 9-BBN through hydroboration/oxidation of a short series of substituted alkenes. Furthermore, the preparation of the reagent is cost-efficient and direct; chemical loading of the resin is high (3.25 mmol/g in boron), and the solid-phase characteristics closely resemble those of the solution-phase reagent. Another chloromethyl polystyrene support of lower loading was also alkylated with cyclooctadienyl lithium to provide the corresponding immobilised COD resin of different loading density. 4-Bromobutyl polystyrene was also alkylated in the same way as for the chloromethyl polystyrene supports to provide a 9-BBN precursor resin with an extended four-carbon linker. The oxidation of immobilised trialkylboranes was investigated using several different reaction conditions, and was found to proceed most efficiently using TBAH/H_2O_2. The Suzuki-coupling of *B*-alkyl derivatives of the supported reagent was also briefly investigated, however, yields of coupled products were low, and it is apparent that the reaction conditions require optimisation. While the hydroborated resin remains somewhat air-sensitive and must be handled under an inert atmosphere, the reagent provides a useful solid-phase alternative to 9-BBN where such handling facilities are available.

We have also successfully demonstrated the use of immobilised cyclooctadiene **2.139** for the scavenging of bromine and iodine from solution-phase reactions. Removal of excess reagents in this way greatly facilitates the isolation of products from crude reactions, which was demonstrated through the application of the scavenger to several halogenation reactions. In each case, reaction yields and product purities were excellent, and aside from the scavenging process, no further purification was required.

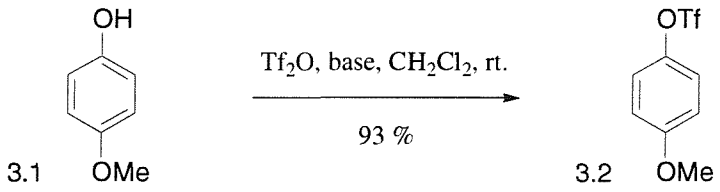
The Development of a Tetrafluoroarylsulfonate Linker

Chapter III

3.1 Synthetic transformations of aryl sulfonates

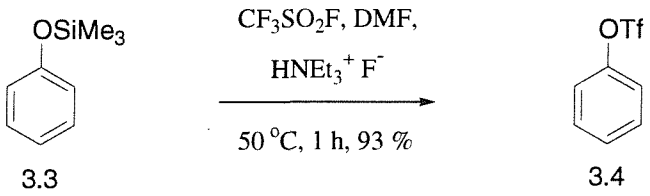
3.1.1 Formation of aryl sulfonates

Over the last 20 years, reports of the use of aryl triflates in the literature has increased dramatically, due in part to the excellent leaving group properties of the trifluoromethanesulfonate group, and the ease of preparation of aryl triflates from the large number of commercially available phenols. The leaving group ability of aryl triflates relative to aryl halides may be generalized in the following order I > Br = OTf >>Cl , although this is obviously to some extent reaction dependent. Recently, the many synthetic transformations of vinyl and aryl triflates were reviewed by Ritter.[116] Aryl triflates are most commonly prepared from phenolic substrates by way of a triflating reagent such as triflic anhydride in the presence of a non-nucleophilic base e.g. triethylamine or pyridine (scheme 3.1).[117]



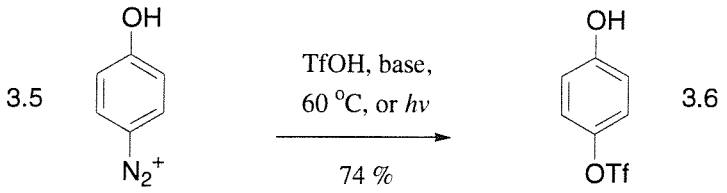
Scheme 3.1 Formation of an aryl triflate from anisole

Aryl fluorosulfonates may also be prepared by the fluoride anion catalysed reaction of perfluoroalkylsulfonyl fluorides with aryl silyl ethers, e.g. **3.3** (scheme 3.2).[118] This method, commonly used for the preparation of triflates and nonaflates, facilitates the use of nonafluorobutanesulfonyl fluoride, a relatively stable liquid, easily handled under regular laboratory conditions.



Scheme 3.2 Formation of perfluoroarylsulfonates from trimethylsilyl ethers

Aryl triflates may also be prepared by the thermal or photochemical decomposition of aryldiazonium salts (scheme 3.3). Given that the formation of the diazonium species **3.5** from an aniline precursor is a reaction tolerant of many other nucleophilic functions, this method is suitable for the preparation of hydroxyphenyl triflates, e.g. **3.6**, which would be difficult to prepare by other methods.[119]

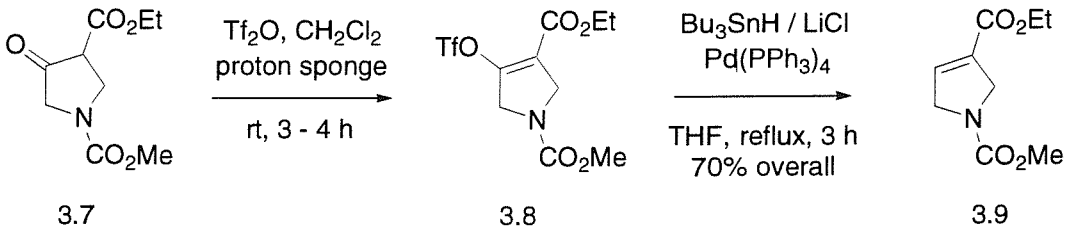


Scheme 3.3 Preparation of aryl triflates from aryl diazonium species

The perfluoroalkylsulfonate group allows electrophilic aromatic substitution reactions such as nitration, sulfonation and halogenation to be performed in the *ortho* and *para* position of aryl substrates bearing such directing sulfonate groups.

3.1.2 Reactions of aryl sulfonates

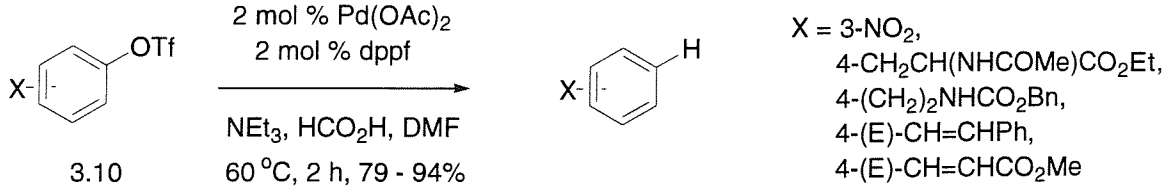
In the presence of a catalytic quantity of Pd(0), and a suitable hydride donor source, vinyl and aromatic triflates are reduced cleanly, through a process known as transfer hydrogenation. Several different hydride sources have been used with good efficiency, including both tributyltin hydride and triethylsilane. In 1991, Dupré and Meyers reported the 2-step reduction of a pyrrolidone **3.7** to the unsaturated cyclic ester **3.9** via the triflate intermediate **3.8** (scheme 3.4).[120]



Scheme 3.4 Transfer hydrogenation of a vinyl triflate

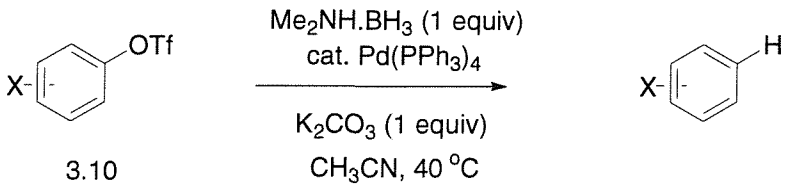
Triethylammonium formate, formed by the *in situ* reaction of formic acid with triethylamine has also been used as an exceptionally mild and selective hydride source in transfer hydrogenation reactions of triflates.

In the presence of catalytic Pd(0) and a suitable ligand such as PPh_3, simple phenyl or naphthyl triflates are cleanly and efficiently reduced, even in the presence of other potentially reactive functions.[121] Sterically hindered or electron-rich phenyl triflates require the use of chelating bis-phosphine ligands such as dppf,[122] or dppp (scheme 3.5).[123]



Scheme 3.5 Transfer hydrogenation of aryl triflates

In 1999, Lipshutz *et al.* demonstrated reductions of arylperfluorosulfonates **3.10** using dimethylamine.borane complex ($Me_2NH.BH_3$) also catalysed by Pd(0).[124] Using these conditions, reductive cleavage was generally effected in 3.5 hours at only 40 °C. This combination of reagents also represents an extremely mild method for achieving reductive cleavage of activated sulfonates (scheme 3.6).



Scheme 3.6 Reductive cleavage of aryl triflates using $Me_2NH.BH_3$

Ortar *et al.* postulated that the mechanism of transfer hydrogenation of triflates involves the oxidative addition of the triflate carbon-oxygen bond to a Pd(0) phosphine ligand. Displacement of the triflate by a formate ion, followed by loss of carbon dioxide results in the formation of an arylpalladium(II) hydride species. Reductive elimination of this complex regenerates the active palladium catalyst, and releases the reduced aromatic compound from the catalytic cycle (figure 3.1).[125]

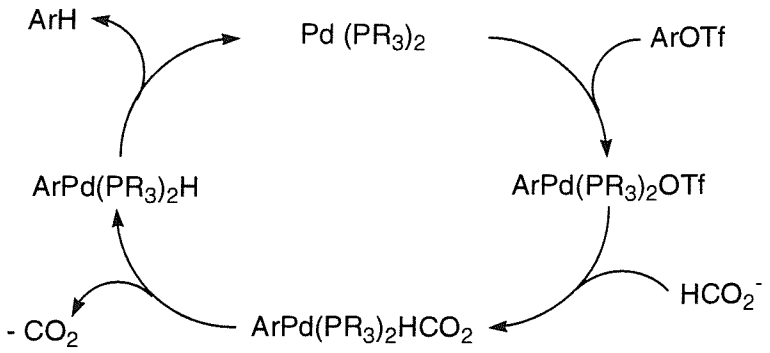


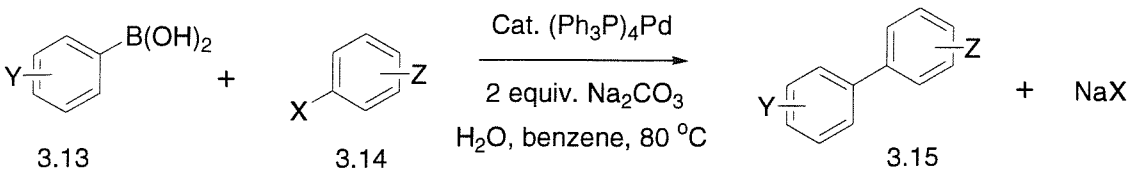
Figure 3.1 Palladium-catalysed transfer hydrogenation of an aryl triflate

If deuterated formic acid is used in place of the protic acid, a deuteride source is produced, and this methodology is expanded to allow isotopic labelling of triflate precursors.[125] Isotopic labeling, for example using deuterium, is an important technique used in the elucidation of reaction mechanisms and kinetic rate calculations, hence the ability to selectively label a molecule is of high research value. Since hydrogen and deuterium are isotopes of the same element, the chemistry of the carbon-hydrogen and carbon-deuterium bond will be identical. However, since these are atoms of different mass, the vibrational frequencies and hence bond dissociation energies will differ, resulting in a difference in relative bond strength. Therefore the rate of reaction about these bonds will be significantly different, allowing for kinetic evaluation.

3.1.3 The Suzuki-Miyaura cross-coupling reaction

Interest in the use of aryl triflates was stimulated greatly when Suzuki reported a palladium-catalysed cross-coupling reaction with aryl boronate esters and boronic acids in the presence of a base. In contrast to preceding methods of aryl carbon-carbon bond formation, the extremely mild conditions and high functional group tolerance of the Suzuki-Miyaura reaction quickly established this as one of the most powerful methods for biaryl formation.[126] Given the significance of the biaryl motif, both from a pharmaceutical and total synthesis perspective, this new ease with which biaryl compounds may be prepared has produced an enormous interest in this methodology. It is then not surprising that today the literature is awash with reports of palladium-catalysed transformations performed upon unsaturated halides and triflates and resulting in the creation of new bonds at sp^2 carbon centers.

During Suzuki's preliminary cross-coupling reactions conducted in benzene, he found that in addition to a catalytic quantity of $Pd(Ph_3P)_4$, 2 equivalents of aqueous Na_2CO_3 are required for successful coupling of substituted phenyl boronic acids **3.13**, and aryl halides **3.14** (scheme 3.8).[127]



Scheme 3.7 The Suzuki-Miyaura palladium-catalysed cross-coupling

The Suzuki-Miyaura reaction is broad with regard to optimal conditions, and it is usually not possible to state a generalized procedure for anything other than the simplest reactants. Consideration of literature examples reveals that a suitable Pd(0) catalyst depends both on the electronic and steric properties of the boronic acid and aryl halide or triflate coupling partners. $Pd(Ph_3P)_4$ was the original catalyst system used by Suzuki[127] and continues to be the most widespread catalyst employed in the Suzuki-Miyaura reaction today. However, many other Pd(0) ligand systems have been exploited with advantage in more exotic applications. Although by no means an exhaustive listing, the following catalytic systems have proven highly efficient: $PdCl_2(Ph_3P)_2$,[128,129,130] $PdCl_2(dppf)$,[131] $Pd(OAc)_2/Ph_3P$,[132] $Pd(OAc)_2$/dppp,[133] $Pd_2(dba)_3$,[134] $Pd(OAc)_2/(o\text{-}Tol)_3P$.[135,136]

In addition, a very wide range of solvent/base mixtures has been employed, each having been optimised for an individual case. The most commonly utilized solvents in order of increasing polarity are PhMe, DME, THF, EtOH, and DMF. However, the selection of solvent is to some extent dictated by the base required.

Bases which are commonly used include the group 1 carbonates Na_2CO_3,[127] K_2CO_3,[137] Cs_2CO_3,[138] and also $Ba(OH)_2$,[139] and K_3PO_4.[140] In 1983 Gronowitz *et al.*[141,142] reported the use of DME and aqueous Na_2CO_3 as a solvent base system ideal for minimizing deboronation commonly observed as a side reaction of electron-rich boronic acids.

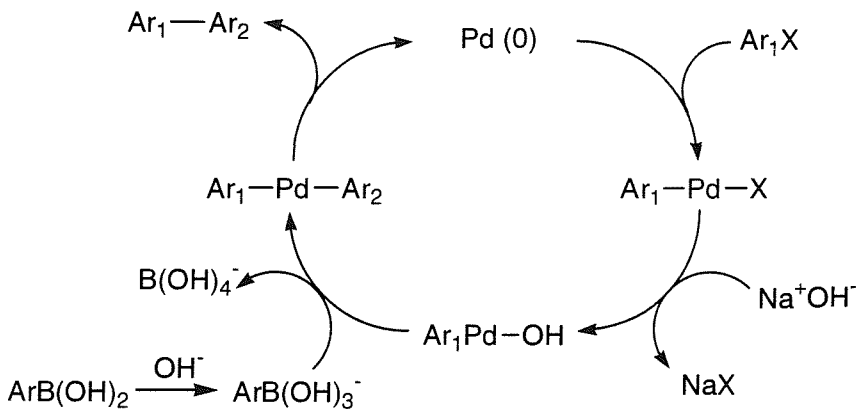


Figure 3.2 Catalytic cycle of the Suzuki-Miyaura cross-coupling reaction

Providing the reaction is conducted under an inert atmosphere, the Suzuki-Miyaura catalytic cycle (figure 3.2) remains active until one of the starting materials is exhausted. Unlike many other organometallic reactions however, the Suzuki-Miyaura reaction may be conducted in the presence of water, and indeed in most cases when an inorganic base is used, water is added in small amounts to allow at least partial dissolution of the base.

3.1.4 Metal catalysed cross-coupling of aryl sulfonates and triflates

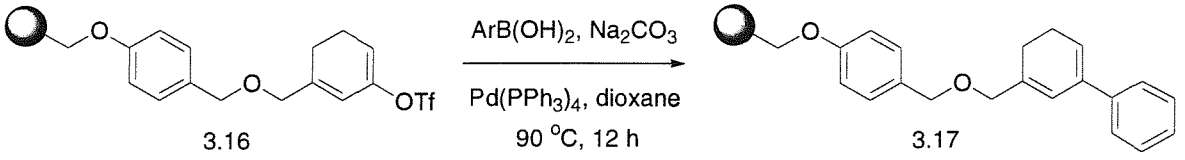
Although aryl and vinyl triflates have recently received attention regarding participation in metal-catalysed cross-coupling reactions, they have traditionally been considered too unreactive, and most reported examples employ aryl and vinyl bromides and iodides. Indeed, when triflates are used directly in place of bromides or iodides, without expecting the need for considerable optimisation of conditions, disappointment usually prevails. However, even under traditional cross-coupling conditions the use of aryl triflates will most often result in the formation of some of the desired product, and this seminal finding paved the way for another generation of cross-coupling methodology. 1995 saw the first of many publications to bring forward unactivated aryl and alkyl sulfonates into the cross-coupling spotlight, and today this methodology is continually advancing. Percec, Bae and Hill addressed the shortfalls of the aryltriflate and arylmesylate, and developed a new cross-coupling protocol for reaction with arylboronic acids.[140]

Sulfonates are base sensitive and prone to hydrolysis under aqueous conditions, however Percec *et al.* found that the use of the weak base K_3PO_4 when finely powdered and suspended in polar solvents such as dioxane or THF fulfils these non-aqueous requirements. Also recognized was the need for a palladium/ligand system more active than $Pd(PPh_3)_4$ and the dinuclear catalyst $PdCl_2$(dppf) was demonstrated as a good successor.

Most notably Percec *et al.* saw the need for addition of LiCl to the reaction mixture, a common additive used in the Stille cross-coupling reactions between triflates and stannanes.[143] Alkali metal halides are expected to prevent premature catalyst decomposition at the oxidative addition stage, the crucial 1st step of the catalytic cycle. The product of oxidative addition of palladium into the arene sulfonate carbon-oxygen bond has been proposed as being 'catalytically incompetent', although ligand substitution with chloride ions results in a catalytically active species.[144] Hence LiCl rescues the reaction from stalling at stage of conception of the catalytic cycle. Using the modified reaction conditions outlined above, Percec *et al.* demonstrated the successful cross-coupling of aryl triflates in place of the more commonly employed bromide and iodide electrophiles in comparable yield, a significant achievement in itself. However, a still more impressive advancement brought various unactivated aryl sulfonates onto the list of coupling contenders. Realising the unreactivity of aryl sulfonates towards Pd(0) species, Percec used instead the analogous Ni(0) catalyst. In a previous publication, Percec, Bae, Zhao and Hill had observed the rapid oxidative addition of aryl sulfonates to Ni(0) complexes as a result of the increased nucleophilicity of Ni(0) over Pd(0).[145] The resulting Ni(II) complexes were found to undergo symmetrical homocoupling in the absence of other electrophilic species to give biaryl products in high yield. Thus when phenylboronic acid and K_3PO_4 suspended in THF was added to the reaction mixture, as expected, successful Suzuki-type cross-coupling was observed in moderate yield. This is a significant finding and represents the first example of Ni(0) catalysed coupling between boronic acids and aryl sulfonates other than triflates. Not only is there financial saving in terms of the catalyst, but also these reaction conditions produce similar yields of coupled compounds. However, there are two notable drawbacks to be considered when using Ni(0) catalysis in this way. Primarily, Ni(0) species are deactivated by protic sources, thus reactions must be conducted under strictly anhydrous conditions. Also, *in situ* reduction of Ni(II) to Ni(0) does not occur spontaneously in the presence of a base as with Pd(II) sources like $Pd(OAc)_2$. This finding obviates the need for an additional additive to the reaction mixture, which through the course of Percec's studies was made in the form of metallic zinc dust. Whilst these constraints do not detract significantly from the virtues of Ni(0) catalysis, they do prompt the experimentalist toward the use of aryl triflates which are still reactive enough to undergo Pd(0) catalysed cross-coupling with boronic acids without the need for special reaction conditions.

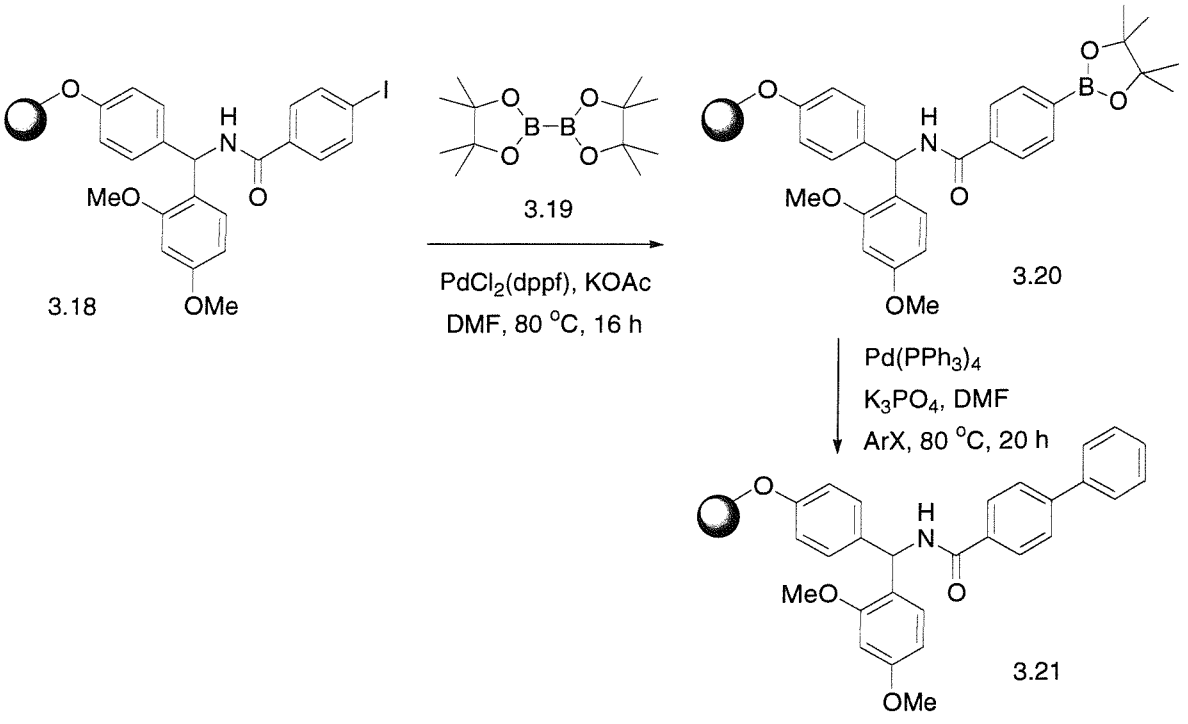
3.1.5 The Suzuki-Miyaura cross-coupling reaction on solid-phase

The efficiency of the Suzuki-Miyaura reaction has translated very well to solid-phase conditions and there are a great number of high yielding applications to complement the analogous solution-phase reactions.[146,147,148,149,150,151] Fraley and Rubino demonstrated the cross-coupling reaction of an immobilised vinyl triflate **3.16**, with several arylboronic acids during a synthesis of resin bound bicyclic compounds **3.17** (scheme 3.9).



Scheme 3.8 Suzuki-Miyaura cross-coupling of an immobilised vinyl triflate

Piettre and Baltzer demonstrated a dual-stage Suzuki-Miyaura cross-coupling reaction of dipinacolatoborane **3.19** with resin bound aryl iodides **3.18** in the synthesis of immobilised boronate esters **3.20,** prior to reaction with aryl halides to give supported biaryl derivatives **3.21** (scheme 3.10).[152] In the presence of catalytic Pd(0), the combination of DMF and K_3PO_4 as solvent and base respectively, was found to give the best coupling yield.



Scheme 3.9 Suzuki-Miyaura cross-coupling of a resin bound aryl iodide

However, the hydrophobic nature of cross-linked polystyrene resins, often requires the use of slightly modified reaction conditions. Inorganic bases used in solution-phase reactions

often do not provide a homogeneous system in solvents compatible with polystyrene based resins, and weak organic bases such as NEt_3 in DMF have been used instead with very good results.[135]

3.1.6 The Heck cross-coupling reaction

Originally reported in 1982, the Heck cross-coupling reaction between aryl or vinyl halides or sulfonates, and alkenes represents another palladium-catalysed process which has developed into an extremely powerful tool for the construction of sp^2 carbon-carbon bonds.[153] In common with the Suzuki-Miyaura cross-coupling, the first step of the Heck reaction (figure 3.3) is oxidative addition of a palladium(0) species with an aryl or vinyl triflate (or bromide or iodide). Insertion of an alkene into this 16 electron species results in carbopalladation; rapid β-hydride elimination then results in the formation of a disubstituted alkene. The catalytic 14 electron Pd(0) species is then regenerated by reaction of the eliminated Pd(II) entity with a base, and the cycle continues until one of the substrates is exhausted.

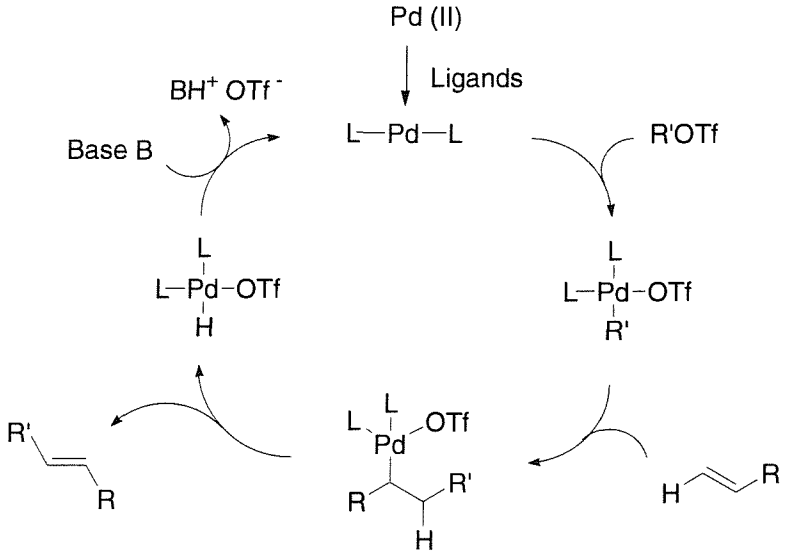
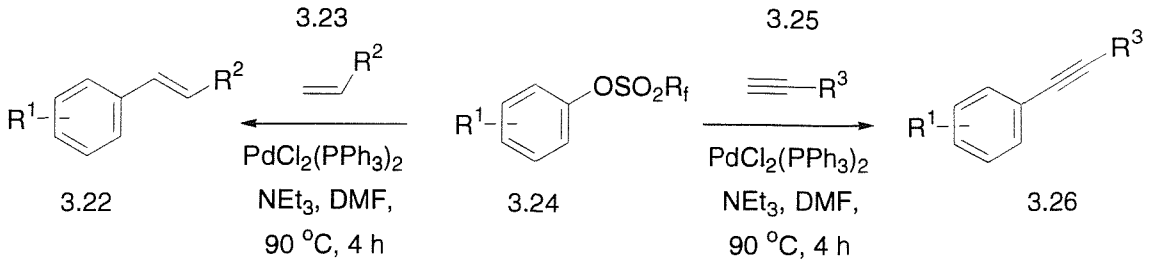


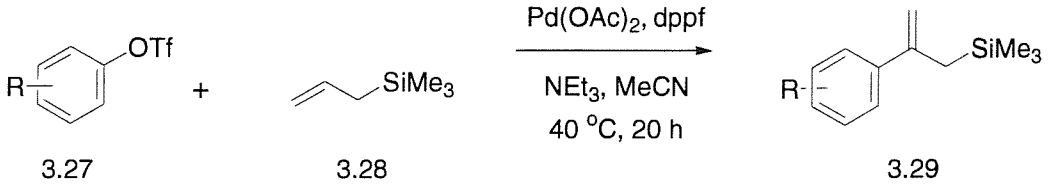
Figure 3.3 The Pd(0) catalysed cycle of the Heck cross-coupling reaction

The first report of a Heck cross-coupling reaction with arylfluoroalkylsulfonates, was made by Chen and Yang in 1986. Optimised reaction conditions revealed $Pd(PPh_3)_2Cl_2$ in combination with triethylamine produced very good yields of substituted styrenes **3.22**, and phenyl acetylenes **3.26** (scheme 3.11).[154]



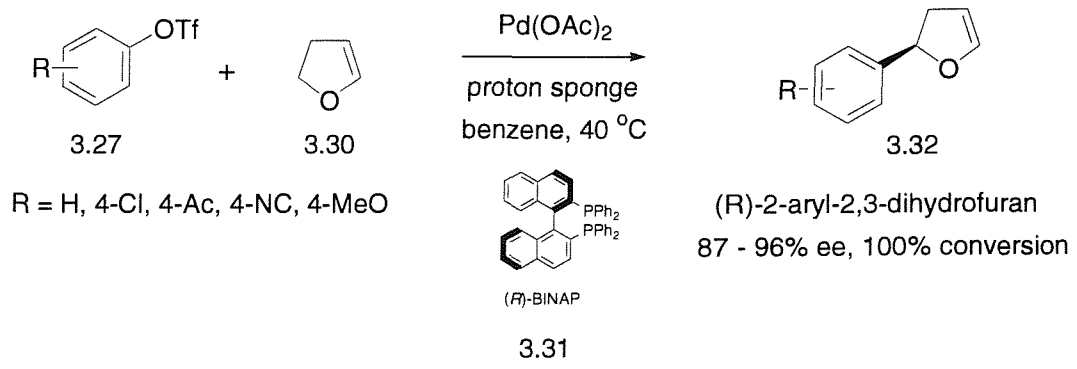
Scheme 3.10 Heck reaction of aryl triflates with olefins and acetylenes

Recently, Olofsson *et al.* reported the solution-phase Heck reaction of aryl triflates **3.27** with allyltrimethylsilane **3.28** using $Pd(OAc)_2$ in combination with dppf, resulting in the highly regioselective formation of branched β-products **3.29** in good yields and purities (scheme 3.12).[155]



Scheme 3.11 Heck coupling of an aryl triflate with allyltrimethylsilane

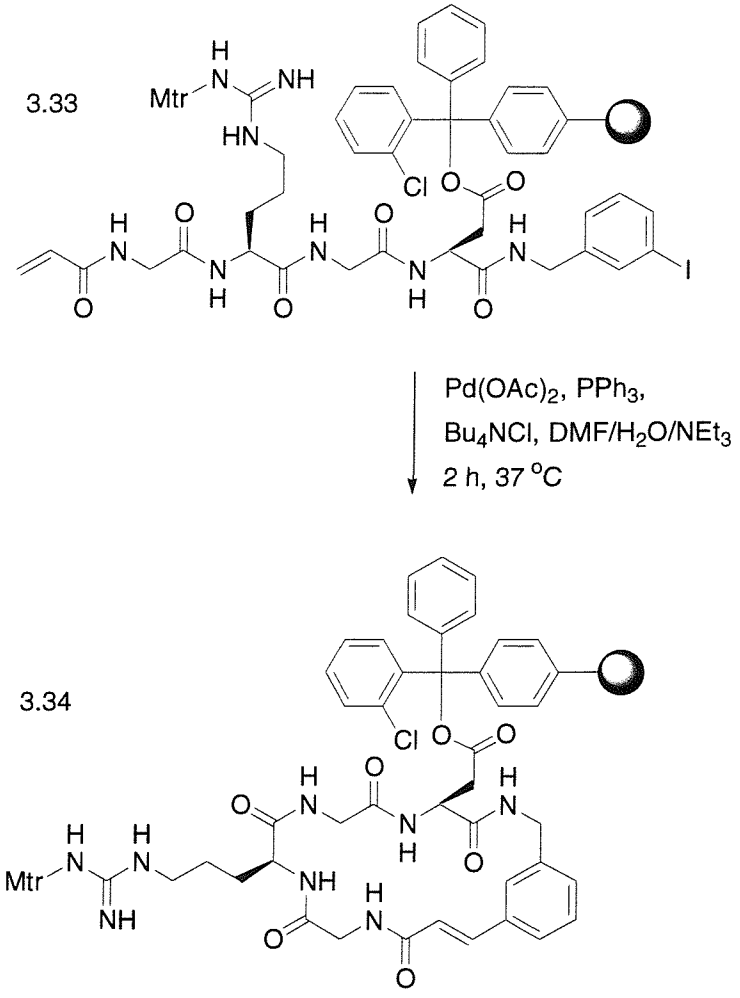
In 1992 Osawa and Hayashi reported the enantioselective synthesis of dihydrofurans **3.32** by means of Heck cross-coupling between 2,3-dihydrofuran **3.30** and a variety of aryl triflates **3.27** using (*R*)-BINAP **3.31** as an asymmetric ligand in combination with $Pd(OAc)_2$ (scheme 3.13). They found that the distribution of products was very strongly influenced by the base, and optimum results were obtained using 1,8-bis(dimethylamino)naphthalene (proton sponge).[156]



Scheme 3.12 Enantioselective Heck cross-coupling of aryl triflates

3.1.7 The Heck cross-coupling reaction on solid-phase

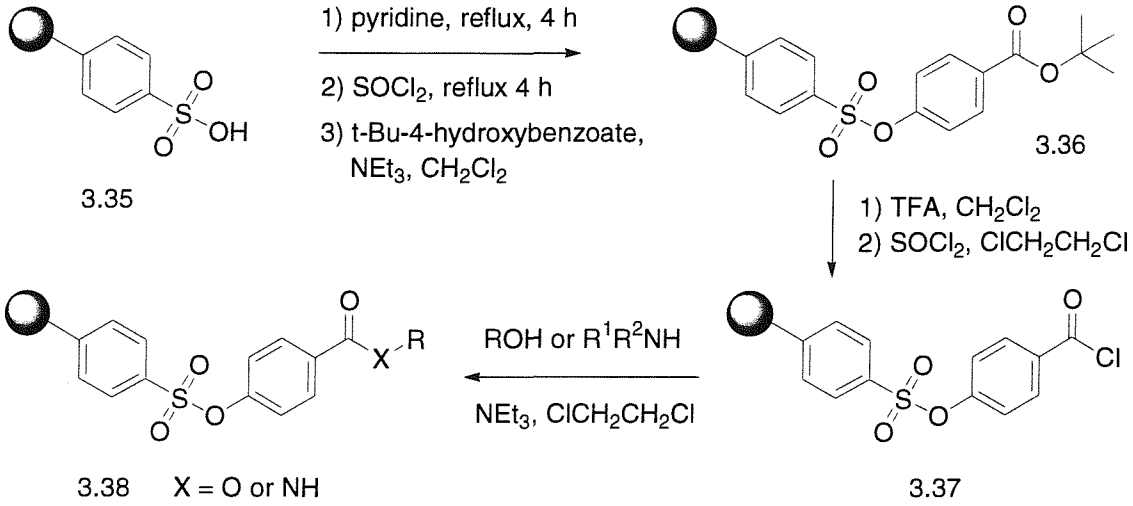
Just as the Suzuki-Miyaura cross-coupling reaction has met with popularity on the solid-phase, so too has the Heck reaction, again increasing the repertoire of useful metal-catalysed bond forming processes available to the solid-phase chemist. At this time there exists an enormous number of publications citing reference to the Heck reaction on solid-phase.[157,158,159] The intramolecular Heck reaction is a very useful method for the formation of 5, 6, and 7 membered rings fused to aromatic nuclei. Akaji *et al.* successfully demonstrated the use of the Heck cross-coupling reaction to perform an intramolecular macrocyclisation upon a bifunctionalised peptidic residue bearing both an aryl iodide and acrylate function.[160] The linear precursor **3.33**, immobilised on chlorotrityl chloride substituted polystyrene was cyclised in the presence of Pd(0) to yield a 20-membered macrocycle **3.34**, released from the support upon acid mediated cleavage (scheme 3.14). Bu_4NCl is used as a phase-transfer agent, permitting the use of water with the supported substrate.



Scheme 3.13 Macrocyclisation using the Heck reaction

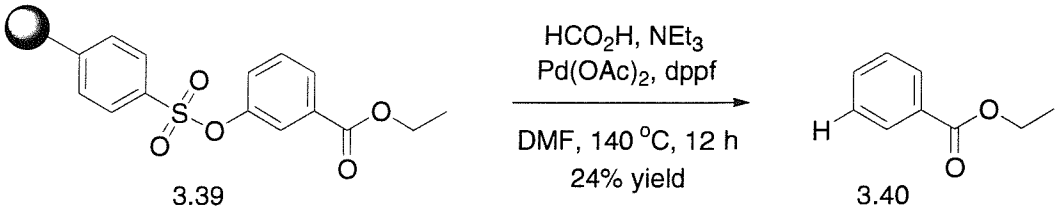
3.1.8 Traceless synthesis with supported aryl sulfonates

Palladium(0) mediated reductive cleavage from immobilised aryl sulfonates was first demonstrated by Wustrow *et al.* in 1998.[161] Sulfonyl chloride functionalised polystyrene derivatised as the sulfonate linked 4-*tert*-butylbenzoate **3.36** was further elaborated at the carboxylate function to provide a small series of ester and amide linked compounds **3.38** (scheme 3.15).



Scheme 3.14 Formation of immobilised sulfonate esters and amides

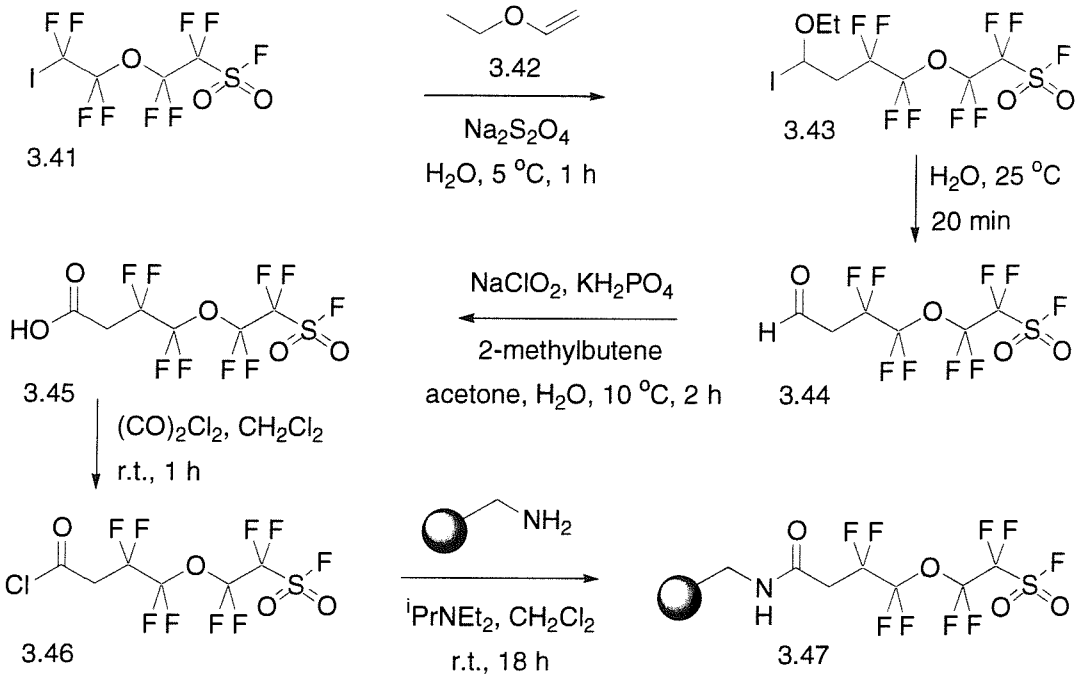
Traceless liberation of the products was brought about by palladium-catalysed transfer hydrogenation, effectively replacing the arylsulfonate linkage with a new aryl C-H bond. This methodology however, was observed to suffer several drawbacks, which prevent this innovative concept from reaching a level of broad applicability. High temperatures and long reaction times are required to achieve cleavage, and even electron deficient substrates must be present in the *para*-position for efficient reduction to occur. These factors place a severe limitation on the range of chemistries possible (scheme 3.16).



Scheme 3.15 Reductive cleavage using the Wustrow linker

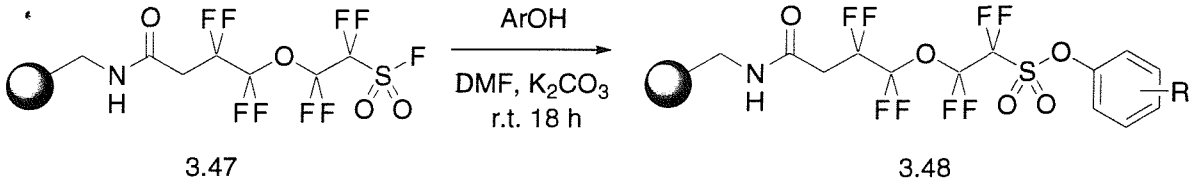
The inadequacies of the Wustrow methodology were later addressed by Holmes *et al.* with a highly reactive perfluoroalkylsulfonate linker **3.47**, shown to allow both reductive cleavage[162] and Suzuki-Miyaura[163] cross-coupling chemistry in good to excellent yields.

However, the Holmes linker is prepared in 5 synthetic steps from a rather expensive (£7.46 $mmol^{-1}$), albeit commercially available perfluoroalkyl iodide **3.41** (scheme 3.17).



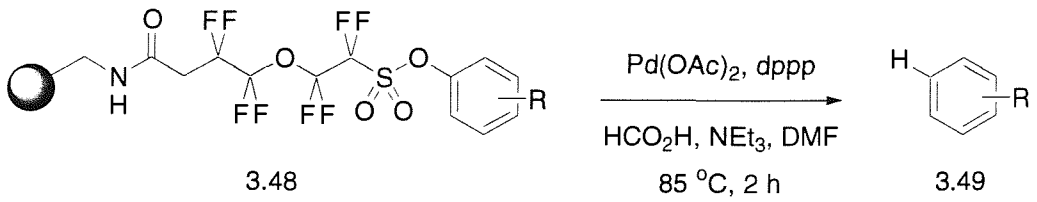
Scheme 3.16 Synthesis of the Holmes perfluoroalkylsulfonate linker

A range of functionally diverse phenolic substrates, were derivatised as the corresponding immobilised sulfonates **3.48**, by reaction with the sulfonyl fluoride linker **3.47** in the presence of a base (scheme 3.18).



Scheme 3.17 Derivatisation of phenolic substrates using the Holmes linker

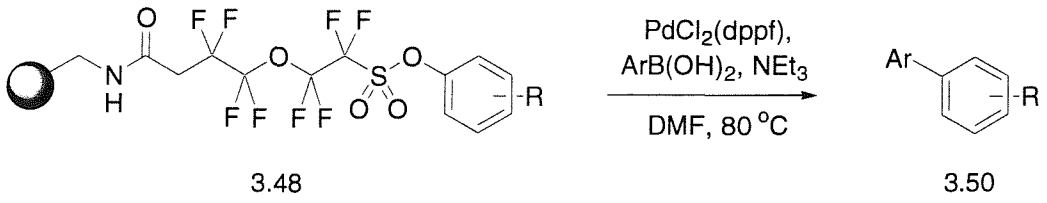
The polymer bound arylsulfonates **3.48** were shown to be reduced efficiently under mild conditions of transfer hydrogenation, to afford good yields of the deoxygenated aryl compounds **3.49** (scheme 3.19).[162]



3.48 3.49

Scheme 3.18 Transfer hydrogenation with the Holmes linker

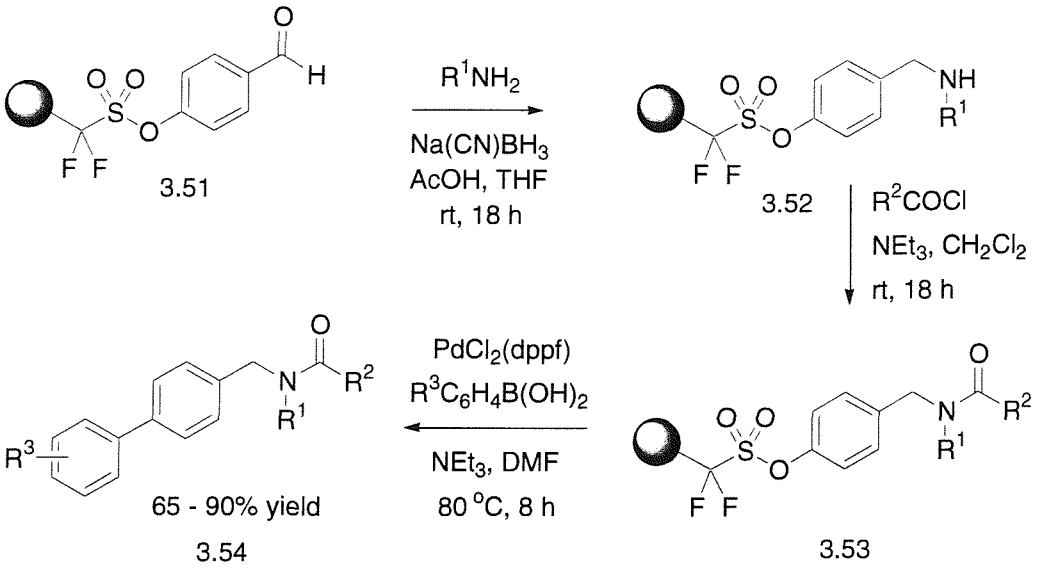
In a separate publication, the Holmes linker was also shown to allow immobilised arylsulfonates to undergo palladium-catalysed Suzuki-Miyaura cross-coupling reactions with a variety of boronic acids, thus increasing dramatically the usefulness of the linker (scheme 3.20).[163]



3.48 3.50

Scheme 3.19 Suzuki-Miyaura cross-coupling with the Holmes linker

Through the screening of several different catalyst/base systems, Holmes concluded that the combination of $PdCl_2(dppf)$ and NEt_3 gives optimum results, and more importantly is of broad applicability over a wide range of substrates. Crucial to the acceptance of the Holmes linker as a new combinatorial platform was the demonstration of its ability to withstand synthetic modification of immobilised sulfonates prior to either reductive cleavage or cross-coupling, without breakdown of the linker itself. Holmes demonstrated the robustness of the linker by preparation of a short series of biarylamides **3.54** through reductive amination and acylation of supported sulfonate residues e.g. **3.51** (scheme 3.21).



Scheme 3.20 Synthesis of biarylamides using the Holmes linker

3.2 Designing a linker for palladium-mediated chemistries

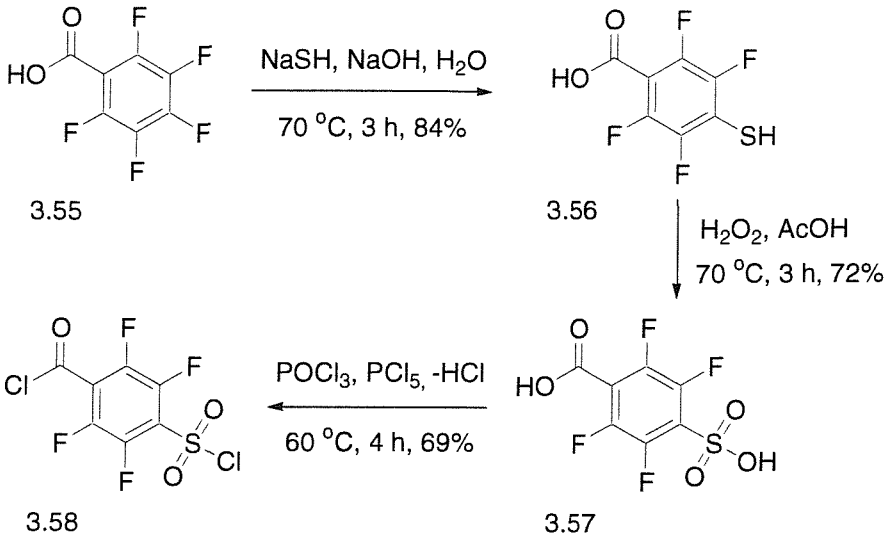
3.2.1 Aims of the project

Optimisation of reaction conditions revealed the Holmes linker to be a broad based tool for a range of possible combinatorial chemistries. However, realisation of the potential for phenolic elaboration in lead discovery, for example, was thwarted somewhat by the synthetic inaccessibility of the linker itself. Although the preparation of the linker is synthetically trivial, it is not inexpensive, and hence has not received the overall attention deserving of its performance. We aimed to rectify the reactivity issues of the Wustrow reductive cleavage chemistry and prohibitory cost of the Holmes linker in one further evolutionary step. Our solution embraces the reactivity brought to the Holmes linker through perfluorination of the alkyl chain, and the simplicity in the approach of Wustrow.

3.2.2 Synthesis of a tetrafluoroarylsulfonate linker

The preparation of 4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoyl chloride **3.58** was published by Fielding and Shirley in 1992,[164] and was considered by us to provide an ideal linker platform for both reductive cleavage and cross-coupling chemistries. Synthesis of the linker started with the S_NAr reaction between pentafluorobenzoic acid **3.55** and sodium hydrosulfide (NaSH) under strongly basic aqueous conditions. As noted by Fielding and Shirley, the stoichiometry and rate of addition of pentafluorobenzoic acid to the basic mixture must be closely controlled to avoid formation of a thioether side-product which is difficult to remove.

In several syntheses of 4-mercaptotetrafluorobenzoic acid **3.56**, the best isolated yield obtained was 84% (scheme 3.22).



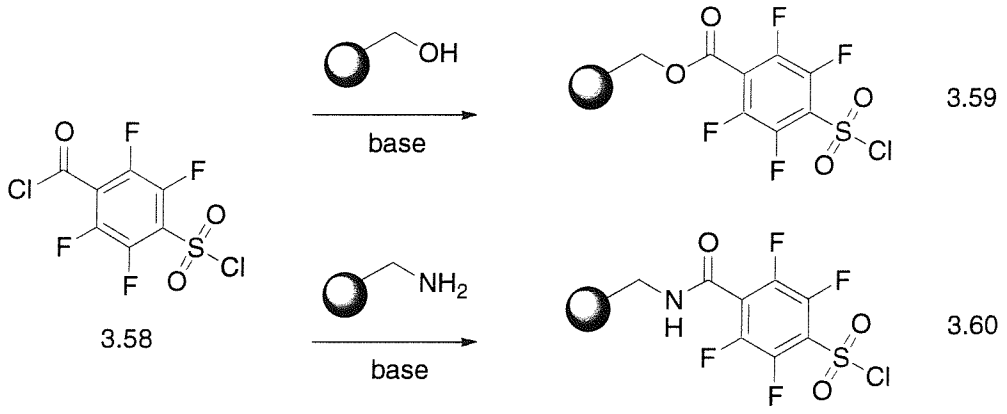
Scheme 3.21 Synthesis of 4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoyl chloride

Oxidation of 4-mercaptotetrafluorobenzoic acid **3.56** to the bifunctional mixed acid **3.57**, was accomplished using H_2O_2 and AcOH. Close temperature regulation over the rate of addition of the substrate to the oxidizing mixture is required since the oxidation itself is highly exothermic. Following oxidation, excess H_2O_2 is destroyed by addition of sodium metabisulfite, and the crude product is isolated by liquid-liquid extraction into EtOAc. Back extraction of the bis-acid **3.57** into water allows isolation of the product after azeotropic removal of water. Absolute purification away from inorganic salts is difficult given the very high solubility of the product in both water and organic solvents.

The best yield of **3.57** obtained over several syntheses was 72% of the pure material. Thorough drying of the mixed acid is essential prior to halogenation by reaction with $POCl_3$ and PCl_5. This is achieved by preliminary drying at 90 °C in a vacuum oven over 24 hours, followed by removal of traces of residual water by desiccation over P_2O_5 *in vacuo*, for a further 24 hours. Halogenation is achieved by addition of the anhydrous acid **3.57** to a mixture of PCl_5 and $POCl_3$ at 60 °C with rapid stirring under argon for 4 hours. Hydrogen chloride gas is released by way of an oil bubbler to maintain an anhydrous atmosphere over the reaction mixture. Removal of excess phosphorus reagents and by-products by low-pressure distillation provides the crude bis-acid chloride **3.58**. High vacuum Kügelrohr distillation provided the pure desired compound as a fuming moisture sensitive colourless liquid. Occasionally the bis-acid chloride **3.58** distilled as a yellow liquid, which despite colouration, reacted in an identical manner to the colourless substance.

3.2.3 Preparation of an immobilised tetrafluoroarylsulfonyl chloride

The significant difference in reactivity between the sulfonyl and acyl chloride groups of this bifunctional aromatic was exploited to our advantage, allowing selective functionalisation of the acyl chloride at the first stage (scheme 3.23).[164]



Scheme 3.22 Reaction of bis-acid chloride with aminomethyl- and hydroxymethyl polystyrene

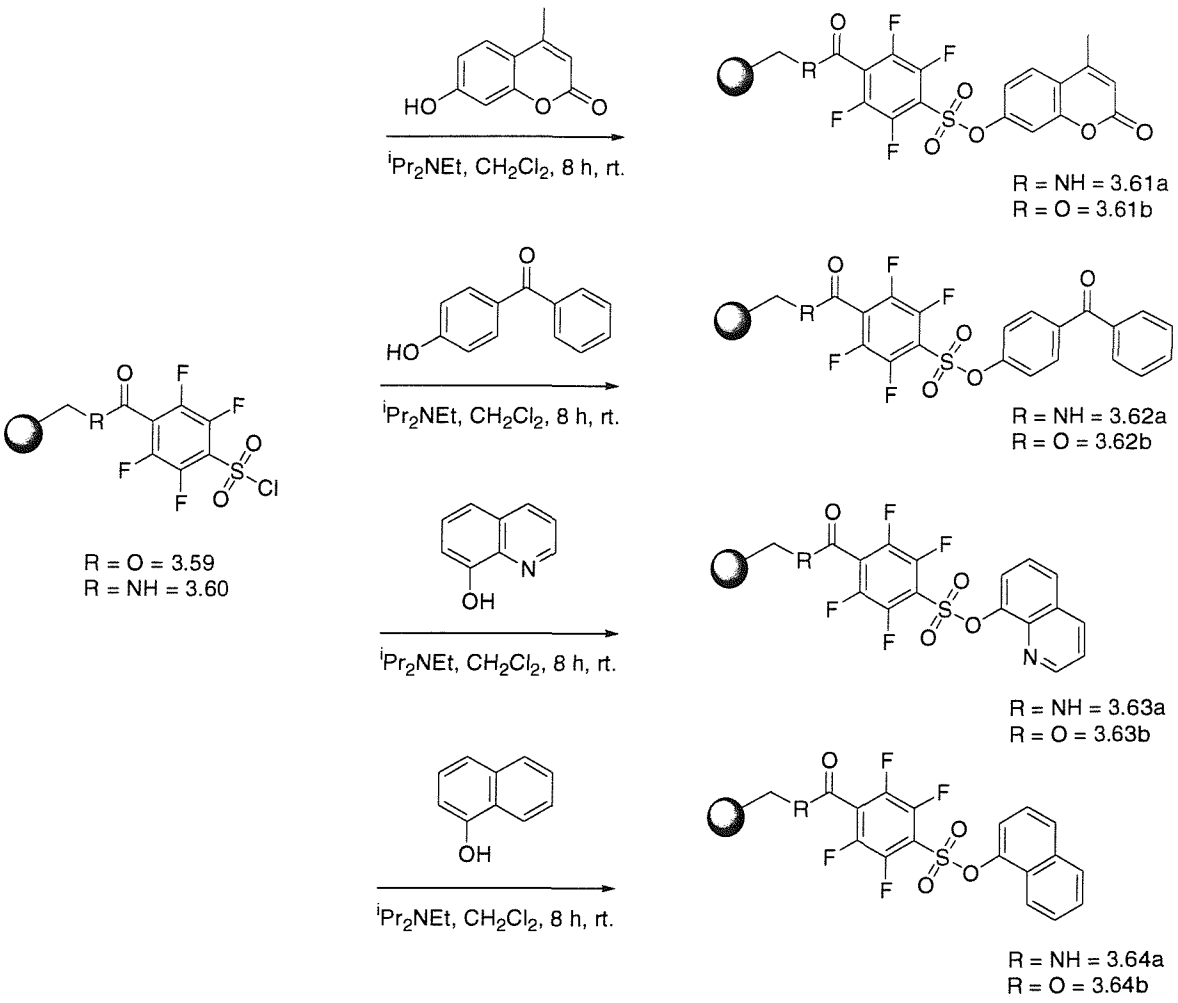
Both the polystyrene immobilised amide and ester linked sulfonyl chlorides **3.59** and **3.60** have previously been prepared,[165] and are termed 2,3,5,6-tetrafluorobenzamido-4-sulfonyl chloride-polystyrene and 2,3,5,6-tetrafluorobenzoyloxymethyl-4-sulfonyl chloride-polystyrene resin respectively. The inventions are listed within the patent **WO 99/67228** published by Salvino, Joseph, M (Inventor), (29.12.99), on behalf of Rhone-Poulenc. These fluorophenyl resin inventions, their respective methods of preparation, and also their use in the solid phase synthesis of amides, peptides, hydroxamic acids, amines, urethanes, carbonates, carbamates, sulfonamides and α-substituted carbonyl compounds are protected. Our preparation and intended use of these resins is however significantly different from that disclosed within the aforementioned patent.[165] Reaction of the bis-acid chloride **3.58** with aminomethyl or hydroxymethyl functionalised polystyrene in the controlled presence of a non-nucleophilic base allowed derivatisation of the support via the amide or ester respectively (scheme 3.23). However, it was found that addition of the bis-acid chloride to a slurry of the resin in excess triethylamine (3 mol equiv) continually resulted in the formation of a highly coloured orange resins, regardless of rate or temperature of addition. Analysis by FTIR showed that even the most highly coloured batches of functionalised sulfonyl chloride resin gave identical absorption spectra; however we attempted to minimise colouration through the evaluation of several different bases. The following bases: pyridine, $^{i}Pr_2NEt$, DMAP, lutidine, Bu_4NOH, Bu_4NHCO_3, were used, and both HMP and AMP resins were slurried in either CH_2Cl_2 or DMF as acylation solvents, and cooled to 0 °C.

Addition of the bis-acid chloride **3.58** in the corresponding solvent invariably resulted in highly coloured resins even after extensive washing procedures. In the cases of Bu_4NOH and Bu_4NHCO_3, addition of the bis-acid chloride gave rise to an exothermic reaction and rapid colouration in both CH_2Cl_2 and DMF.

Inverse addition of a dilute solution of the base to a mixture of the bis-acid chloride and resin slurried in CH_2Cl_2 was found to give far superior results. The most satisfactory results were obtained by preliminary addition of the bis-acid chloride to the resin in anhydrous CH_2Cl_2 at 0 °C followed by agitation at this temperature for 1 hour. To the cooled reaction mixture was added dropwise over 30 minutes a dilute solution of $^iPr_2NEt$ in CH_2Cl_2 (10% v/v) maintaining low temperature and vigorous agitation throughout the addition. Under these optimised conditions, the sulfonyl chloride remained unreacted as shown in the FTIR spectra, and almost colourless resins were obtained after washing and drying therefore providing an ideal site for phenolic attachment by sulfonate formation.

3.2.4 Sulfonate formation by reaction with phenols

With small batches of both HMP **3.59** and AMP **3.60** tetrafluoroarylsulfonyl chloride resins in hand, formation of sulfonate derivatives was pursued by reaction of the resin with several phenolic compounds in the presence of a base (scheme 3.24). For initial studies, four readily available substrates were chosen for derivatisation: 7-hydroxy-4-methylcoumarin, 4-hydroxybenzophenone, 8-hydroxyquinoline and 8-hydroxynaphthalene.



Scheme 3.23 Phenolic derivatisation using the tetrafluoroarylsulfonyl chloride linker

Each substrate was dissolved in a small quantity of CH_2Cl_2, and added in one portion to a slurry of the sulfonyl chloride resin **3.59** or **3.60**, pre-swelled in CH_2Cl_2. In the case of 7-hydroxy-4-methylcoumarin, which is only sparingly soluble in CH_2Cl_2, a minimum volume of DMF was added to aid dissolution. A 3-fold excess of Hünig's base was added, and the reaction mixture was agitated at room temperature for 8 hours, providing after thorough washing, the respective immobilised sulfonate ester.

3.2.5 Transfer hydrogenation of immobilised sulfonates

In order to evaluate the reactivity of these immobilised sulfonate esters (scheme 3.24) under conditions of transfer hydrogenation, the standardised procedure adopted by Holmes was employed with exciting results. The supported sulfonate esters were individually pre-swelled in anhydrous DMF, which was previously degassed with argon immediately prior to use. A mixture of 10 mol % $Pd(OAc)_2$ and 15 mol % dppp was found to act as an adequate

Pd/ligand system, and in the presence of an excess of anhydrous formic acid and triethylamine at 80 °C all immobilised sulfonate esters were reduced to the des-hydroxyaryl compounds in good to excellent yields (table 3.1a). In all four cases, the reduced aromatic product was obtained in slightly higher yield when cleaved from the supported sulfonate prepared from aminomethylated polystyrene **3.60** (table 3.1b).

TLC analysis of the crude reaction mixtures in each case showed that using the AMP rather than the hydroxymethylated support resulted in cleaner overall reaction, and subsequent sulfonate esters were prepared exclusively on AMP.

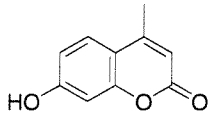
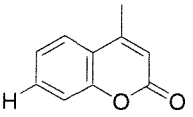
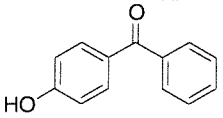
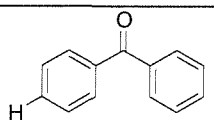
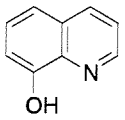
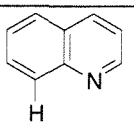
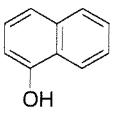
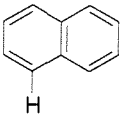
Substrate	Reductive cleavage	Entry	Yield (%)
		**3.65a**	71
		**3.65b**	74
		**3.65c**	62
		**3.65d**	63

Table 3.1a Isolated yields for transfer hydrogenation of sulfonate esters on hydroxymethylpolystyrene (HMP). For all entries, spectroscopic data was identical to that obtained from commercially available compounds

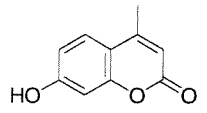
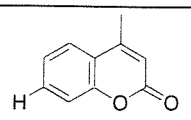
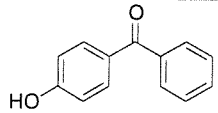
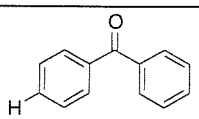
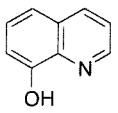
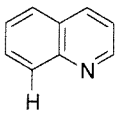
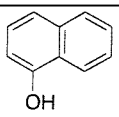
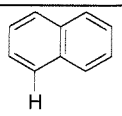
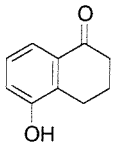
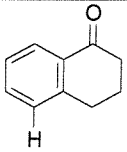
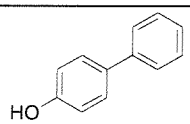
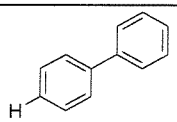
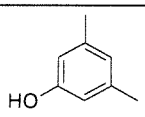
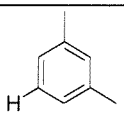
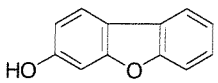
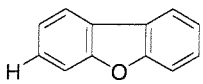
Substrate	Reductive cleavage	Entry	Yield (%)
		**3.65a**	82
		**3.65b**	89
		**3.65c**	76
		**3.65d**	80
		**3.65e**	66
		**3.65f**	79
		**3.65g**	72
		**3.65h**	81

Table 3.1b Isolated yields for transfer hydrogenation of sulfonate esters on aminomethylpolystyrene (AMP) For all entries, spectroscopic data was identical to that obtained from commercially available compounds

It can be seen from these results that the immobilised tetrafluoroarylsulfonate AMP linker indeed functions as intended and even using conditions which are not optimized for this linker furnished results which are extremely competitive against those obtained using the Holmes linker.

3.2.6 Transfer deuteration of immobilised sulfonates

Given the excellent results obtained using the tetrafluoroarylsulfonate linker under transfer hydrogenation conditions, similar yields of deuterated aromatic compounds were anticipated on exchanging HCO_2H for DCO_2D. In order to avoid any possibility of proton exchange, DMA was used instead of DMF as the reaction solvent.

Under otherwise identical reaction conditions of $Pd(OAc)_2$/dppf and triethylamine, we were pleased to obtain excellent isolated yields of the isotopically labelled deuterioaryl compounds (table 3.2).

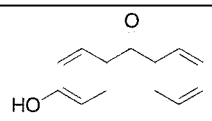
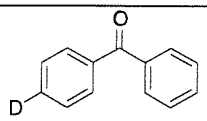
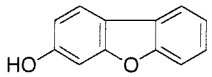
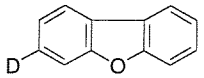
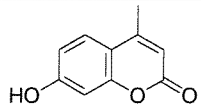
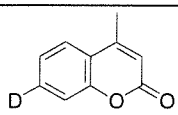
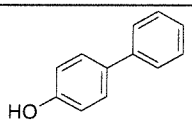
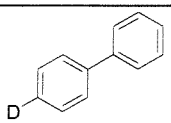
Substrate	Reductive deuteration	Entry	Yield (%)
		**3.67a**	84
		**3.67b**	76
		**3.67c**	80
		**3.67d**	77

Table 3.2 Transfer deuteration cleavage products

3.2.7 Suzuki-Miyaura cross-coupling of immobilised sulfonates

In addition to reductive cleavage, we found that conditions optimised by Holmes for Suzuki-Miyaura cross-coupling are also suitable in many cases for the same chemistry with our sulfonate functionalised linker. As a starting point, we followed the Holmes procedure using 10 mol % $PdCl_2$(dppf) as catalyst, 6 molar equivalents of triethylamine as base, and 3 molar equivalents of phenylboronic acid as the coupling partner. Addition of these reagents to a slurry of the sulfonate substituted AMP resin in degassed DMF, followed by heating to 80 °C with agitation for 8 hours results in the formation of the cross-coupled compound, generally in good yield (table 3.3). The yields remain good with electron rich aromatic systems. In the case of 8-hydroxyquinoline, Suzuki-Miyaura cross-coupling resulted in a rather complex mixture of compounds which made isolation of the desired product impossible.

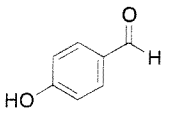
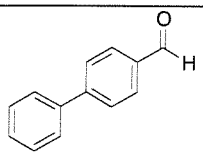
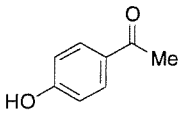
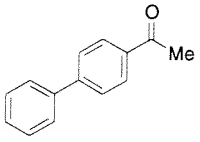
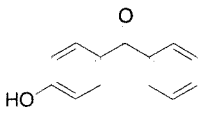
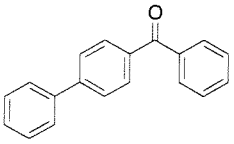
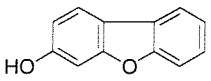
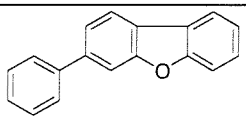
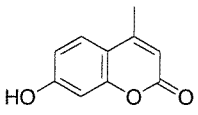
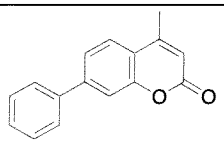
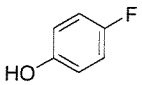
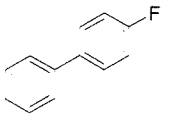
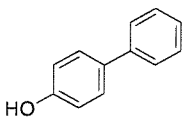
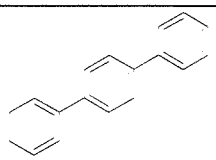
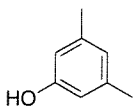
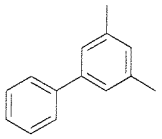
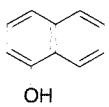
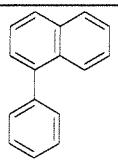
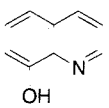
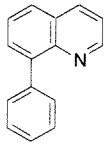
Substrate	Suzuki-Miyaura cross-coupling	Entry[ref]	Yield (%)
		**3.66a**[166]	80
		**3.66b**[167]	78
		**3.66c**[166]	86
		**3.66d**[168]	82
		**3.66e**	76
		**3.66f**[169]	71
		**3.66g**[170]	77
		**3.66h**[171]	76
		**3.66i**[172]	79
		**3.66j**[173]	0, 69*

Table 3.3 Suzuki- Miyaura cross-coupling products. Reactions were conducted using 10 mol % $PdCl_2$(dppf). *Reaction was conducted using 10 mol % $Pd(OAc)_2$ in conjunction with Xphos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl).

3.2.8 Optimisation of cross-coupling conditions

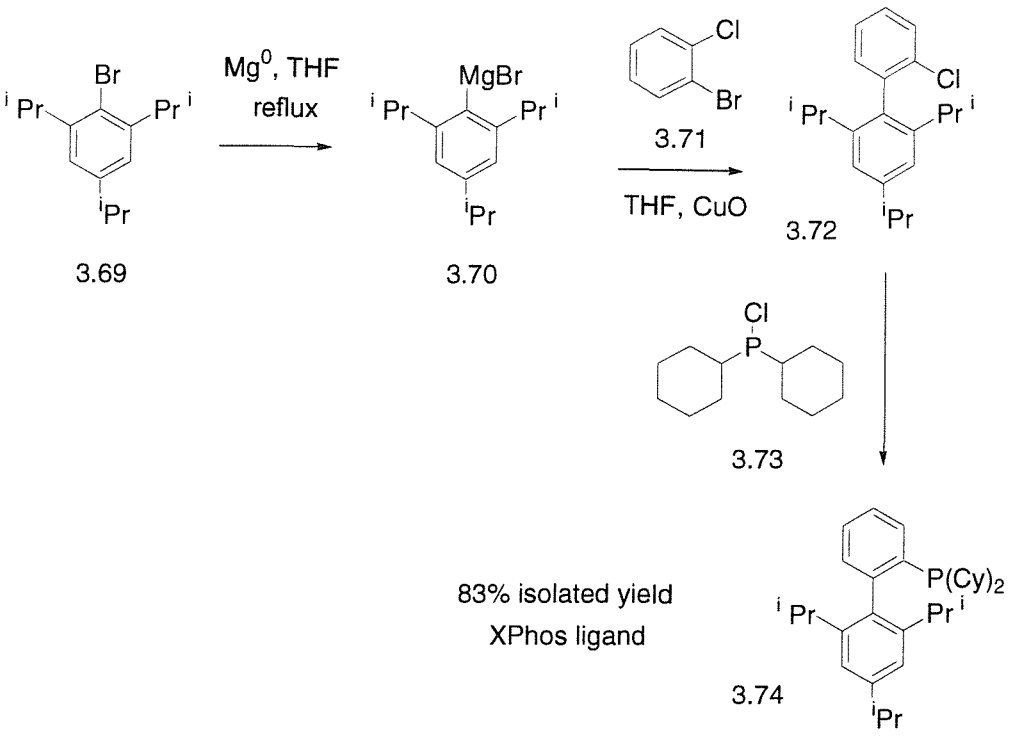
In order to optimise the isolated yields obtained using the AMP immobilised sulfonates, several different catalyst/ligand systems were evaluated in the cross-coupling of phenylboronic acid with the derivatised 7-hydroxy-4-methylcoumarin. However, in keeping with findings reported by Holmes, $Pd(OAc)_2$/dppp, $Pd(OAc)_2/PPh_3$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ all resulted in lower isolated yields in conjunction with triethylamine and phenylboronic acid, and $PdCl_2$(dppf) prevails as the optimal system overall (table 3.4, entries 1-5).

Entry Number	Catalyst/ligand system	Isolated yield (%)
1	$Pd(OAc)_2$/dppp	68
2	$Pd(OAc)_2/PPh_3$	54
3	$PdCl_2(PPh_3)_2$	68
4	$Pd_2(dba)_3$	62
5	$PdCl_2$(dppf)	76
6	$Pd(OAc)_2$/XPhos	74

Table 3.4 Isolated yields of 7-phenyl-4-methylcoumarin using various different catalyst/ligand systems

Recently, Buchwald and co-workers reported successful Suzuki-Miyaura cross-coupling of unactivated arylsulfonates using the ligand 'Xphos' (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) **3.74** (scheme 3.25).[174] In combination with $Pd(OAc)_2$, Xphos results in far superior coupling yields for reaction between aryl sulfonates and boronic acids in which neither partner contains an ortho substituent larger than a methoxy group. The successful coupling of arylsulfonates represents a significant advancement in cross-coupling methodology due to their ease of preparation from phenolic precursors. Given the excellent results reported by Buchwald, we anticipated similar or better findings in conjunction with our more reactive tetrafluoroarylsulfonate linker. The high cost of Xphos prompted us to synthesise the ligand according to the procedure detailed by Buchwald *et al.* (scheme 3.25).[175,176]

Entry 6 of table 3.3 shows the result of the coupling reaction using a combination of $Pd(OAc)_2$ and XPhos. It can be seen that while $PdCl_2$(dppf) results in the highest overall isolated yield, $Pd(OAc)_2$/Xphos also results in a very good conversion.



Scheme 3.24 One-pot preparation of the Buchwald 'XPhos' ligand

However, when the $Pd(OAc)_2$/Xphos was used as the cross-coupling catalyst/ligand system for reaction of the immobilised 8-hydroxyquinoline sulfonate **3.63a**, a vast improvement in the outcome of the reaction was evident. Using the conditions and catalyst system developed by Holmes, the reaction was messy and the desired product was not isolated. However, the combination of $Pd(OAc)_2$ (10 mol%) and Xphos (20 mol%) produced a far cleaner crude reaction, and allowed a more straightforward isolation of the product **3.66j** in 69% yield (Table 3.3).

3.2.9 Heck cross-coupling with methyl acrylate

To expand the scope of methodology available for use with this linker, it was anticipated that the immobilised sulfonates should readily undergo Heck cross-coupling in the presence of a suitable catalyst and methyl acrylate. Preliminary experiments were conducted using 10 mol% $PdCl_2$(dppf) with 10 equivalents of triethylamine in dry DMF, as these conditions had seemed broadly applicable for a range of coupling reactions both by Holmes[163] and ourselves. Heating of immobilised (4-hydroxybenzaldehyde)sulfonate resin **3.104** to 40, 60 and 80 °C for 24 hours in the presence of 10 equivalents of methyl acrylate produced a very complicated crude reaction mixture by TLC analysis.

Following *in vacuo* removal of excess methyl acrylate, ^{1}H NMR analysis of the crude reaction mixture showed no presence of any olefinic protons as would be expected had the reaction been successful. The addition of LiCl to the reaction mixture, in either catalytic (10 mol%) or stoichiometric (2 mol equivalents) quantities did not make any noticeable difference, hence prompting the search for a different modifier. Addition of 2 molar equivalents of Bu_4NI to the reaction mixture as outlined above greatly influenced the outcome of the reaction, and pleasingly the desired products were obtained through preparative TLC of the concentrated crude reaction mixture following aqueous workup and extraction of the products into diethyl ether. Table 3.5 gives the results obtained through the Heck cross-coupling of 4 immobilised sulfonates prepared in the usual manner from the substrates shown.

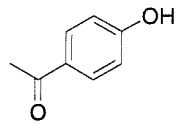
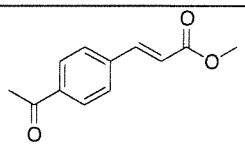
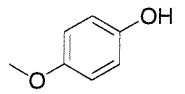
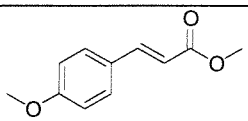
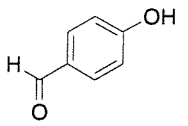
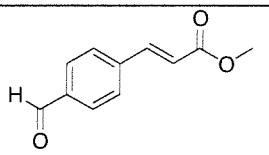
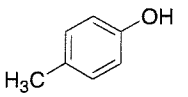
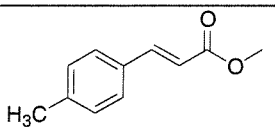
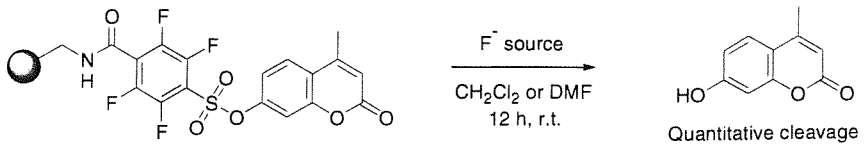
Substrate	Heck cross-coupling	Entry[ref]	Yield (%)
		**3.68a**[177]	81
		**3.68b**[178]	64
		**3.68c**[179]	69
		**3.68d**[178]	72

Table 3.5 Heck cross-coupling reaction products

3.2.10 Reaction of immobilised sulfonates with a fluoride source

As part of an investigation into selective fluorination of aromatic compounds, the reaction of immobilised tetrafluoroarylsulfonate esters with a fluoride source was hypothesised as a possible route. However, reaction of 7-hydroxy-4-methylcoumarin immobilised as the tetrafluoroarylsulfonate ester **3.61a** with TBAF (aq), NH_4F (anhydrous) or NaF invariably led to hydrolytic cleavage of the S-O bond of the sulfonate group, and quantitative isolation of 7-hydroxy-4-methylcoumarin. Hence although this method is not suitable for introduction of a fluoride atom in place of the sulfonate tether, it does serve as a useful method for the quantitative analysis of substrate loading following derivatisation.



3.61

Scheme 3.25 Quantitative cleavage of 7-hydroxy-4-methylcoumarin by a fluoride source

3.2.11 Stability studies of the tetrafluoroarylsulfonyl chloride linker

Commercial suppliers of sulfonyl chloride substituted polystyrene recommend storage of the resin under dry and inert conditions, and preferably at low temperature over long time periods. In order to assess the storage properties and long-term stability of the tetrafluorarylsulfonyl chloride substituted AMP resin **3.60**, a control test was made over a period of three months. A batch of freshly prepared immobilised tetrafluoroarylsulfonyl chloride **3.60** was washed and dried thoroughly prior to division into four portions; each was treated as follows:

Batch 1 was reacted with 7-hydroxy-4-methylcoumarin under the normal conditions for sulfonate formation; the resulting resin was washed and dried thoroughly and stored at room temperature under air in a sealed container for three months.

Batch 2 of the sulfonyl chloride resin was stored at room temperature under air in a loosely sealed container for three months.

Batch 3 of the sulfonyl chloride resin was stored at room temperature under argon in a sealed glass peptide vessel for three months.

Batch 4 of the sulfonyl chloride resin was stored at approximately –4 °C under argon in a sealed glass peptide vessel for three months.

Following the three month storage period, samples of batches 2, 3 and 4 were reacted with 7-hydroxy-4-methylcoumarin under the standard reaction conditions, washed and dried thoroughly.

All batches of the sulfonate derivatised resin were then subjected individually to the standard conditions developed for reductive cleavage, and a comparison of product yield was made to assess reactivity of the differently treated starting sulfonyl chloride resin batches. After isolation of the coumarin cleavage product, it was shown that as expected, the tetrafluoroarylsulfonyl chloride resin is susceptible to atmospheric decomposition, and batch 2 of the resin produced only traces of the desired product upon cleavage.

Resin batches 1, 3 and 4 upon cleavage produced essentially identical results, which surprisingly showed that as long as the supported sulfonyl chloride is stored under moisture free and inert conditions, its functionality is unaffected over a period of three months storage. This result also serves to prove the long-term stability of the derivatised sulfonate ester (batch 1 was stored for three months prior to cleavage), and pleasingly shows that no special storage conditions are required once the starting sulfonyl chloride is derivatised.

3.2.12 Conclusions

In summary we have demonstrated the immobilisation of 4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoyl chloride **3.58** onto both aminomethyl and hydroxymethyl polystyrene resin through formation of the ester **3.59** or amide **3.60** respectively. We have also shown the suitability of these so formed sulfonyl chloride resins to the immobilisation of phenolic compounds as sulfonate esters. Furthermore we have proven that both transfer hydrogenation and deuteration are possible, and that Suzuki-Miyaura and Heck cross-coupling reactions proceed in good to excellent yields for a variety of substrates.[244]

3.2.13 Future Directions

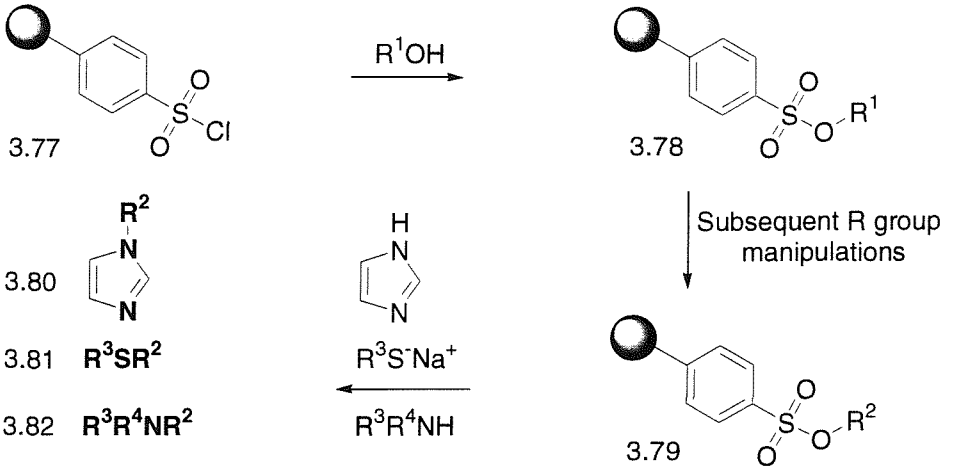
There is a very large literature precedent for the use of aryl triflates in the Stille cross-coupling reaction, and though not yet investigated, it should be expected that the immobilised tetrafluoroarylsulfonate esters will also be extremely good substrates for this reaction. Heating of chemical reactions by focused microwave irradiation has received widespread attention recently for its ability to generally reduce reaction times from hours to minutes, and in some cases producing better overall yields. Larhed *et al.* demonstrated the use of microwave acceleration for the following solid-supported Suzuki-Miyaura cross-coupling reaction, which following optimisation could be completed in less than 4 minutes (scheme 3.27).[180]

3.75 3.76

Scheme 3.26 Microwave acceleration of Suzuki-Miyaura reaction on solid-phase

Since reactions using our tetrafluoroarylsulfonate linker are conducted in the dipolar solvent DMF, controlled microwave heating might also be effective in decreasing reaction times of reductive cleavages, or cross-coupling reactions whilst still maintaining good yields.

Recently, Reitz demonstrated the use of immobilised alkylsulfonates **3.79** as good substrates for cleavage with amines, thiolates and imidazoles, providing good yields and high purities of the respectively substituted alkyl compounds **3.80**, **3.81** and **3.82** (scheme 3.28).[181]



Scheme 3.27 Alkylative cleavage of supported arylsulfonate esters

Given that our tetrafluoroarylsulfonate linker displays higher reactivity in such reactions as reductive cleavage when compared to the Wustrow linker,[161] it can reasonably be expected that it should also give good results in such alkylative displacement reactions. These reactions would extend the scope of useful synthetic transformations possible with this linker.

3.2.14 Solid-phase synthesis of Valsartan methyl ester using the tetrafluoroarylsulfonate linker

In order to further investigate the synthetic use of the tetrafluoroarylsulfonate linker, the solid-phase synthesis of the important pharmaceutical drug Valsartan was considered. Valsartan, an angiotensin II receptor blocker, was chosen as a suitable target since it contains a biphenyl moiety which may be disconnected through a Suzuki-Miyaura reaction using our linker. To facilitate the manipulation and purification of the desired biphenyl compound, the preparation of the methyl ester of Valsartan **3.83** (figure 3.4) was investigated rather than the parent acid. The parent acid is itself prepared from the methyl ester by basic hydrolysis.,[182,183] hence **3.83** represents an important intermediate.

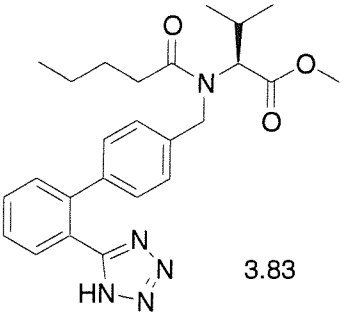


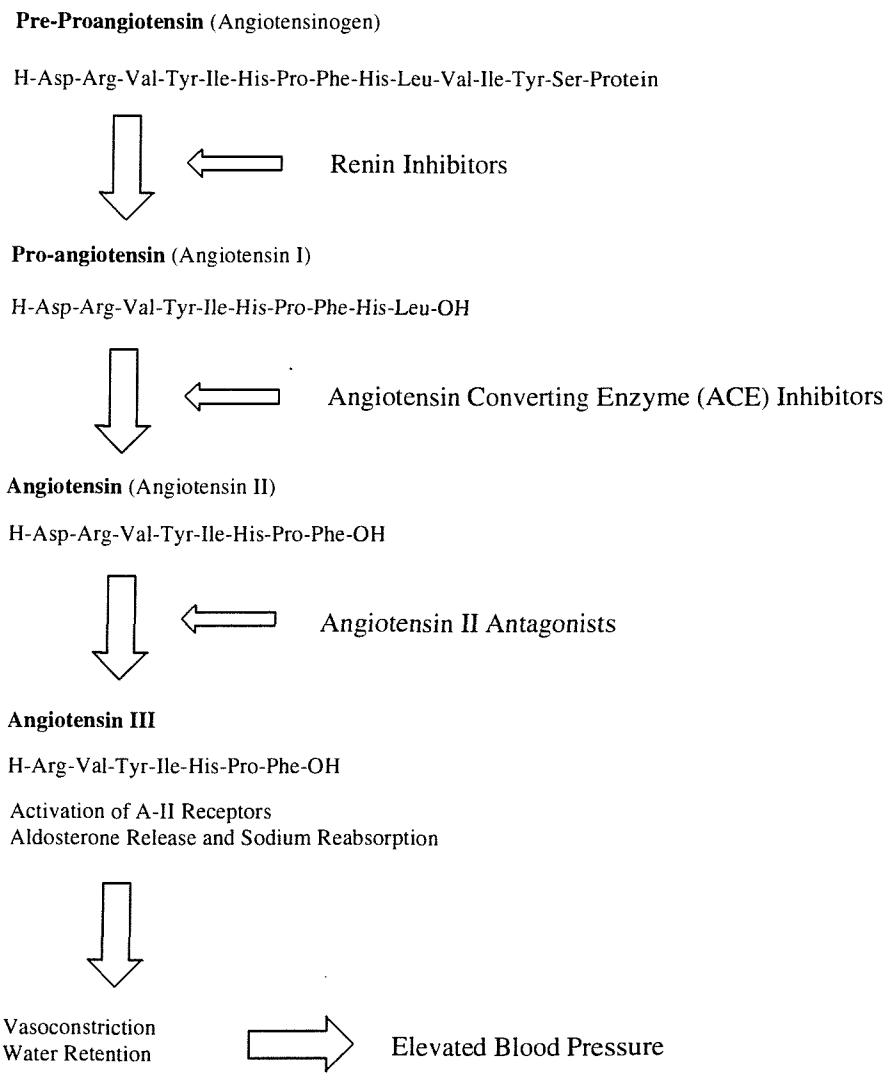
Figure 3.4 Valsartan methyl ester

3.3.1 Introduction: Angiotensin II Converting Enzyme Inhibitors

3.3.1.1 The renin-angiotensin system

Mammalian homeostatic factors such as blood pressure, electrolyte balance and blood volume are primarily regulated by the several feedback mechanisms of the renin-angiotensin system (scheme 3.29), which is itself orchestrated by a group of peptidic hormones known as the angiotensins.[184] The angiotensins target the endopeptidase renin, produced by the juxtaglomerular cells of the kidneys.

A decrease in blood pressure or sudden depression of blood sodium levels caused by loss of blood stimulates the kidneys to secrete the proteolytic enzyme renin. Renin acts upon the circulating glycoprotein angiotensinogen, produced in the liver, and from this cleaves off angiotensin I.



Scheme 3.28 The renin-angiotensin cascade

Angiotensin I is an inactive decapeptide, which itself is cleaved in the lungs and kidneys by angiotensin converting enzyme (ACE) initially to the octapeptide angiotensin II, a powerful vasoconstrictor and further to its degradation product, the heptapeptide angiotensin III. Either of these two hormones initiates the secretion of aldosterone from the adrenal gland, resulting in the reservation of blood volume by stimulation of antidiuresis, and hence overall retention of sodium and water, and increased blood pressure.

Rapid hydrolysis of the angiotensins means that their effects are fleeting, and hence suitable for continuous regulation of blood pressure. A multitude of further regulatory factors such as vasopressin, thromboxane and the prostaglandins also exert their effects on the cardiovascular system in a complex and intimate manner. In the healthy individual, these effects are well coordinated and blood pressure remains essentially static. Certain pathological conditions however, can cause disruption of this important regulatory system resulting initially in hypertension, and more seriously in potentially fatal conditions of the heart. Therapeutic intervention at several positions on the renin-angiotensin cascade has proven possible, with the actions of three target sites amenable to specific medicinal control, namely renin inhibition, angiotensin receptor antagonism, and angiotensin converting enzyme inhibitors.

3.3.1.2 Renin inhibition

Certain naturally occurring phospholipids and synthetic phosphatidylethanolamine derivatives are selective inhibitors of renin, the rate limiting enzyme in the renin-angiotensin cascade. Pepstatin, a pentapeptide isolated from *Streptomyces* strains (figure 3.5) results in the temporary lowering of blood pressure upon intravenous administration.

NH_2-Iva-Val-Val-Statin-Ala-Statin-CO_2H

Figure 3.5 Pepstatin

However, the peptidic composition of pepstatin prevents oral administration, and owing to its rather shortlived effects, its use in the treatment of hypertension and congestive heart conditions is severely limited.

3.3.1.3 Angiotensin receptor antagonists

Modification of the angiotensin molecule has led to the development of angiotensin receptor antagonists, a collection of drugs based around chemically manipulated angiotensin II.

The most potent of these modified hormones is the drug Saralasin, [Sar^1, Val^5, Ala^8] angiotensin II (figure 3.6).

Sar-Arg-Val-Tyr-Val-His-Pro-Ala-CO_2H

Figure 3.6 Saralasin

However, owing to the rapid hydrolysis of these molecules *in vivo*, continual intravenous administration is necessary to maintain therapeutic effect; thereby restricting the use of such medications to hospitalized patients.

3.3.1.4 Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors have become established as the most effective treatment against hypertension and congestive heart failure. The first drug within this therapeutic category to be properly developed was the nonapeptide Teprotide (figure 3.7). The presence of 4 proline residues and a pyroglutamate moiety prevent digestive decomposition, and Teprotide displays a long lasting effect. Teprotide competitively inhibits the degradation of angiotensin I via ACE, however it does not display antihypertensive effects.

pyroGlu-Trp-Pro-Arg-Pro-Glu-Ile-Pro-Pro-OH

Figure 3.7 Teprotide

In 1977, Ondetti and Cushman published clinical results of a new drug, Captopril (figure 3.8), which is 10 times more active than Teprotide. Captopril was the first drug of its kind specifically designed to inhibit carboxypeptidase A, the active site of which is known to closely resemble that of angiotensin converting enzyme. Captopril however, is not orally active.

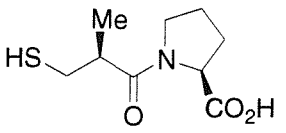


Figure 3.8 Captopril

Following observations of mild cardiovascular activity during the testing of drug molecules which were originally intended as anti-inflammatory agents, 1982 saw the dawn of a new line of defence in hypertension. Three competing compounds **3.84**, **3.85** and **3.86** emerged, and were marketed by different companies (figure 3.9).

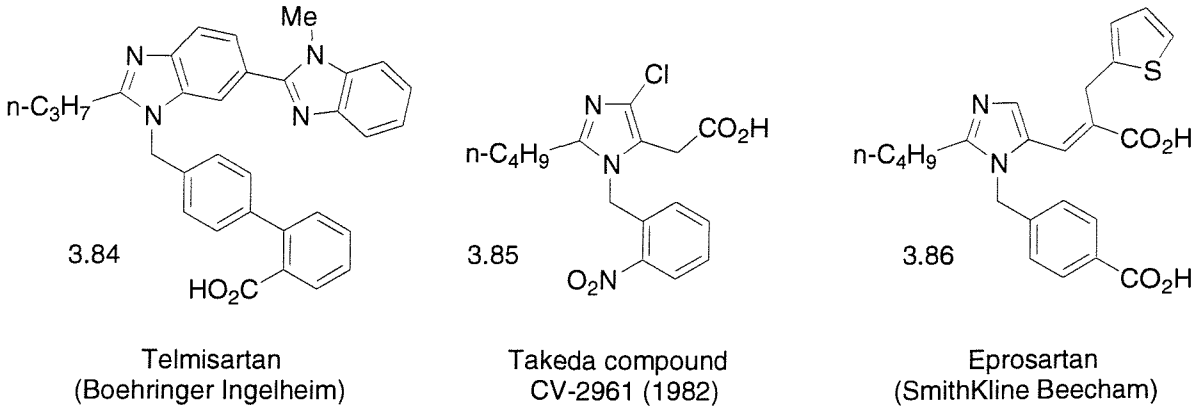


Figure 3.9 Angiotensin-II receptor inhibitors

These new non-peptidic candidates are orally-bioavailable, and although initially only weakly active and non-selective, molecular modelling studies of the angiotensin-II receptor site eventually led to the development of the biaryl compound Losartan **3.89** (scheme 3.10). Unlike preceding ACE inhibitors, which exhibit affinity for both the angiotensin type I and II (AT_1 and AT_2) receptor sites, Losartan and its family of structurally related compounds shows high affinity only for the AT_1 receptor, and are known collectively as angiotensin receptor blockers (ARBs). ACE is also partly responsible for bradykinin catabolism, and accumulation of which in pulmonary tissues caused by inhibition of ACE activity is the suspected cause of the dry non-productive cough observed in as much as 20% of patients (and as much as 50% of Asian patients).[185] ARBs are more selective in their action, and are free from such side-effects. Blockade of the AT_1 receptor results in the beneficial alleviation of cardiovascular effects observed in the hypertensive patient, such as suppression of vasopressin and aldosterone release, and stimulation of renal sodium reabsorption. However, ARBs are not inhibitors of the AT_2 receptor site, and hence the negative effects associated with ACE inhibitors are not present as a result of the administration of ARBs. Therefore the useful therapeutic effects associated with angiotensin II, such as vasodilation remain. Of these structurally related compounds, Losartan **3.89** has become widely prescribed given its long duration of action. This unexpected feature was later attributed to the biological activity of secondary metabolites of Losartan produced through cytochrome P450 oxidative metabolism in the liver.

Like Losartan, Candesartan cilexetil **3.87** is also a prodrug, and undergoes conversion to the active therapeutic compound **3.88** during gastrointestinal digestion. Of the following drug candidates to challenge Losartan, only one, Valsartan **3.90**, approved in 1996 has proven worthy to hold popularity.

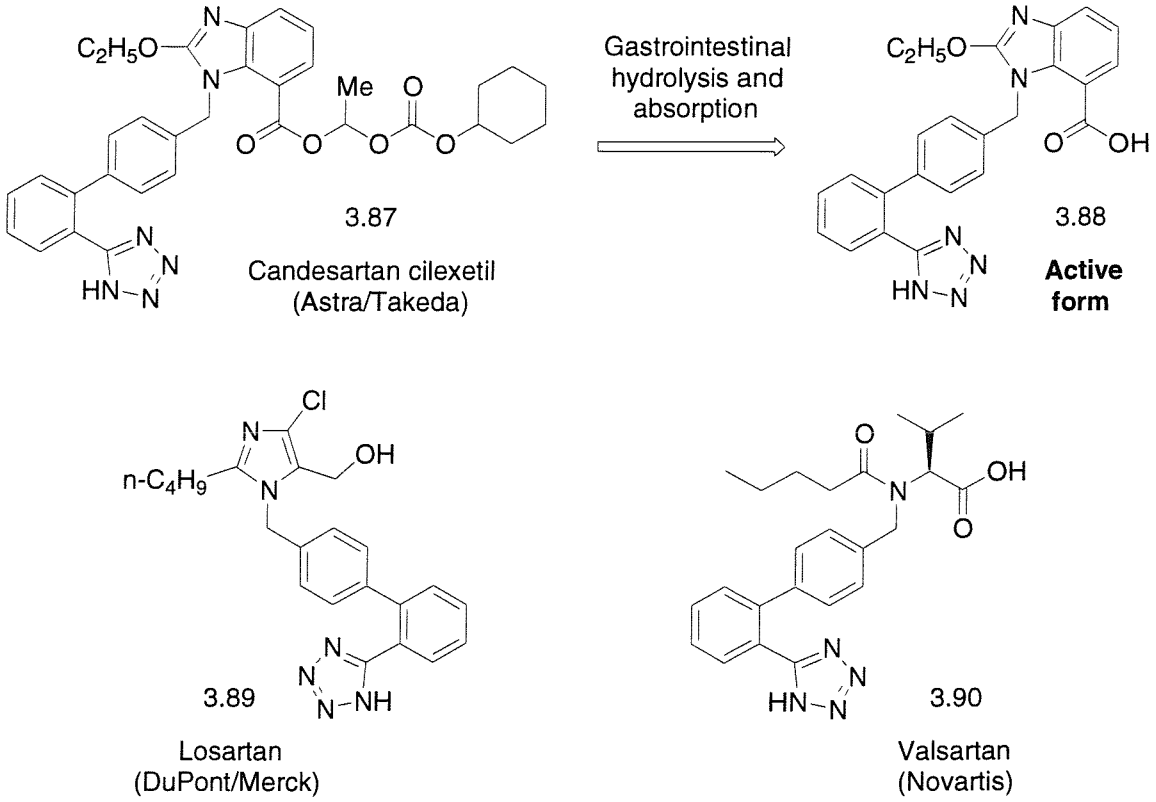


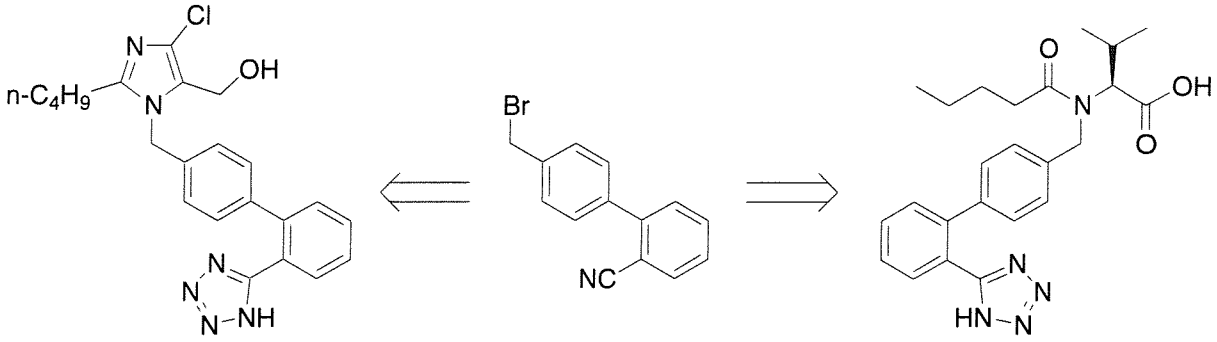
Figure 3.10 Angiotensin-II receptor blockers

Unlike Losartan, Valsartan is the active compound in its own right, and has a short blood plasma half-life resulting in an effective duration of between 4-6 hours following administration. Readministration can therefore be checked frequently and monitored closely in patients suspected of juvenile hypertension.

The ARBs share several structural features, including a biphenyltetrazole moiety, which is largely responsible for competitive binding at the AT_1 receptor site. Although the tetrazole moiety present in all of these molecules has a pKa comparable with that of a carboxylic acid, it is far less susceptible to metabolic degradation and is therefore often used medicinally as an effective bioisostere. The tetrazole ring system offers excellent opportunity for hydrogen-bonding interactions, and the linear hydrophobic biphenyl moiety offers the chance of π-electron interactions with aromatic groups, both of which are important features for effective receptor site binding.

Negative charge delocalisation over all 4 nitrogen atoms of the tetrazole heterocycle result in derivatives exhibiting a higher log P and hence better oral bioavailability and cell membrane permeation.

Although several groups have reported independent strategies for the synthesis of ARBs, in particular Losartan, these syntheses are all closely related, and usually commence from a pre-formed biaryltetrazole or close synthon such as the biarylnitrile shown in scheme 3.29.



Losartan 3.89 Valsartan 3.90

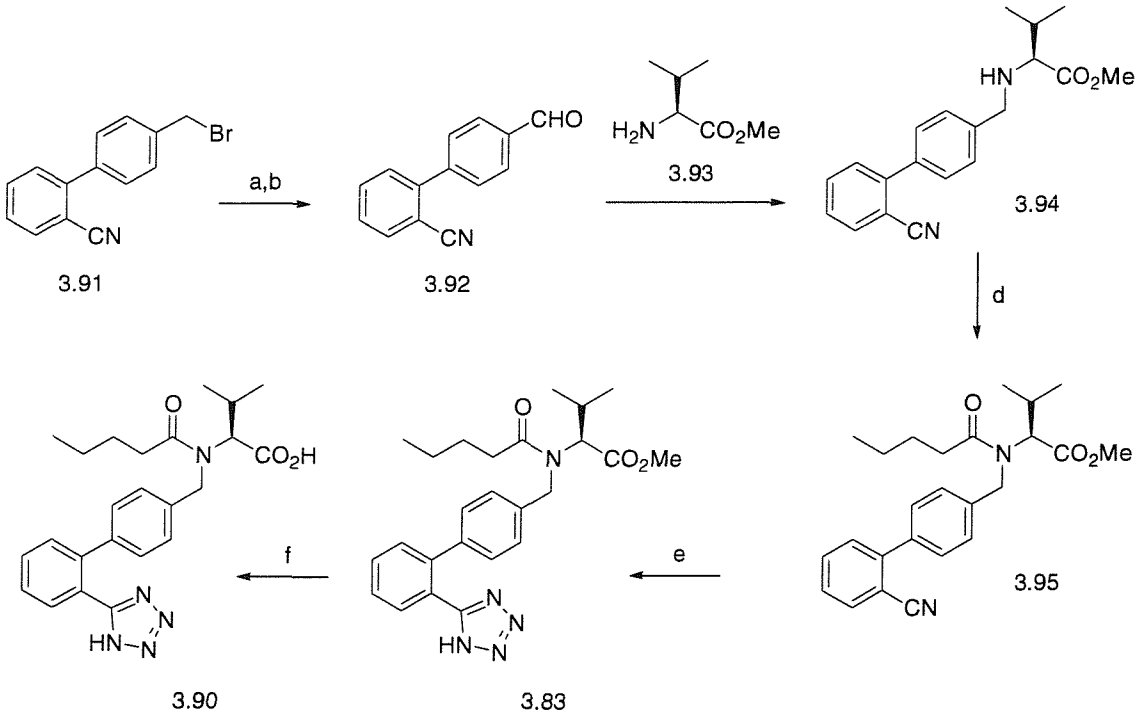
Scheme 3.29

We supposed that given the successful preparations achieved using our tetrafluoroarylsulfonate linker, a solid phase synthesis of an ARB might be possible. Considering the chemical structures of Losartan and Valsartan, and the solution-phase precedents available in the literature,[182,183] it is obvious that Valsartan is more easily accessible through chemistry suited to the solid-phase. Given the inaccessibility of the Losartan imidazole heterocycle and the obvious need for its multistep preparation on solid-phase, it was decided that a synthesis of Valsartan methyl ester should commence.

3.3.2 Evaluating a solid-phase synthesis of Valsartan methyl ester

3.3.2.1 Discussion of possible solution-phase routes to Valsartan

The industrial solution-phase preparation of Valsartan **3.90** commences with a halogen displacement of 4'-(bromomethyl)-2-cyanobiphenyl **3.91**,[186] to give the benzyl alcohol. Swern oxidation, and reductive amination of the resulting aldehyde **3.92** with L-valine methyl ester **3.93** gives the secondary amine **3.94**, which is acylated with valeryl chloride to provide amide **3.95**. Cycloaddition of the nitrile function of **3.95** with tributyltin azide under forcing conditions affords the tetrazole methyl ester compound **3.83**, which is saponified with aqueous NaOH to provide Valsartan **3.90** (scheme 3.30).



Scheme 3.30 Patented pilot-scale route to Valsartan (**US Patent, 1995, 5,399,578**)

Reagents: (a) NaOAc, HOAc, reflux 16 h; then NaOH, H_2O, EtOH, 16 h, reflux; (b) $(COCl)_2$, CH_2Cl_2, DMSO, -60 °C, 2 h; then NEt_3, -60 °C to rt; (c) $Na(BH)_4$, MeOH, THF, 5 °C, then rt, 24 h; (d) NEt_3, n-valeryl chloride, CH_2Cl_2, 0 °C, then rt, 16 h; (e) Bu_3SnN_3, xylene, reflux 24 h; (f) 1N NaOH, rt, 10 h.

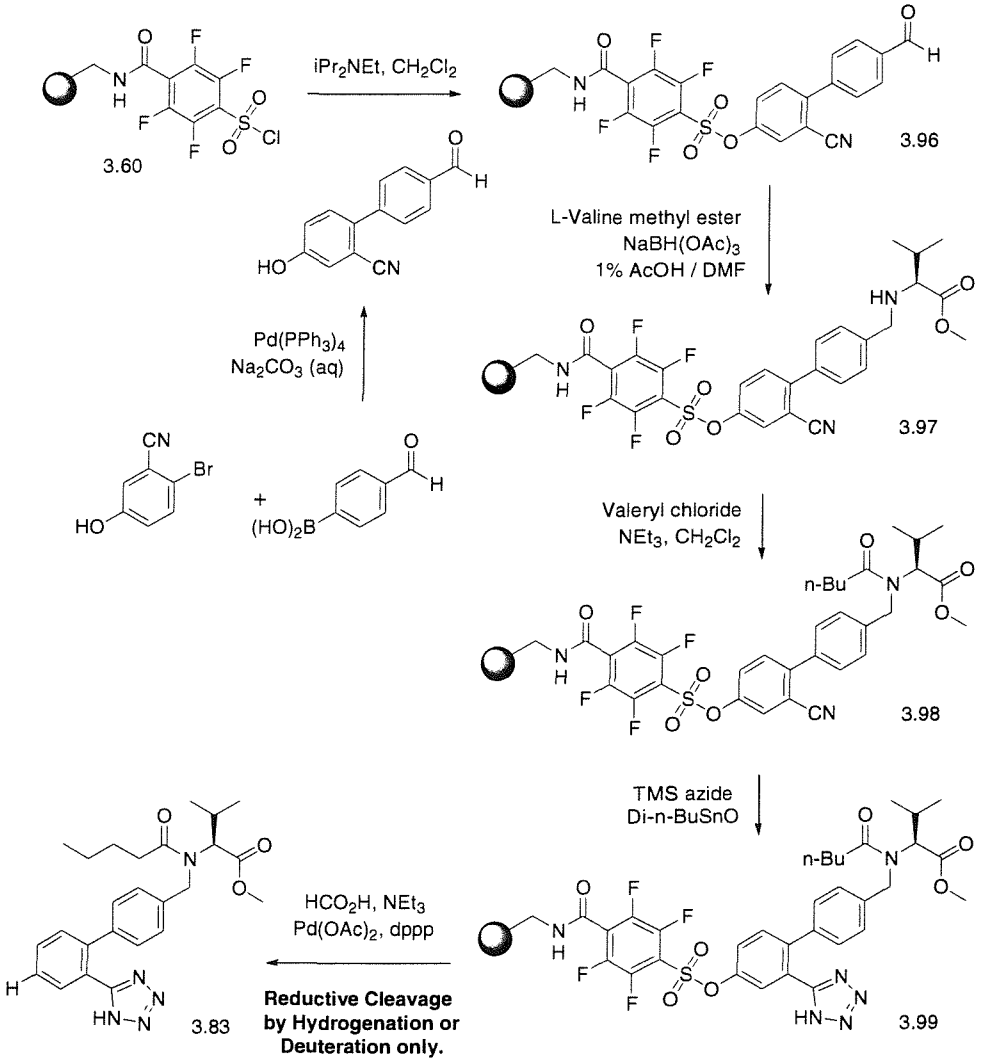
3.3.2.2 Designing a solid-phase synthesis of Valsartan methyl ester

As shown in scheme 3.30, the patented solution-phase synthesis of Valsartan commences with (bromomethyl)biphenyl nitrile **3.91**, and is therefore not immediately suitable for adaptation to the solid-phase. Ideally we would like to develop a route in which the final Pd(0) mediated step releases Valsartan methyl ester directly, without the need for further chemical manipulation.

Consideration of the structure of Valsartan reveals several possible disconnections back to the key building blocks of L-valine, valeraldehyde, and the biaryl tetrazole moieties. From a design perspective, phenolic linkage to the supported tetrafluoroarylsulfonate could feasibly be made at 3 different points of this biaryl function, either by reductive cleavage, cleavage by Stille cross-coupling, or by Suzuki-Miyaura cross-coupling.

3.3.2.3 Reductive Cleavage

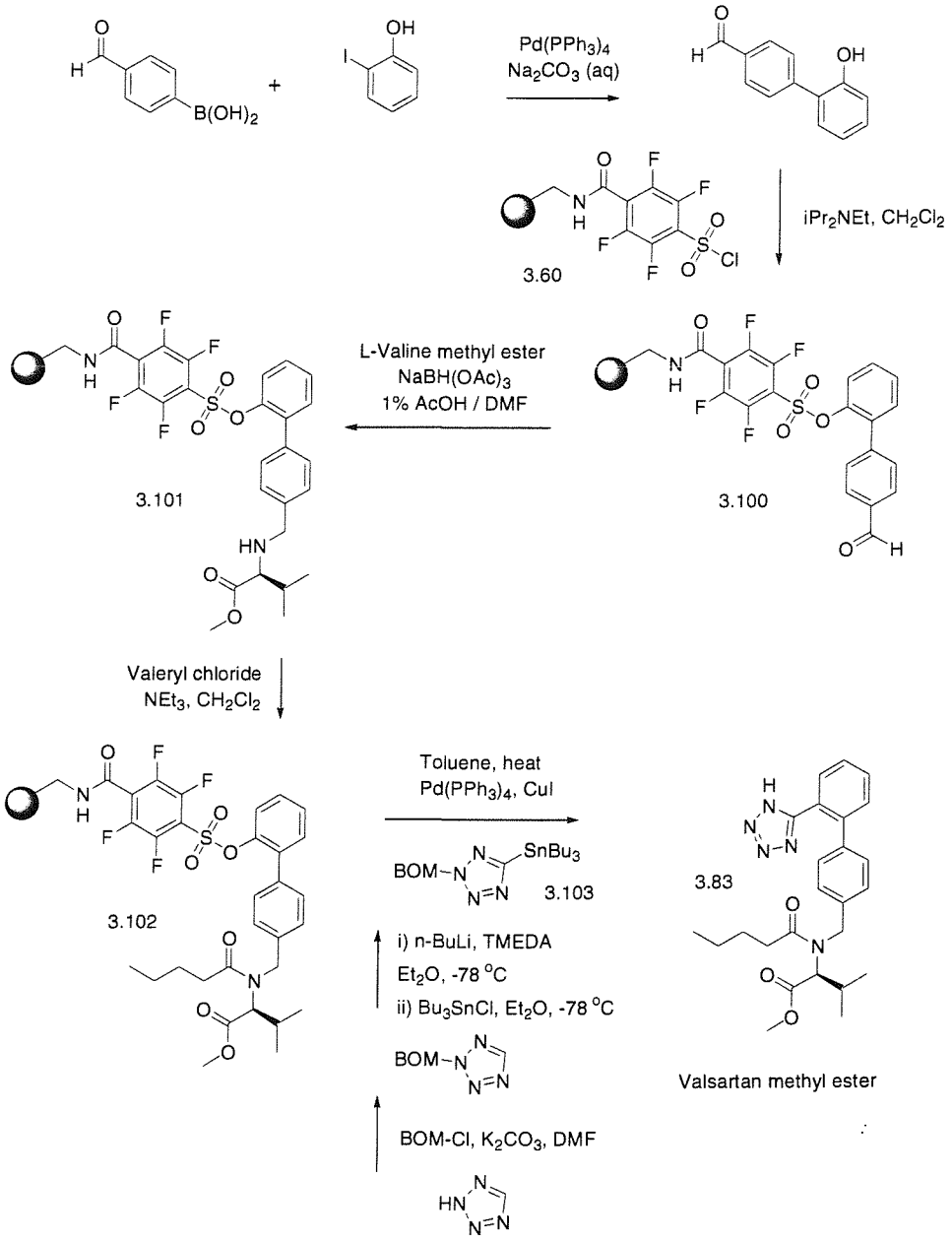
The linker **3.60** could be used to immobilise the phenolic component (scheme 3.31), however this strategy brings with it two important consequences: firstly, traceless disconnection from the support now requires reductive cleavage, which does not allow provision for elaboration outside protonation or deuteration. Secondly, preparation of the biaryltetrazole component represents a significant proportion of the challenge of this overall synthesis, and would greatly detract from the elegance of its construction on the solid-phase.



Scheme 3.31 Hypothetical solid-phase route to Valsartan methyl ester via reductive cleavage

3.3.2.4 Cleavage by Stille cross-coupling

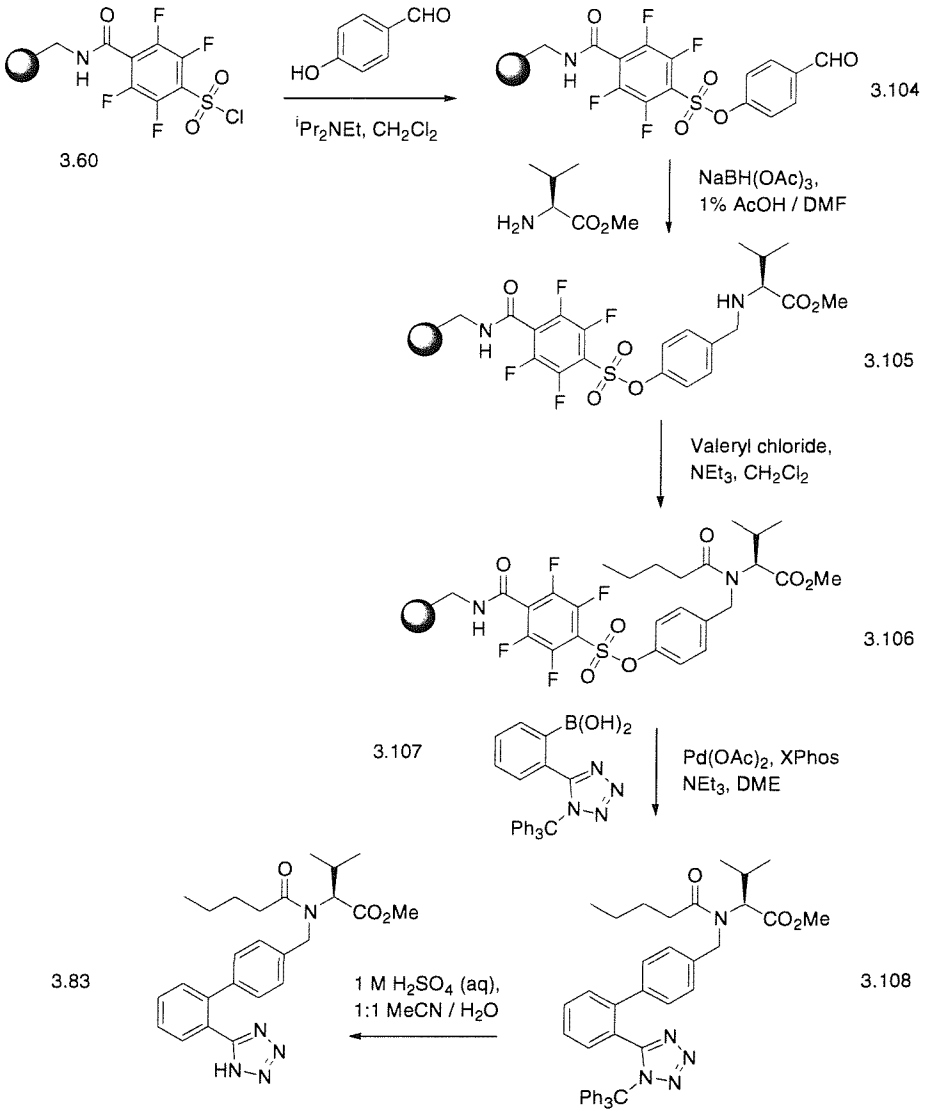
A second set of disconnections could ultimately result in a Stille-type coupling which would release the desired product from the resin support. Although preparation of the necessary tetrazole stannane component **3.103** was reported by Bookser,[187] the overall route remains lacking in its ability to bring diversity into the Pd(0) coupling/cleavage step (scheme 3.32).



Scheme 3.32 Hypothetical solid-phase route to Valsartan methyl ester via Stille cross-coupling

3.3.2.5 Suzuki-Miyaura cross-coupling strategy

In order to more fully exploit the capability of this linker, we decided to employ the Suzuki-Miyaura reaction as our key disconnection, providing cleavage of Valsartan methyl ester from the sulfonate **3.106**. In doing so we build into the synthesis the opportunity for cross-coupling with different boronic acids if so desired, allowing diversification if required (scheme 3.33).

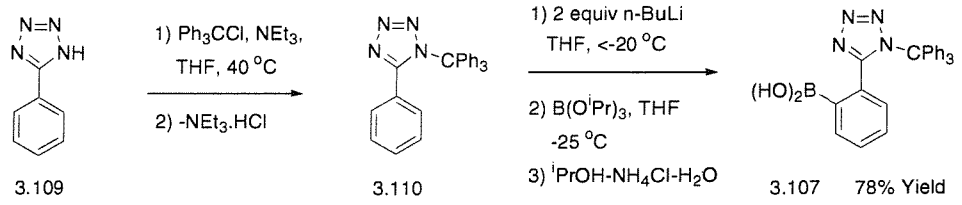


Scheme 3.33 Proposed solid-phase route to Valsartan methyl ester via Suzuki-Miyaura cross-coupling

This synthetic route does however require the use of 2-tetrazolylphenyl boronic acid, which is not available commercially. However in 1994 Larson *et al.* reported the synthesis of Losartan using this boronic acid.[188] Larson mentions the need to protect the N_1 nitrogen atom as the trityl-tetrazole derivative **3.107**, since the unprotected tetrazole does not undergo Suzuki-Miyaura coupling efficiently due to coordination of the free nitrogen with the palladium catalyst.

Following the cross-coupling reaction, deprotection of the tetrazole ring is achieved using dilute aqueous sulfuric acid in acetonitrile to hydrolyse the trityl group. The resulting colloid was stirred at room temperature for 2 hours when complete detritylation was observed, allowing isolation of losartan as desired **3.89** (Figure 3.10).

As detailed by Larson, the trityl-protected 2-tetrazolylphenyl boronic acid **3.107**, was prepared with the intention of employing the same disconnection on solid-phase and in the synthesis of Valsartan methyl ester (scheme 3.34). In a one-pot reaction, phenyltetrazole **3.109** was protected as the trityl compound **3.110** by reaction with trityl chloride in the presence of triethylamine. Triethylamine hydrochloride, which separated during the reaction, was removed by filtration, and the reaction mixture was dried by the dropwise sacrificial addition of n-BuLi. Upon obtaining completely anhydrous conditions, excess trityl chloride was converted by more n-BuLi to the bright red triphenylmethyl anion, thereby acting as an internal indicator. When a persistent red colour was obtained, a main charge of n-BuLi (1.05 mol equiv) was added to generate the *ortho*-lithiated intermediate. The metallated anion was quenched with triisopropyl borate to give the boronate ester, which was subsequently hydrolysed to the boronic acid by the sequential addition of isopropanol, aqueous ammonium chloride solution (20% w/v), and water. Ammonium chloride was used in order to maintain a reaction mixture pH between 8 – 11, thereby preventing detritylation of the tetrazole heterocycle. 5-(2'-boronophenyl)-2-(triphenylmethyl)-2H-tetrazole **3.107** was prepared as the tetrahydrofuran hydrate in 78% isolated yield (scheme 3.34).



3.109 3.110 3.107 78% Yield

Scheme 3.34 One-pot preparation of 5-(2'-boronophenyl)-2-(triphenylmethyl)-2H-tetrazole

3.3.2.6 Results of Suzuki-Miyaura cross-coupling strategy

Our solid-phase synthesis of Valsartan methyl ester then commenced with reaction of 4-hydroxybenzaldehyde with tetrafluorophenylsulfonyl chloride on aminomethyl polystyrene (**3.60**). The immobilised aldehyde **3.104**, was then reductively aminated using the protocol described by Ellman *et al.*[189] In order to minimize racemisation of the amino acid, it is important that immediate reduction of the intermediate imine take place, rather than allowing the amino acid and aldehyde components to come to equilibrium with the imine.

On the solid-phase, this may be achieved through premixing of the reducing agent $NaBH(OAc)_3$ and the immobilised aldehyde using a solvent system of acetic acid in DMF (1% v/v), followed by addition of the amino acid component. Reductive amination of immobilised 4-hydroxybenzaldehyde on the tetrafluoroarylsulfonate linker (**3.104**) was monitored using FTIR to follow the diminishing intensity of the aldehyde stretch at 1693 cm^{-1}, and increase in intensity of the amino acid methyl ester carbonyl stretch at 1732 cm^{-1}. After agitation of the reaction mixture for 12 hours, an aliquot of the resin reaction mixture was washed thoroughly and dried *in vacuo* and showed no further decrease of the aldehyde stretch region present in the starting resin. This region of the IR spectrum is obscured by the amide stretch formed upon reaction of the tetrafluorophenylsulfonyl chloride with aminomethyl polystyrene. It appears that as a result of the electron withdrawing effect of the tetrafluorophenyl moiety of the linker, the amide vibrating frequency has been increased from an expected 1650 to 1692 cm^{-1}. The whole reaction mixture was drained and washed thoroughly, and the clean resin was dried overnight *in vacuo* at 40 °C. Acylation of the immobilised secondary amine **3.105** was achieved using a standard protocol. To a mixture of the slurried resin **3.105** and a 10 fold excess of $^{i}Pr_2NEt$ in dry CH_2Cl_2 was added 5 equivalents of n-valeryl chloride dropwise over 30 minutes at 0 °C. The slurry was then agitated for 12 hours, and the reaction judged complete after this time, when the FTIR spectra of a washed and dried aliquot of the resin no longer showed any increase in the intensity of the amide carbonyl stretch at 1662 cm^{-1}. Once again the reacted slurry was washed and then dried *in vacuo* to afford **3.106**. The resulting resin was subjected to the Suzuki-Miyaura coupling reaction conditions outlined by Larson for the solution-phase synthesis of Losartan. Larson notes that an explicit set of reaction conditions were necessary to give a good yield of the coupled product. Larson used a Pd(0) source generated *in situ* from $Pd(OAc)_2$ and PPh_3, having recognized the difficulty and expense associated with using preformed catalysts such as $Pd(PPh_3)_4$ on large scale.[188] THF alone was found to have a boiling point too low to provide an effective rate of reaction, and although several other general solvent systems were considered, a mixture of a 1:4 THF/DEM (diethoxymethane) was found to be most suitable. Larson also found the order of addition of reagents critical to the success of the reaction, and notes the necessary pre-formation of catalyst, followed by boronic acid as the THF solvate and then the addition of 2.3 equivalents of water. The exact quantity of water appears critical, and Larson notes that a deficit causes the reaction to cease, whereas an excess causes agglomeration of the K_2CO_3 base.

Addition of 2.5 equivalents of the base, and 1 equivalent of the aryl bromide, followed by heating of the reaction mixture at reflux (80 °C) for 3 – 6 hrs gave an isolated yield of 93% of trityl Losartan.

Given that our proposed Suzuki-Miyaura cross-coupling is to be performed on the solid-phase and also with a different substrate, we recognized the need for modification to the Larson procedure. However our initial experiments were performed using conditions following as closely as possible those set out by Larson.

A 1 g batch of the sulfonate linked Valsartan precursor **3.106** was swollen in degassed THF and agitated for 30 minutes to ensure complete wetting of the resin. To the slurry was added a catalyst mixture of $Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %); followed by trityltetrazolylphenyl boronic acid **3.107** and K_2CO_3 in water/DMF. After heating of the reaction at 70 °C with agitation for 18 hrs, the black mixture was filtered, and the resin thoroughly washed. Following aqueous workup of the filtrate, extracts were combined and concentrated to provide an orange/brown gum, which was applied to a preparative TLC plate. Elution of the plate and isolation of the appropriate compound band afforded after extraction, a heavy yellow gum, which was subsequently confirmed as the desired trityl Valsartan methyl ester product **3.108**. However, we were disappointed upon obtaining the compound only in 9% yield. Optimisation of reaction conditions was subsequently made, focusing particularly on the use of different catalysts, solvent and base systems (table 3.6).

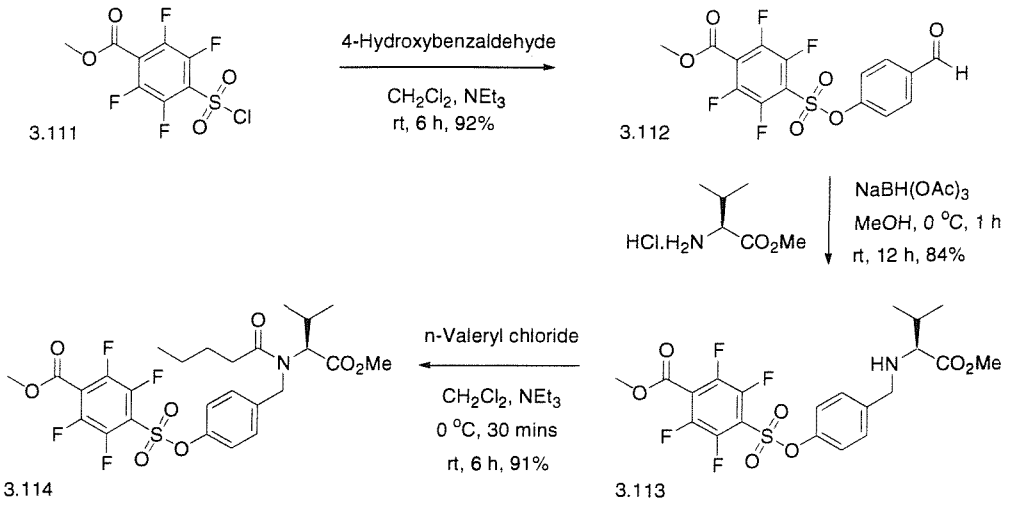
Entry	**Solvent system**	**Catalyst system [mol % Pd]**	**Base [equiv]**	**Temperature (°C)**	**Yield (%)**
1	THF	$Pd(OAc_2/PPh_3$ [5]	K_2CO_3 [3]	70	9
2	THF/DMF	$Pd(OAc_2$/dppf) [5]	$CsCO_3$ [3]	70	13
3	THF/DMF	$PdCl_2$(dppf) [5]	NEt_3 [10]	80	22
4	DME	$PdCl_2$(dppf) [5]	NEt_3 [10]	80	27
5	DME	$PdCl_2$(dppf) [5] + Xphos [10]	NEt_3 [10]	80	39

Table 3.6

Although optimization of this experiment was successful to some extent, the isolated yield of the trityl compound **3.108** remains unimpressive, and at best reached only 39%.

3.3.2.7 Solution-phase optimization studies

In order to evaluate more thoroughly the reasons for low coupling yields obtained on solid-phase, it was decided that a solution-phase synthesis should ensue (scheme 3.35).



Scheme 3.35 Solution-phase preparation of a Valsartan methyl ester coupling precursor

According to literature examples, methyl chlorosulfonyl-2,3,4,5-tetrafluorobenzoate[164] **3.111** was prepared and subsequently reacted with 4-hydroxybenzaldehyde in CH_2Cl_2 in the presence of NEt_3 to give the sulfonate compound **3.112** in 92% yield. Racemisation-free reductive amination[189] of a mixture of the aldehyde and $NaBH(OAc)_3$ was performed in MeOH upon addition of L-valine methyl ester, providing on aqueous workup the 2° amine **3.113** in 84% isolated yield. Acylation of the 2° amine with n-valeryl chloride in the presence of NEt_3 subsequently provided upon isolation, the sulfonate derived amide **3.114** in 91% yield. With the Valsartan precursor in hand, further optimization experiments were performed, focusing around the use of Buchwald's Xphos ligand used in conjunction with a number of different bases and solvent systems. From table 3.7, it can be seen that this coupling reaction seems heavily dependent on the reaction solvent, and would explain why Larson used a mixture of dimethoxymethane and THF for the final coupling reaction of Losartan.[188] However, it is surprising that there should be such a large difference in the reaction yield obtained from reactions conducted in neat THF and neat DME (entries 4 and 5). This might be partially explained by the additional solvatory effect of the bis ether DME, over the monoether THF. Since the best isolated yield obtained on solid-phase and in solution were both under the same reaction conditions, any further attempts at optimization were considered a waste of time.

The solid-phase yield of 39% was considered too low to demonstrate usefulness of the tetrafluoroarylsulfonate linker, and a modified strategy was sought.

Entry	Solvent System [v/v]	Catalyst system [mol % Pd]	Base [mol equiv]	Isolated yield (%)
1	THF/BuOH [3/1]	$Pd(OAc)_2$ [5] / Xphos [10]	$K_3PO_4.H_2O$ [3]	18
2	THF/BuOH [3/1]	$Pd(OAc)_2$ [5] / Xphos [10]	Cs_2CO_3 [3]	22
3	THF/BuOH [3/1]	$Pd(OAc)_2$ [5] / Xphos [10]	NEt_3 [10]	24
4	THF	$Pd(OAc)_2$ [5] / Xphos [10]	NEt_3 [10]	15
5	DME	$Pd(OAc)_2$ [5] / Xphos [10]	NEt_3 [10]	48
6	DME	$PdCl_2(dppf)$ [5] / Xphos [10]	NEt_3 [10]	54

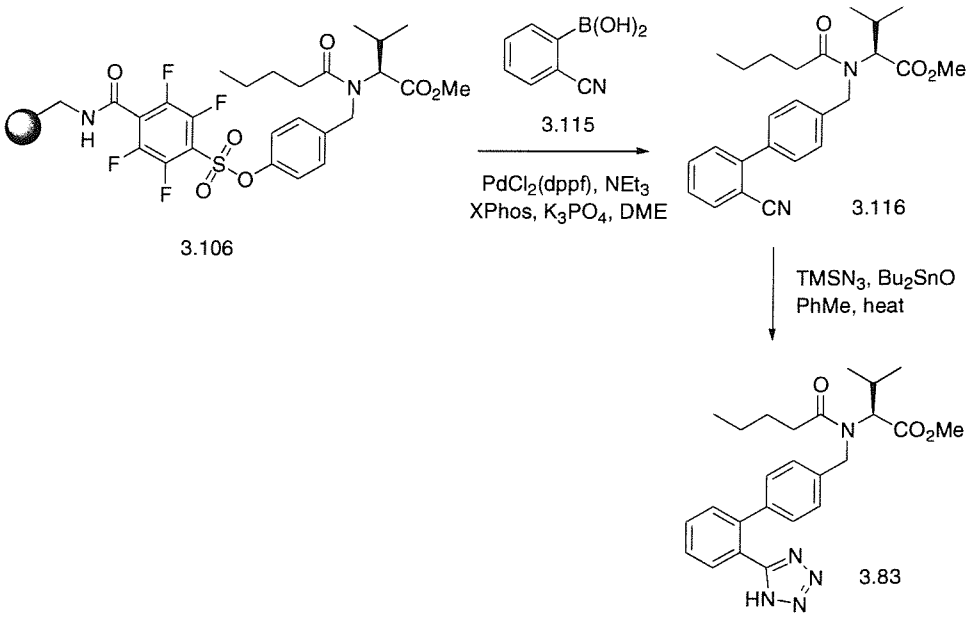
Table 3.7 All reactions were conducted at 80 °C for 18 hours under Ar (g) using degassed solvents. In the case of entries 1 and 2, bases were added to the reaction mixtures as 2.0 mol dm^{-3} solutions in water

De-tritylation of the coupled tetrazolyl compound **3.108**, was performed as described by Larson (scheme 3.33). Tritylvalsartan was added to a dilute solution of H_2SO_4 in acetonitrile/water (1:1 v/v). The resulting colloid was stirred at room temperature for 6 hours, when the substrate appeared consumed by TLC analysis. Isolation of the resulting Valsartan methyl ester **3.83** proved difficult, and it appeared that acidic hydrolysis of the methyl ester had also occurred, giving the highly polar free acid in addition to the de-tritylated tetrazole methyl ester. The mixture was basified with 1.0 mol dm^{-3} NaOH solution to pH 8, when a flocculent precipitate formed. The precipitate, isolated by filtration, was washed with diethyl ether to remove adventitious organic residues. The ^1H NMR spectrum of the solid, which was dried thoroughly *in vacuo* prior to analysis also proved difficult to obtain due to its sparse solubility in a variety of polar solvents. However in comparison to the NMR spectra obtained for the trityl precursor compound, de-tritylation had taken place, and although broad, the spectrum was consistent with that expected for Valsartan. Spectroscopic data have not been reported for Valsartan, hence we were motivated to obtain such information, and sought to prepare Valsartan as the free acid from the sodium salt obtained. Ion-exchange using a strongly acidic silica derivative however proved unfruitful, and no product was obtained. Given that an extra de-tritylation step is still necessary after isolation of the product from the initial solid-phase route, this method was abandoned and coupling of commercially available 2-cyanophenyl boronic acid, followed by cycloaddition of the nitrile group with TMS azide chosen instead (scheme 3.36).

Although this novel route involves an equivalent number of steps, including an undesirable post-coupling cyclisation, we anticipated more facile cross-coupling of this simpler boronic acid given its less hindered nature.

3.3.2.8 Modified solid-phase Suzuki-Miyaura cross-coupling strategy

The modified strategy would now be conducted as given in scheme 3.36.



Scheme 3.36 Modified Suzuki-Miyaura cross-coupling strategy to Valsartan methyl ester

Table 3.8 gives the yields for cross-coupling of 2-cyanophenyl boronic acid with resin bound Valsartan sulfonate precursor over 18 hours under the specified reaction conditions.

Entry	Solvent	Catalyst [mol % Pd]	Base [mol equiv]	Temp (°C)	Yield (%)
1	THF	$PdCl_2$(dppf) [5] + Xphos [10]	NEt_3 [10] + K_3PO_4 [2]	70	25
2	DMF	$PdCl_2$(dppf) [5] + Xphos [10]	NEt_3 [10] + K_3PO_4 [2]	90	31
3	DME	$PdCl_2$(dppf) [5]	NEt_3 [10]	80	37
4	DME	$PdCl_2$(dppf) [5] + Xphos [10]	NEt_3 [10] + K_3PO_4 [2]	80	59

Table 3.8

Entry 4 shows the best result obtained using a combination of $PdCl_2$(dppf) in conjunction with Xphos. Comparison between entries 3 and 4 shows the effect of addition of Xphos to the reaction mixture, and proves its activity with regard to the coupling of aryl sulfonates.

Although the maximum yield of the biarylnitrile **3.116** obtained was only 59%, consideration must be given to the fact that the reaction was performed on solid-phase, and with sterically restricted substrates.

Cycloaddition of $TMSN_3$ to the nitrile Valsartan precursor **3.116** was performed under reaction conditions developed by Wittenberger *et al.* (figure 3.11).[190]

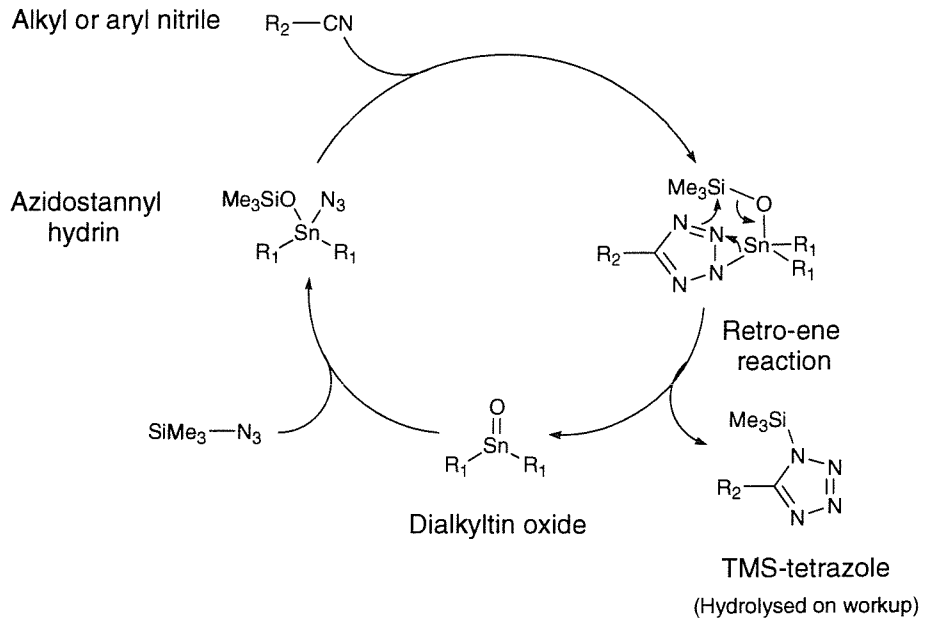


Figure 3.11 Catalytic formation of 5-substituted tetrazoles

Tetrazole formation was performed using 5 molar equivalents of $TMSN_3$ in the presence of 10 mol % dibutyltin oxide in refluxing toluene over 48 hours, when the starting material nitrile methyl ester **3.116** appeared totally consumed by TLC analysis. Valsartan methyl ester **3.83** was isolated as a colourless glass in 87% yield following chromatography on silica. In conclusion we have demonstrated the utility of the tetrafluoroarylsulfonate linker through the synthesis of the pharmaceutically important drug precursor Valsartan methyl ester.

3.4 Conclusions

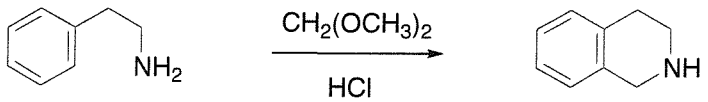
In conclusion we have successfully demonstrated the use of our tetrafluoroarylsulfonate linker for the synthesis of the pharmaceutically important drug compound precursor Valsartan methyl ester. These results have now been published by ourselves.[244]

The *N*-Acyliminium Pictet-Spengler Route to Cialis™

Chapter IV

4.1.1 The protic Pictet-Spengler reaction

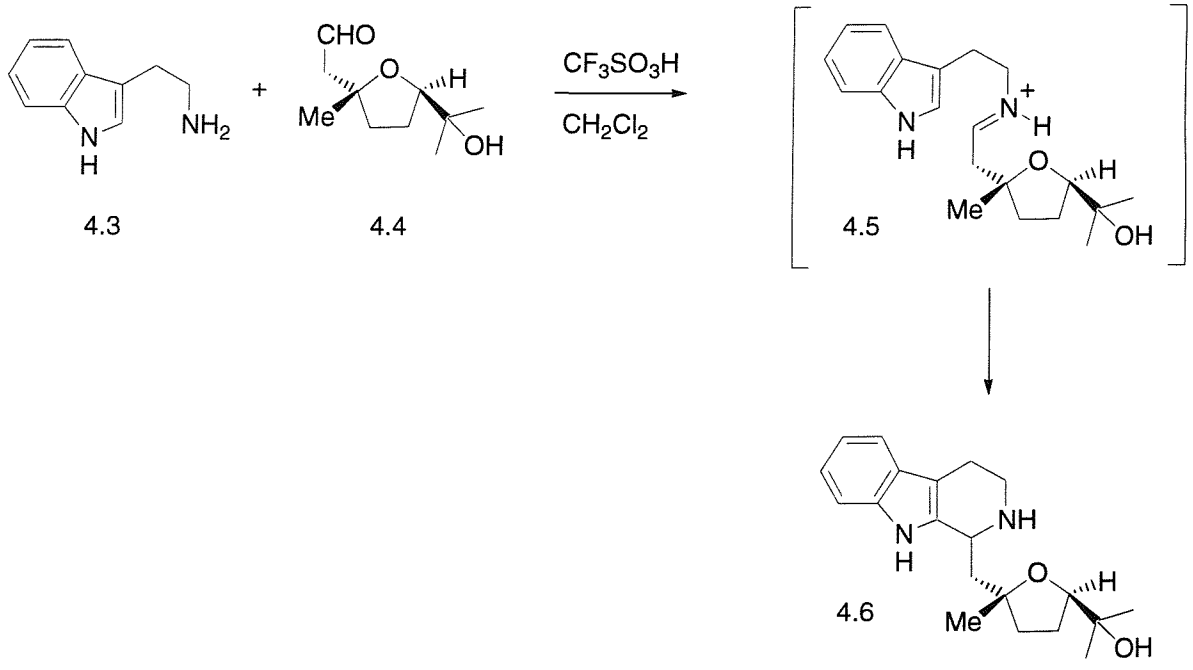
In 1911, researchers Amé Pictet and Theodore Spengler discovered a condensation reaction between phenylethylamine **4.1** and the masked formaldehyde equivalent methylal (dimethoxymethane) and subsequent cyclisation of the imine formed, providing good yields of tetrahydroisoquinoline **4.2** (scheme 4.1).[191] Many excellent reviews discussing all aspects of the Pictet-Spengler reaction have been published at significant intervals since the first reports of the reaction.[192,193,194,195,196]



4.1 4.2

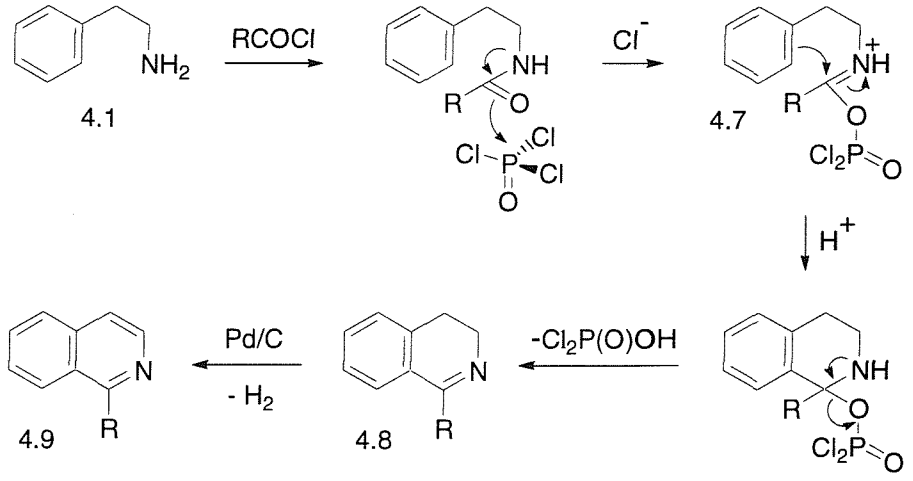
Scheme 4.1 Pictet-Spengler condensation of phenylethylamine and dimethoxymethane

Most commonly, however, the aldehyde compound is used directly, allowing a very wide range of possible substrate combinations. The Pictet-Spengler reaction, as it became known, has since become exploited in the synthesis of a wide range of indole and isoquinoline alkaloids, and has established itself as a powerful means for the total synthesis of natural products and target molecules bearing such motifs. For example, Liang *et al.* demonstrated the utility of the reaction in the synthesis of the naturally occurring compound chrysotricine **4.6** (scheme 4.2).[197]



Scheme 4.2 Liang's synthesis of chrysotricine using the Pictet-Spengler cyclisation

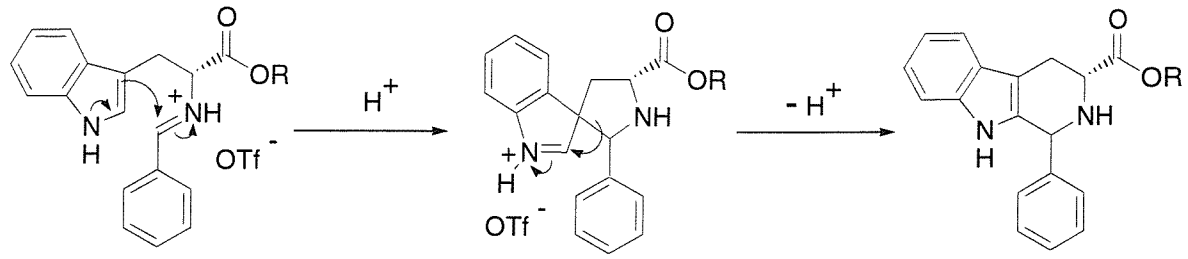
Reaction of tryptamine **4.3** with the tetrahydrofuranyl aldehyde **4.4** in the presence of triflic acid (CF_3SO_3H) produces the intermediate iminium salt **4.5**, which under the low pH of the reaction medium, subsequently undergoes a Friedel-Crafts-type cyclisation generating the tetrahydro-β-carboline product **4.6** in 70% yield. The amino acid tryptophan is also a good substrate for imine formation and Pictet-Spengler reaction as demonstrated by Cook *et al.*[195] Of the general synthetic routes to isoquinoline containing molecules,[198] the Pictet-Spengler reaction is of fundamental importance because of the relatively mild reaction conditions under which it occurs. From a mechanistic perspective, the Pictet-Spengler reaction bears the closest resemblance to the Bischler-Napieralski reaction, first reported in 1893.[199] This reaction involves preparation of an amide from a β-arylethylamine **4.1**, and formation of a highly reactive intermediate iminium-phosphate species **4.7** using a reagent such as phosphorus oxychloride or phosphorus pentoxide.[200,201,202] Cyclisation of this transient species under acidic conditions, results in the elimination of the phosphate moiety, and produces a new unsaturated 6-membered ring. Dehydrogenation of the so-formed dihydroisoquinoline **4.8,** using palladium on charcoal may be performed if the isoquinoline **4.9** is required (scheme 4.3).



Scheme 4.3 Reaction mechanism of the Bischler-Napieralski reaction

During the Pictet-Spengler cyclisation, a different reactive iminium species is generated through protonation (or acylation) of the imine nitrogen atom **4.10**, derived in turn from reaction of a β-arylethylamine and an aldehyde under dehydrating conditions. Trimethyl orthoformate is commonly the reagent of choice regarding imine formation, since its volatility and unreactive side-products (methanol) permit its use in large excess, which does not later complicate purification.[203]

Cyclisation of the aromatic ring onto the electrophilic iminium carbon atom is normally conducted in the presence of a dilute acid source, and occurs through a Mannich type process. However, the Pictet-Spengler reaction does not make use of the excellent leaving group properties of a phosphate ester as does the Bischler-Napieralski reaction, hence activating substituents must be present in the substrate. Structural features enhancing the nucleophilicity of the aromatic nucleus such as heteroatoms, increase the rate of the cyclisation process, and indole derivatives have proven to be very versatile substrates. Hence this route is more atom efficient, avoids the use of hazardous phosphorus reagents and time incurred during extra synthetic steps of the Bischler-Napieralski approach (scheme 4.4).



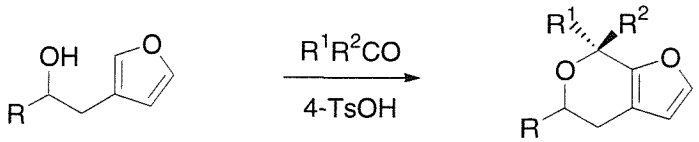
4.10 — Protonation of imine, and cyclisation to spirocyclic intermediate

4.11 — Migration of benzylic carbon, forming fused 6-membered ring system

4.12 — Re-aromatisation of indole system

Scheme 4.4 Reaction mechanism of the protic Pictet-Spengler cyclisation

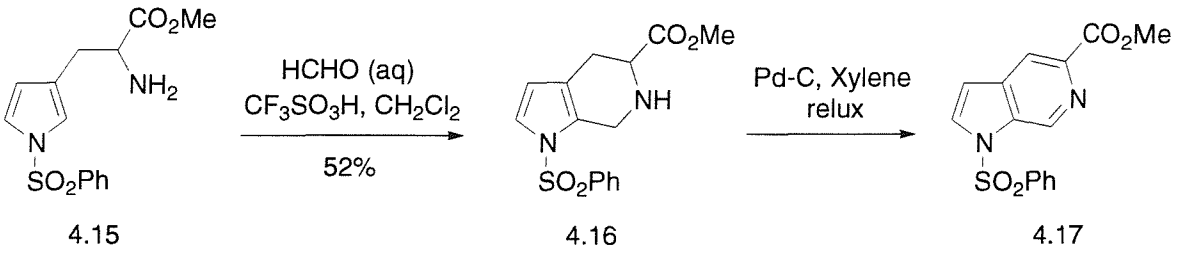
Miles demonstrated an oxa-Pictet-Spengler reaction between 1-(3-furyl)alkan-2-ols **4.13**, and aldehydes or ketones catalysed by 4-toluenesulfonic acid, giving good yields of the corresponding *cis*-5,7-disubstituted 4,5-dihydro-7H-furano[2,3-c]pyrans **4.14** (scheme 4.5).[204]



4.13 4.14

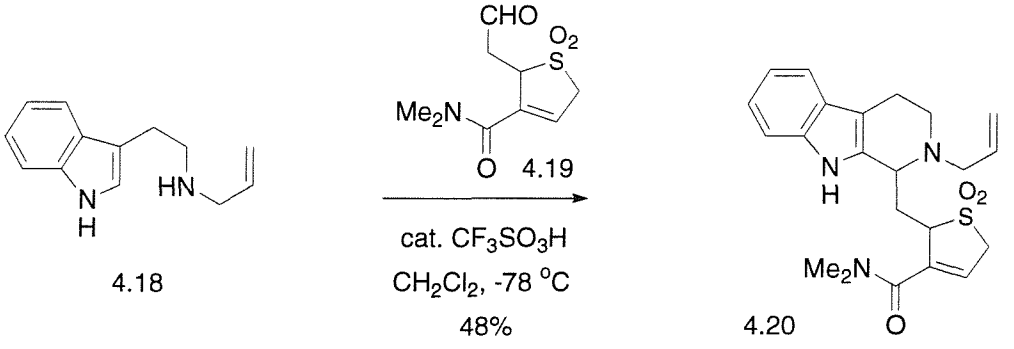
Scheme 4.5 Miles's oxa-Pictet-Spengler route to furano[2,3]pyrans

Dodd more recently demonstrated the Pictet-Spengler cyclisation of an *N*-sulfonylpyrrole derivative **4.15**, with formaldehyde, in the presence of triflic acid (scheme 4.6).[205] Dehydrogenation of the Pictet-Spengler product **4.16**, allows for the preparation of 6-azaindoles **4.17**, which would by other routes be far more difficult to obtain so directly.



Scheme 4.6 Dodd's Pictet-Spengler synthesis using *N*-sulfonylpyrroles

Leonard demonstrated the one-pot Pictet-Spengler cyclisation of allyltryptamine **4.18** and the sulfolane-containing aldehyde **4.19**.[206] Initial attempts were made to effect the cyclisation under the relatively mild conditions of glacial acetic acid in methanol and CH_2Cl_2, although none of the desired product could be isolated. Once again, cyclisation could only be performed under the strongly acidic conditions of triflic acid.[207] However, Leonard was still only able to isolate his desired compound **4.20** in 48% yield (scheme 4.7).

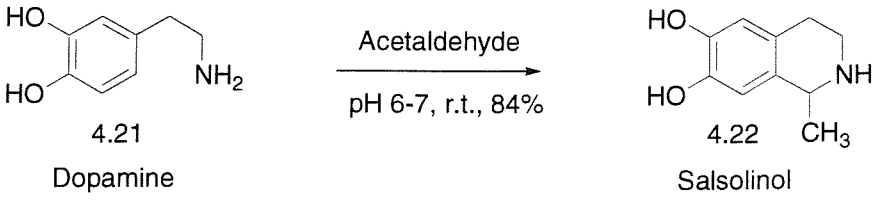


Scheme 4.7 Leonards' synthesis of Diels-Alder precursors of apoyohimbines

4.1.2 The effects of activating substituents on cyclisation conditions

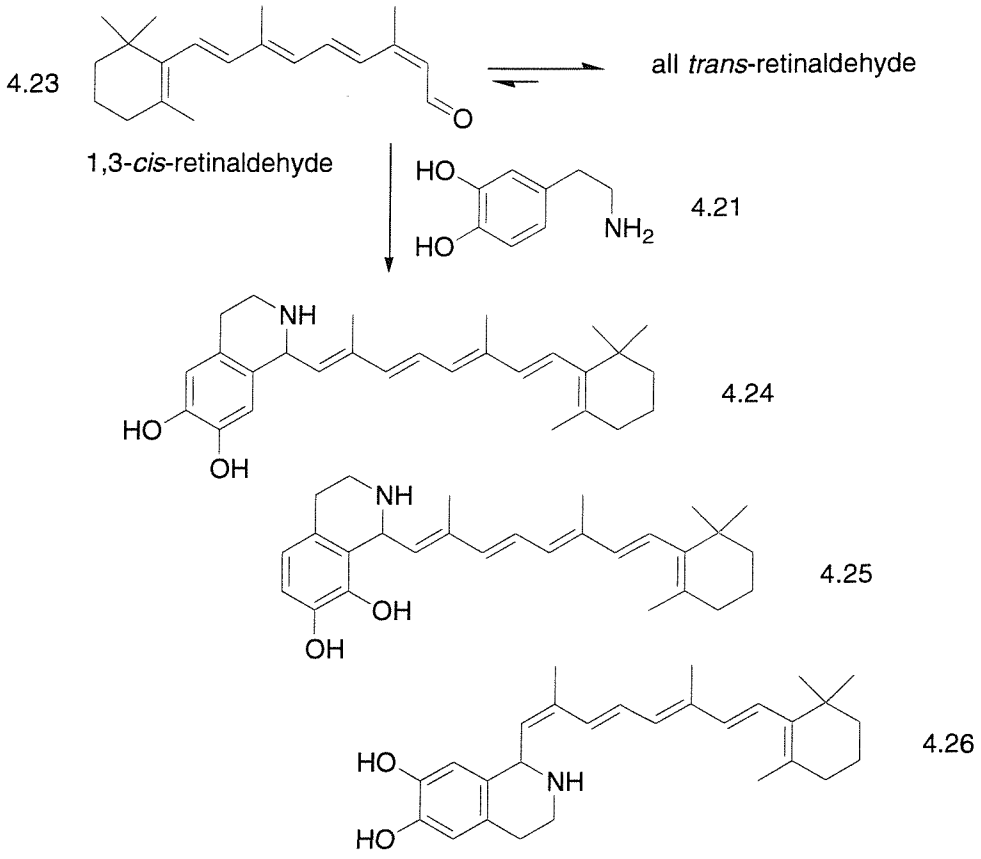
When activating substituents are present on the aromatic ring, Pictet-Spengler cyclisation of its imine becomes more facile, and it is often no longer necessary to employ highly acidic conditions. In 1940, Schöpf and Salzer demonstrated the high yielding Pictet-Spengler cyclisation of the highly activated 3,4-dihydroxyphenylethylamine **4.21** (dopamine) under very mild 'physiological conditions'(scheme 4.8).[208,209]

The product of the reaction **4.22**, is known as salsolinol, and is considered to play an important role as a neurotoxin in the pathomechanism of Parkinson's disease.[210]



Scheme 4.8 Formation of salsolinol from dopamine under very mild reaction conditions

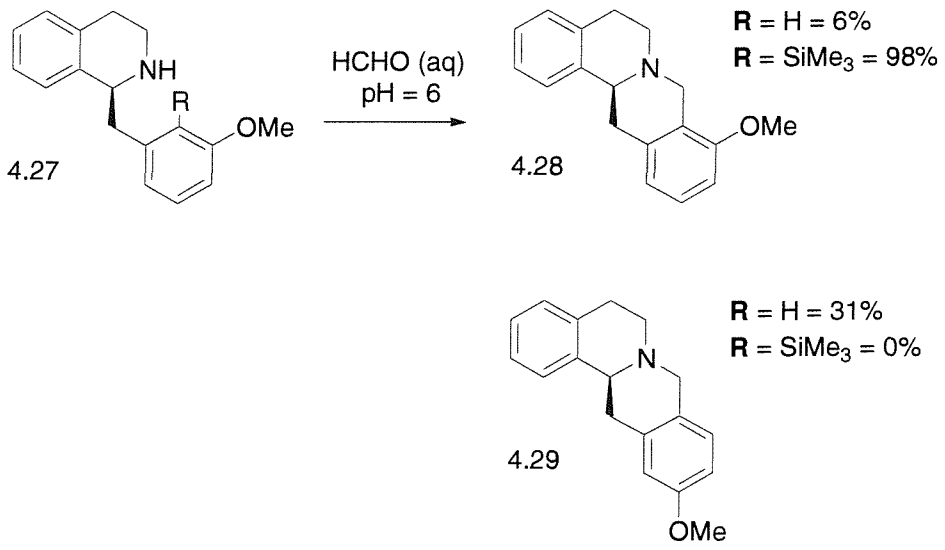
In 2002, Pezzella and Prota demonstrated the formation of novel tetrahydroisoquinoline retinoids **4.24**, **4.25** and **4.26**, by Pictet-Spengler reaction of dopamine **4.21** and 1,3-*cis*-retinaldehyde **4.23** under biologically relevant conditions (scheme 4.9).[211]



Scheme 4.9 Pezzella's synthesis of tetrahydroisoquinoline retinoids

Cyclisation proceeded readily in a reaction mixture developed to mimic biological environments, consisting of 0.1 M phosphate buffer at pH 7.4 and sodium dodecyl sulfate (1-2% w/w). When dopamine **4.21** and 1,3-*cis*-retinaldehyde **4.23** were added to the buffer, the formation of tetrahydroisoquinoline cyclisation products was observed by HPLC within 10 minutes.

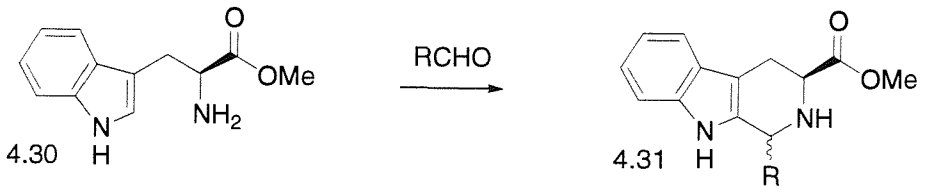
Also in 2002, Schore *et al.* synthesised several naturally occurring protoberberines **4.28** and **4.29**, by means of a silyl-directed Pictet-Spengler reaction. The placement of a trimethylsilyl group in the 2-position of the substrate **4.27**, induces *ipso*-substitution, and in this example, results in an extremely high regioselectivity which in the absence of the TMS group is almost totally absent (scheme 4.10).[212]



Scheme 4.10 Schore's regioselective silyl-directed Pictet-Spengler synthesis

4.1.3 Diastereoselectivity of the Pictet-Spengler cyclisation

Aromatic substrates which bear chiral groups in the pendant arylethylamine chain give rise to *cis*/*trans* isomers upon cyclisation, the distribution of which is dependent on a number of factors including solvent, temperature and pH of the reaction media. When tryptophan methyl ester **4.30** is cyclised with aldehydes in CH_2Cl_2 at 0 °C, the carboxymethyl substituent shows a slight preference for the *cis* isomer. However an identical reaction conducted in refluxing benzene produces slightly more of the *trans* product (scheme 4.11). This outcome is noted as being a thermal effect rather than one of solvent, and higher *cis* selectivity is generally observed at lower temperatures.



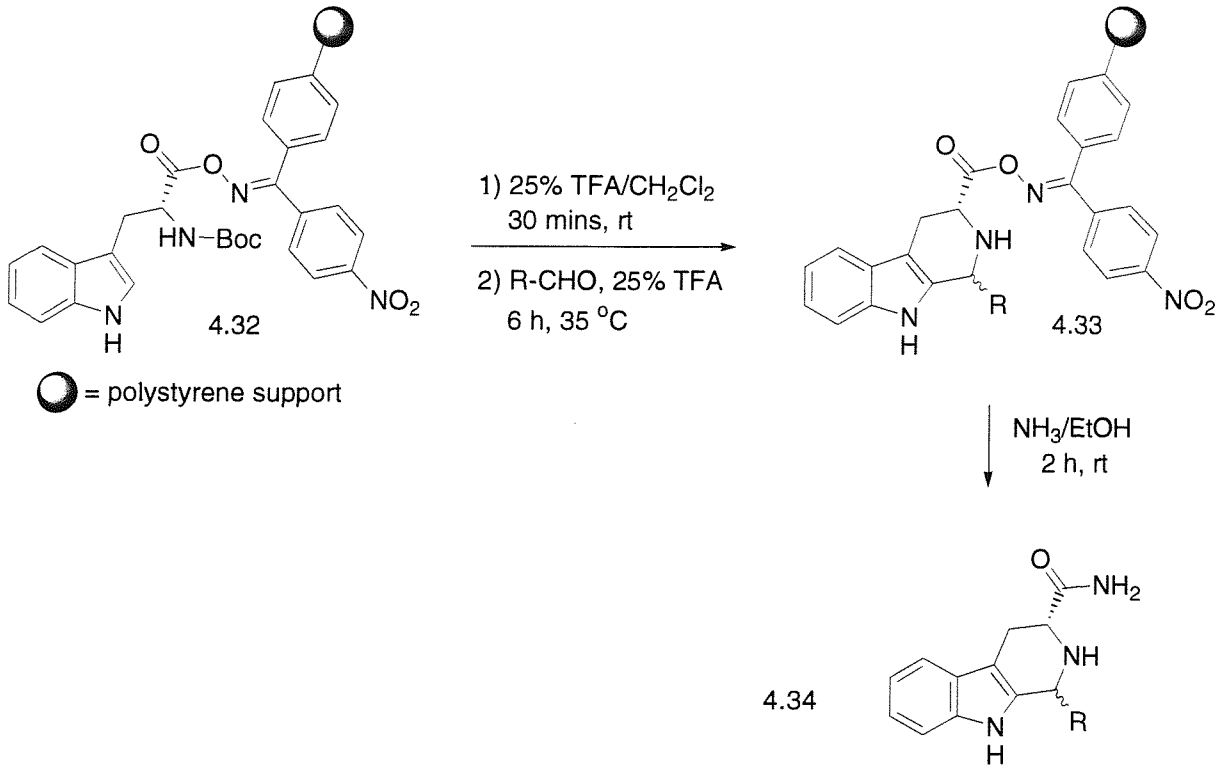
R	Solvent	Temperature °C	cis/trans	% Product
Ph	CH_2Cl_2	0	82:18	74
	PhH	reflux	37:63	76
C_6H_{11}	CH_2Cl_2	0	71:29	71
	PhH	reflux	59:41	85
$MeCH_2CH_2$	CH_2Cl_2	0	80:20	72
	PhH	reflux	47:53	88
Me_2CHCH_2	CH_2Cl_2	0	83:17	82
	PhH	reflux	43:57	76

Scheme 4.11 Effect of temperature on the diastereoselectivity of Pictet-Spengler cyclisation

These reactions were carried out without deliberate addition of acid catalysts, although it is possible that trace amounts of acid were present. In the absence of the carboxymethyl group, the analogous reaction of tryptamine with these aldehydes, produces imines which are far less electrophilic and hence far less reactive. These imines do not tend to undergo Pictet-Spengler cyclisation in non-acidic aprotic reaction media, and addition of acid must be made to increase the electrophilicity of the iminium species and induce cyclisation. The lower pKa of tryptophan methyl ester (pKa = 7.29) relative to that of tryptamine (pKa = 10.2) results in the formation of a far more reactive iminium species through condensation of tryptophan methyl ester with aldehydes, since electron density on the nitrogen atom is lowered through the inductive effect of the carboxymethyl substituent.[195,213]

4.1.4 Solid-phase Pictet-Spengler reactions

In 1980, Kaiser and DeGrado demonstrated the use of polymer-bound oxime esters for a range of different peptide synthesis applications.[214] The rapid parallel synthesis of 1,2,3,4-tetrahydro-ß-carboline (THBC) compounds, e.g. **4.34**, by Pictet-Spengler cyclisation of tryptophan substituted oxime resin **4.32**, was published in 1996 by Mohan *et al.*[215] Boc-tryptophan was immobilised on the oxime linked support using standard coupling conditions (DIC). Removal of the tryptophan Boc group using TFA, and reaction of the free amine with a series of aldehydes under protic conditions yielded supported carbolines **4.33**. THBC derivatives **4.34**, were cleaved from the washed support using a saturated solution of ammonia in ethanol for 2 hours, producing typical product purities of 80% (scheme 4.12).[215]



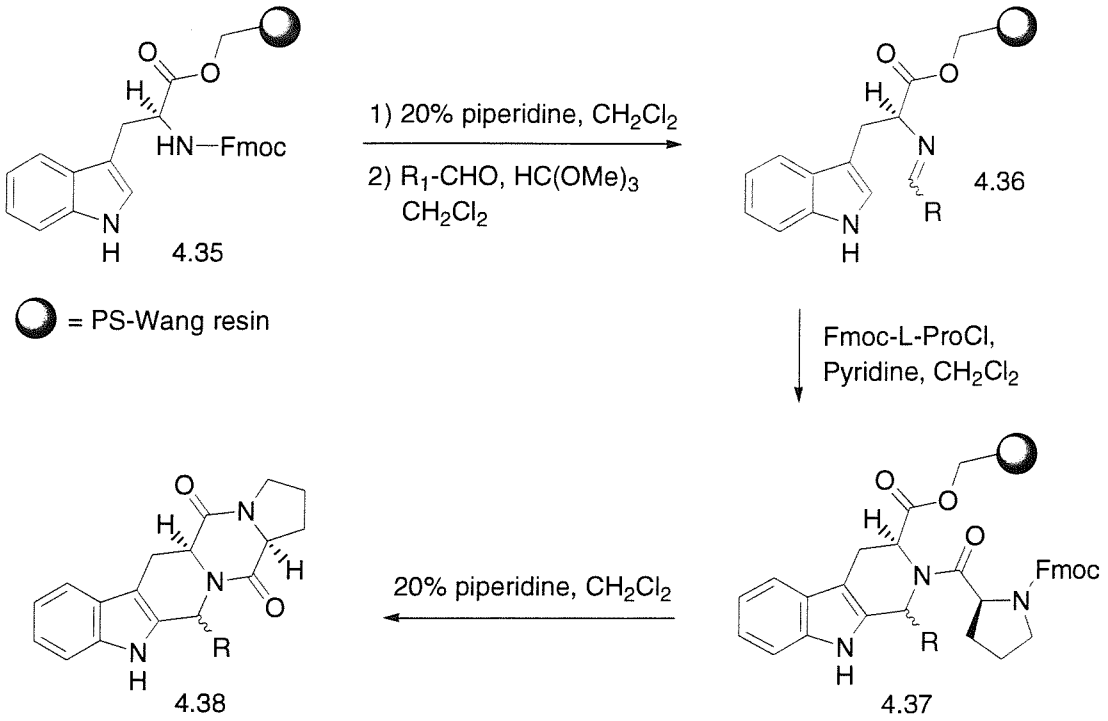
Scheme 4.12 Synthesis of 1,2,3,4-tetrahydro-ß-carbolines using a supported oxime linker

Such THBC derivatives were further shown to exhibit interesting pharmacological properties and are useful substrates for further elaboration by reaction with acid chlorides, sulfonyl chlorides and isocyanates.

4.1.5 Solid-phase *N*-Acyliminium Pictet-Spengler cyclisation

Using an alternative approach to the classic protic Pictet-Spengler reaction conditions, Ganesan and Wang demonstrated the high-yielding solid-phase synthesis of demethoxyfumitremorgin C analogues **4.38**, using an *N*-Acyliminium method.[216] In contrast to the acid-mediated mechanism which involves formation of an electrophilic iminium cation through imine protonation, the *N*-Acyliminium route generates a similarly reactive intermediate via acylation of the imine **4.36**. This method then, adds a further degree of complexity to the products of cyclisation, providing a more powerful synthetic tool.

The transient *N*-Acyliminium species is generated, by reaction of immobilised Fmoc-deprotected tryptophan derivative **4.35**. Subsequent reaction with various aldehydes under dehydrating conditions, generates the imine, which undergoes Pictet-Spengler cyclisation upon treatment with Fmoc-amino acid chlorides, resulting in a mixture of supported *cis* and *trans*-tetrahydro-β-carbolines **4.37**.



Scheme 4.13 Ganesan's solid-phase *N*-Acyliminium Pictet-Spengler synthesis of demethoxyfumitremorgin analogues

Fmoc deprotection using piperidine/CH_2Cl_2 results in a second concomitant cyclisation, giving rise to a new diketopiperazine ring through cyclative cleavage from the support (scheme 4.13). Synthesis of demethoxyfumitremorgin analogues in this manner is more concise than by separate protic-Pictet-Spengler/acylation operations, and since the *N*-Acyliminium route avoids the use of acidic reaction media, greater functional group tolerance can be expected. Furthermore, the increased electrophilicity of the *N*-Acyliminium species over an iminium salt, allows for the use of more unreactive aldehydes.

4.1.6 Stereochemistry of 1,3-disubstituted tetrahydro-β-carbolines

The formation of *cis* and *trans*-isomeric carbolines through Pictet-Spengler condensation of tryptophan esters and aldehydes in aprotic reaction media has led to the requirement of simple and reliable methods for isomeric identification. Brossi *et al.* proved circular dichroism as a useful assignment technique, however absolutely pure compounds must be used, and given that in many cases *cis* and *trans* isomers are not entirely separable, this method has not become general.[217]

The most reliable method for isomer identification involves careful interpretation of NMR spectra. However, proton spectra are often complicated by overlapping *C*1 signals (refer to figure 4.1).

The greater shift range of ^{13}C NMR spectra allows accurate interpretation of diastereoisomer mixtures, and single isomers can be identified given the characteristic *C*1 and *C*3 signal shifts.[218] Wenkert *et al.* published experimental data for several yohimbinoid and ajmalicinoid alkaloids, isomers of which were identified using ^{13}C NMR.[219] Further studies, extending the limits of ^{13}C NMR assignment were made by Sandrin *et al.* regarding the compression effect observed in ^{13}C NMR spectra of tetrahydro-β-carbolines. These studies now allow one to unequivocally assign the stereochemistry of two individual isomers using 1-dimensional NMR techniques in all but the most complex examples.[220,221] Figure 4.1 gives a conformational depiction of the two possible twist chair structures for both the *cis* and *trans* isomers from Pictet-Spengler cyclisation of tryptophan methyl ester imines. Considering the *trans* isomer, structure A should represent the more stable conformer, since B suffers a 1,4-gauche interaction between the hydrogen atom at *C*1 and the carboxymethyl substituent at *C*3. Furthermore it can be seen that conformer B also suffers from 1,2-A strain, between the indole NH and the equatorial R_1 phenyl substituent on *C*1. Conformer A is devoid of these unfavourable interactions and represents the more stable structure which would be expected to be observed through NMR spectroscopy.

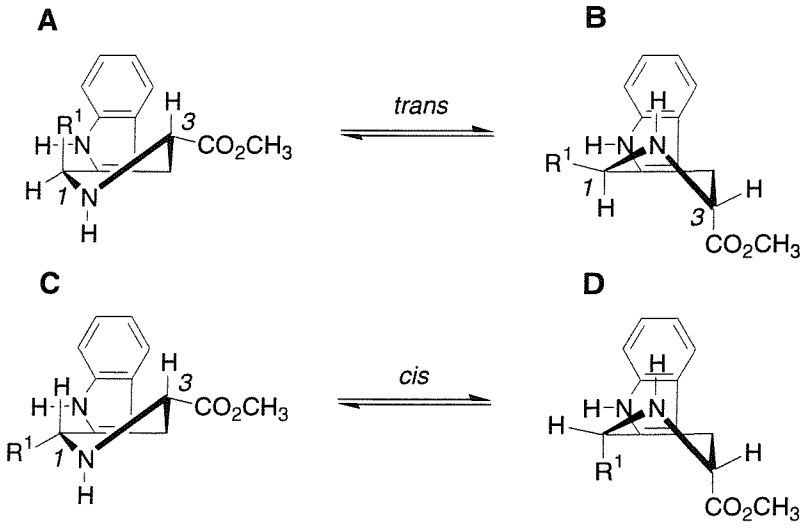


Figure 4.1 Conformational analysis of *cis* and *trans* isomers of β-carbolines from Pictet-Spengler cyclisation of tryptophan methyl ester imines

Similar analysis of the *cis* isomer leads to the conclusion that structure C should be more thermodynamically stable than structure D. There is a large 1,4-gauche interaction between the phenyl substituent on *C*1 and the carboxymethyl group; conformer C is without this ^{13}C-γ gauche effect. ^{13}C NMR reveals that carbon atoms *C*1 and *C*3 of the *trans* isomer (with a ^{13}C-γ gauche interaction) appear at a higher field than respective signals of the *cis* structure.

4.1.7 *N*-Acyliminium Pictet-Spengler formation of the tetrahydro-β-carboline compound Cialis™

The tetracyclic diketopiperazine compound Cialis™ **4.39** (figure 4.2) is of commercial importance, since *in vitro* studies indicate that the *R*, *R*-diastereoisomer is a potent inhibitor of cGMP-specific phosphodiesterase PDE5. PDE5 has been identified as the target of the well-known drug Sildenafil citrate (Viagra™). It is a multi-domain protein, which appears to be regulated primarily by phosphorylation as well as the binding of cGMP to allosteric sites at the *N*-terminus. PDE5 inhibitors have recently received attention as potential treatments for penile erectile dysfunction,[222] and Cialis™, the patent for which is owned by Lilly Icos Llc, is currently in clinical trials as a competitor compound for the same indication.

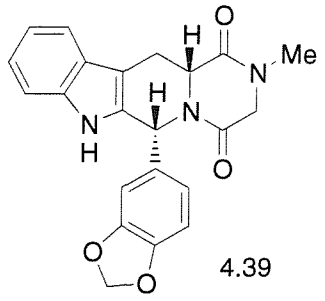


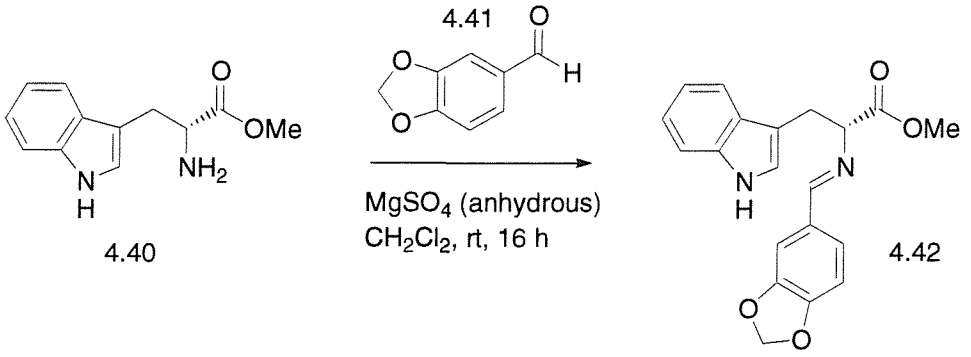
Figure 4.2 The structure of the PDE5 inhibitor Cialis™

It is believed that the Lilly route involves an acid-catalysed Pictet-Spengler reaction of D-tryptophan methyl ester **4.40**, followed by acylation of the tricyclic intermediate and base-mediated cyclisation to give the final tetrahydro-β-carboline **4.39**.[223] However, if the Pictet-Spengler reaction is carried out in an aprotic solvent and under mildly basic conditions, the mechanistic pathway is somewhat different, and an *N*-Acyliminium reaction ensues.[224,225,226] Recently we have investigated this alternative pathway towards Cialis™, utilising the *N*-Acyliminium Pictet-Spengler method. Optimisation of reaction conditions has led to an efficient route to this compound, which may be of commercial importance.

4.2 Results and Discussion

Scheme 4.14 details the preparation of the required imine formed through reaction of D-tryptophan methyl ester **4.40**, and piperonal **4.41**, using either trimethyl orthoformate or anhydrous magnesium sulfate as a dehydrating agent. Preliminary studies were however, conducted using the less expensive L-tryptophan methyl ester enantiomer.

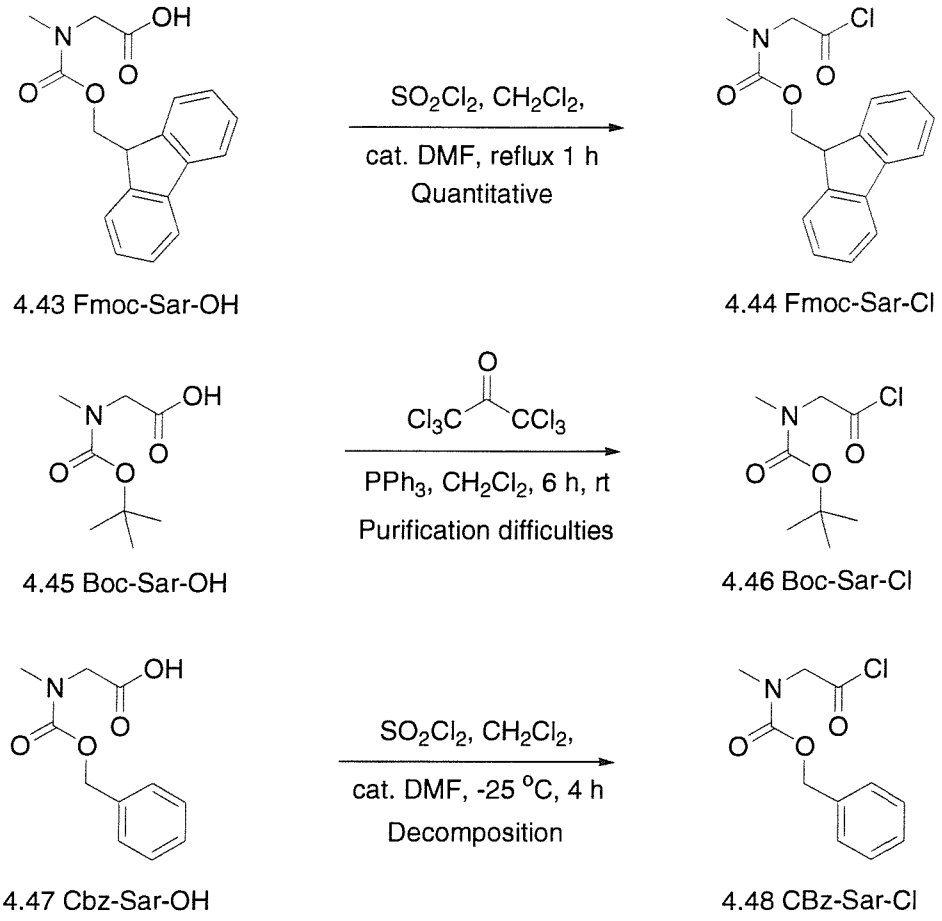
D-tryptophan methyl ester was used only in the final preparation of the biologically active *R*, *R*-diastereoisomer. Formation of the imine **4.42** was found to progress to completion cleanly and rapidly at room temperature in dichloromethane. Removal of magnesium sulfate by filtration is trivial, and favored over the removal of excess orthoformate under high vacuum; hence the reagent of choice is $MgSO_4$.[227] The imine so formed is remarkably stable to air and moisture, and recrystallisation from CH_2Cl_2/hexane (10% v/v) leads to a very pure product with seemingly no hydrolysis observed.



Scheme 4.14 Formation of a Schiff-base from D-tryptophan methyl ester and piperonal

N-Acyliminium Pictet-Spengler reactions were primarily carried out using 3 different *N*-protected sarcosine derivatives, the Fmoc-, Boc-, and Cbz- free acids, all available commercially. Attempted conversion of the free acids to the acyl chlorides was undertaken, however, satisfactory procedures were not found for Cbz and Boc sarcosine compounds (scheme 4.15).

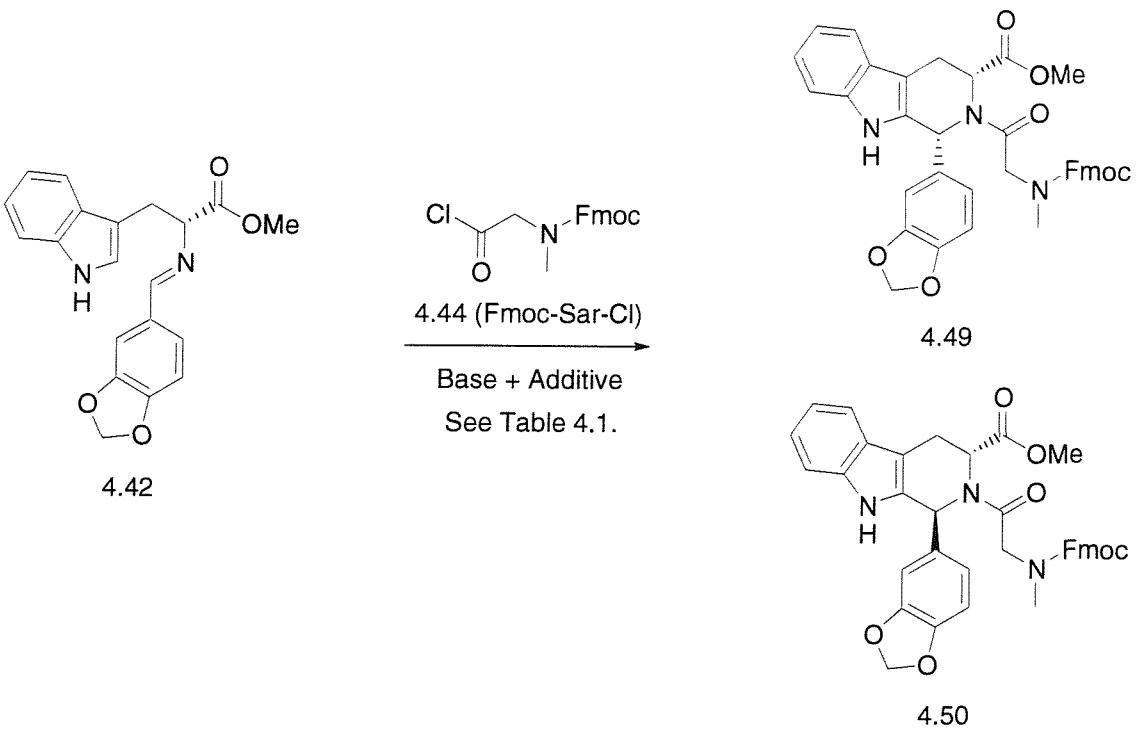
In order that the Boc sarcosine acid chloride be prepared, neutral reaction conditions were sought to avoid *in situ* deprotection. Conditions developed by Villeneuve[228] involving the use of hexachloroacetone and triphenylphosphine gave rise to the desired product, although isolation from triphenylphosphine oxide proved difficult. Subsequent use of impure material in Pictet-Spengler reactions returned only hydrolysed starting materials after workup. In an attempt to free the reaction product from phosphine impurities, Polymer-supported triphenylphosphine was used with limited success. Formation of the acid chloride was successful, as shown by *in situ* conversion to the amide by reaction with benzylamine (88% isolated yield). However, reaction under the *N*-Acyliminium Pictet-Spengler conditions failed persistently. Reaction studies were continued, omitting the Boc-Sar-Cl from further consideration as a substrate.



Scheme 4.15 Attempted preparation of 3 different *N*-protected sarcosine acid chlorides

Reaction of the Fmoc-Sar-OH with oxalyl chloride in CH_2Cl_2 led only to degradation products even after careful workup under moisture-free conditions. More vigorous reaction conditions using excess thionyl chloride[229] (catalytic DMF) produced quantitatively a clean crystalline acid chloride that was rendered free from traces of thionyl chloride by trituration with pentanes (scheme 4.15).

Preparation of the Cbz-Sar-Cl was attempted similarly using an excess of freshly distilled thionyl chloride in anhydrous CH_2Cl_2. The reaction was maintained between -10 and -25 °C over 4 hours, since the mixture darkened rapidly at room temperature. Even at low temperature, a clean sample of the Cbz-Sar-Cl was not obtained, and isolated product appeared to derive from acid-catalysed deprotection of the Cbz function. The use of both Boc- and Cbz-sarcosine acid chlorides was not investigated further, and attention was turned towards the use of the Fmoc-protected sarcosine compound. Fmoc-sarcosine acid chloride was found to undergo the Pictet-Spengler reaction producing the expected diastereomeric mixture of intermediates in each case (scheme 4.16).



Scheme 4.16 *N*-Acyliminium Pictet-Spengler cyclisation of imine **4.42** using Fmoc-Sar-Cl

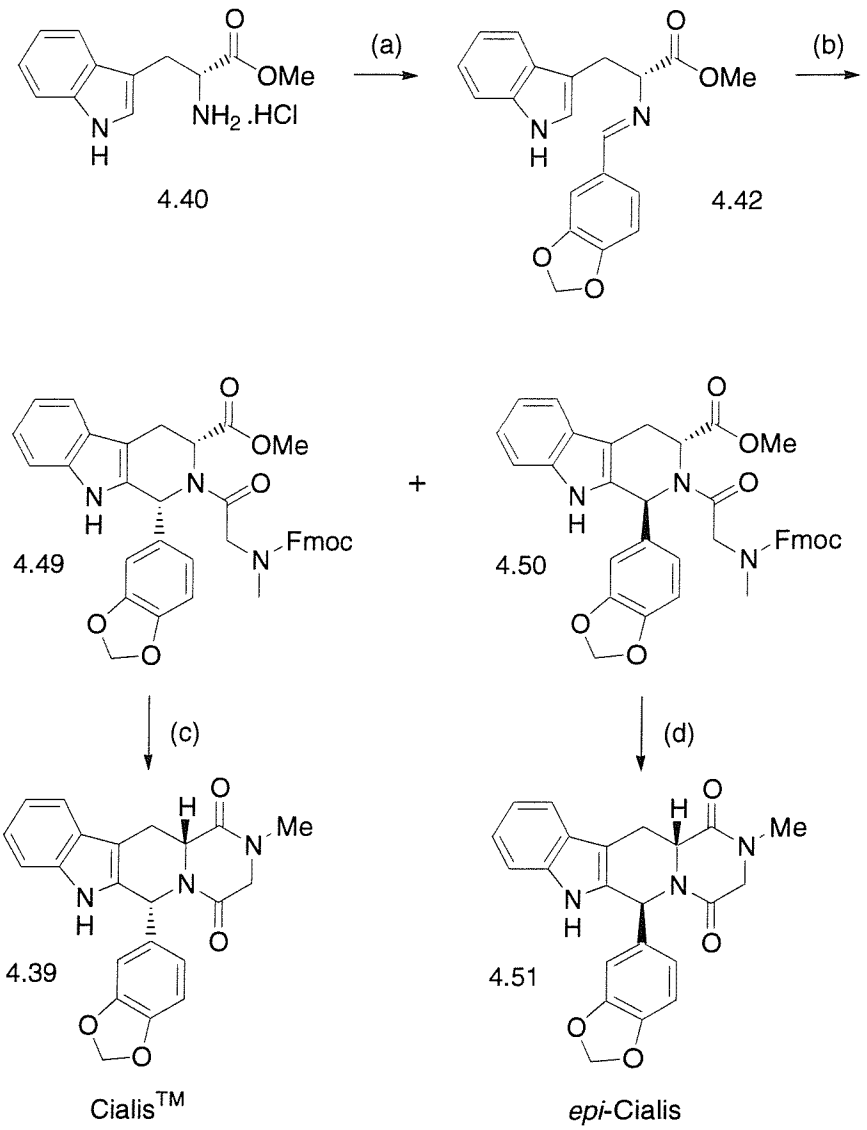
A series of reactions was conducted using 3 mol equiv of the Fmoc-sarcosine acid chloride and several different combinations of bases and additives, relative to 1 mol equiv of the D-tryptophan piperonyl imine (Table 4.1).

Base	**Additives**	**Yield of 4.49 + 4.50 (%)**	***Cis* : *Trans***
3 mol equiv DMAP	None	59	1:1
1 mol equiv K_2CO_3	1 mol equiv basic Al_2O_3	49	1.1:1
10 mol % DMAP	3 mol equiv basic Al_2O_3	62	1.1:1
None	2 mol equiv basic Al_2O_3	50	1:1
None	2 mol equiv basic Al_2O_3 + 3 mol % BF_3.OEt	52	1:1
4 mol equiv Lutidine	None	Failed	N/A

Table 4.1.

The reaction introduces a second stereocentre in the benzylic position, and it is the *cis* isomer (*R*, *R*) **4.49** which is therefore the desired reaction product in the synthesis of **4.39**. Cyclisation using Fmoc-Sar-Cl **4.44** under this range of conditions, produced the desired tetrahydro-β-carbolines **4.49** and **4.50** in between 0% and 62%. The use of 2,6-lutidine was found to be totally inadequate, and no product was isolated from the reaction.

The best combination of base and additive, was that using 10 mol % of DMAP and 3 mol equivalents of basic alumina (relative to the imine). These reaction conditions also produced the most favourable 1.1:1 distribution of *cis:trans* isomers after chromatography. In both examples (L and D tryptophan), it is the *cis* isomer which is the less polar of the two as indicated by TLC *Rf* values. However, upon cyclisation to the diketopiperazines **4.39** and **4.51**, the *cis* isomer becomes more polar than the *trans*. Deprotection of the Fmoc group of **4.49** and **4.50** was accomplished with piperidine/DMF (20 % v/v) to afford the corresponding product of spontaneous cyclisation, i.e. the (*R*, *R*) **4.39** or (*R*, *S*) **4.51** diastereoisomers (scheme 4.17).

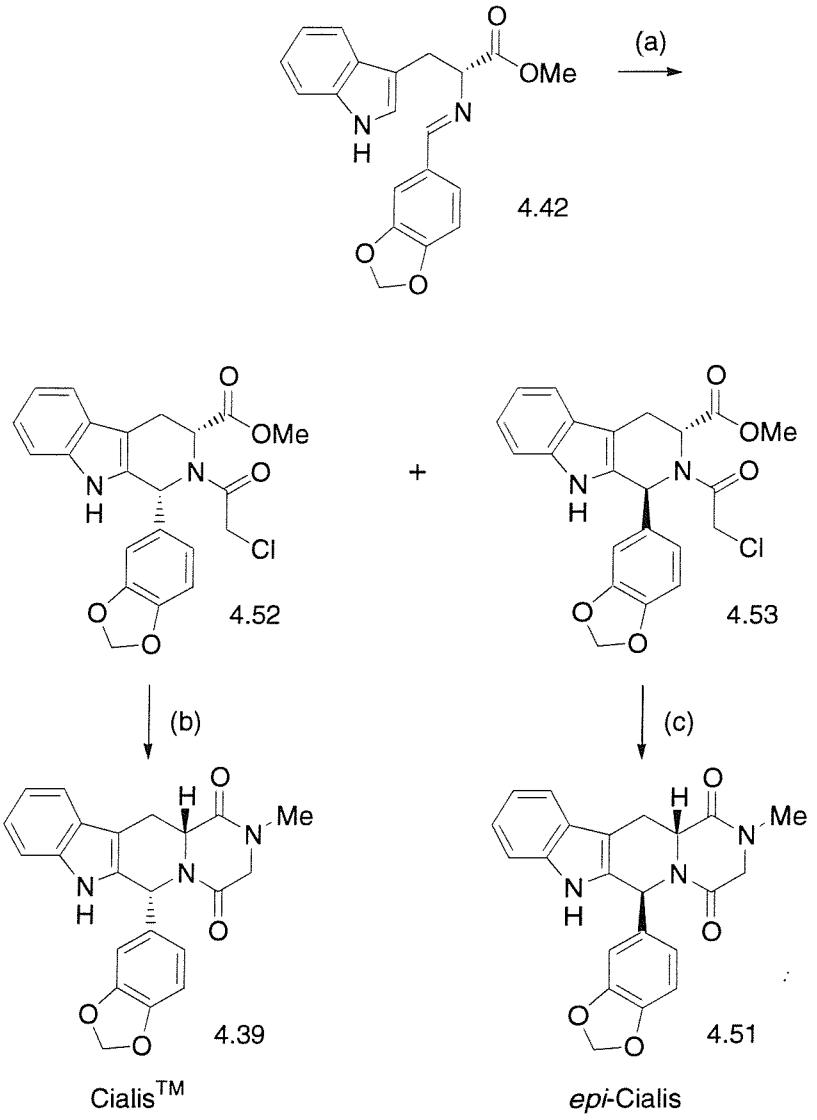


Scheme 4.17 First generation *N*-Acyliminium Pictet-Spengler route to Cialis™

Conditions (a) 1.05 equiv piperonal, 1.01 equiv NEt_3, 5 equiv $MgSO_4$, CH_2Cl_2, 24 h (95%); (b) 3 equiv Fmoc-Sar-Cl, 0.1 equiv DMAP, 3 equiv basic alumina, CH_2Cl_2, -25 °C to rt, 2 h (62%, 1.1:1 *cis/trans*); (c) 20% piperidine/DMF, rt, 1 h (92%); (d) 20% piperidine/DMF, 50 °C, 24 h (86%).

It was noted however that while Fmoc deprotection of the *cis* product **4.49** was rapid and clean (92%, 1 hour), the *trans* compound **4.50** was less readily cyclised and the reaction did not proceed well without heating to 50 °C over 24 hours. The *N*-protected sarcosine derivatives used in our initial studies are by far the most expensive reagents used in the synthesis.

We subsequently noted that the use of chloroacetyl chloride as the *N*-acylating component avoids the use of protecting groups altogether, and is a more cost efficient route to Cialis™. Scheme 4.18 details the synthesis using chloroacetyl chloride under conditions of basic catalysis.



Scheme 4.18 Second generation N-Acyliminium Pictet-Spengler route to Cialis™

Conditions (a) 3 equiv $ClCOCH_2Cl$, 3 equiv DMAP, CH_2Cl_2, 2 h (78%, 1.3:1 *cis/trans*); (b) $MeNH_2$, MeOH, 50 °C, 16 h (92%); (c) $MeNH_2$, MeOH, 50 °C, 24 h (89%).

Table 4.2 shows the results of experiments performed using 3 mol equiv of chloroacetyl chloride relative to 1 mol equiv of the D-tryptophan imine **4.42** using the additives indicated. From these experiments we can see that yields of both chloroacetyl tetrahydro-β-carboline isomers **4.52** and **4.53** are higher than those obtained when using the sarcosine derivatives. These diastereoisomers are readily separable by chromatography; the greatest separation in *Rf* values was obtained when using neutral deactivated alumina.

Base	Additives	Yield %	*Cis* : *Trans*
3 mol equiv DMAP	None	78	1.3:1
None	3 mol equiv basic Al_2O_3	69	1.1:1
10 mol % DMAP	3 mol equiv Al_2O_3	72	1:1

Table 4.2.

Cyclisation to the corresponding diketopiperazine products Cialis™ **4.39**, and *epi*-Cialis **4.51** was performed by heating the respective chloroacetyl tetrahydro-β-carbolines with a solution of methylamine in MeOH at 50 °C. In common with the Fmoc-derivatives **4.49** and **4.50**, cyclisation of the *cis*-compound **4.52** was more rapid than for the *trans*-compound **4.53** (16 hours for the *cis*-compound, 24 hours for the *trans*-compound). The reaction products were isolated in high yield by silica chromatography, with the previously noted changeover in polarity between the *cis* and *trans* isomers. Pure compounds were obtained by recrystallisation from analytical ethanol, and the geometry of the *cis* isomer was confirmed by a Nuclear Overhauser enhancement ^{1}H NMR experiment. The *cis* isomer demonstrated an enhancement between the two irradiated *cis* protons, while the *trans* material gave no such enhancement.[230]

4.3 Further studies of the *N*-Acyliminium Pictet-Spengler reaction

Attempts were also made to investigate the use of acylating reagents other than acid chlorides; benzoyl derivatives were chosen (table 4.3). Each experiment was performed using 3 mol equiv of DMAP and 2 mol equiv of the appropriate acyl compound to ensure that the reaction medium remained basic throughout. Reactions were conducted in anhydrous CH_2Cl_2 and stirred overnight at room temperature under nitrogen.

Acid chloride X	Yield %
Benzoyl Fluoride	**0**
Benzoyl Chloride	**68**
Benzoyl Bromide	**19**
Benzoyl Cyanide	**0**

Table 4.3.

The only reaction that proceeded to any extent other than the chloride control experiment, was that involving the use of benzoyl bromide. However there appears to be a very large difference in the reactivity of acid bromides and chlorides.

Benzoyl fluoride and benzoyl cyanide failed to react at all, and no product was isolated in these cases. Also of interest with regard to the acyliminium Pictet-Spengler reaction is the use of active ester intermediates formed initially by reaction of an acid and coupling reagent plus a co-catalyst. We investigated modifications to the reaction using benzoic acid, and a number of different reagents commonly used in peptide coupling reactions, (Table 4.4).

Coupling Reagent	Co-catalyst	Yield (%)
CDI	**None**	**0**
DCC	**PFP + DMAP**	**0**
DIC	**HOBt + DMAP**	**0**
MSNT	**None**	**0**
PyBOP	**None**	**0**

Table 4.4.

Disappointingly however, none of the reactions conducted produced any isolable product, and only the imine and its products of hydrolysis were isolated after each reaction.

4.4 Conclusions

In summary, the *N*-Acyliminium Pictet-Spengler reaction is readily adaptable to the synthesis of Cialis™ **4.39**. The previously published Icos route takes 5 days for the acid-catalysed Pictet-Spengler reaction of D-tryptophan methyl ester and piperonal, followed by an acylation reaction.

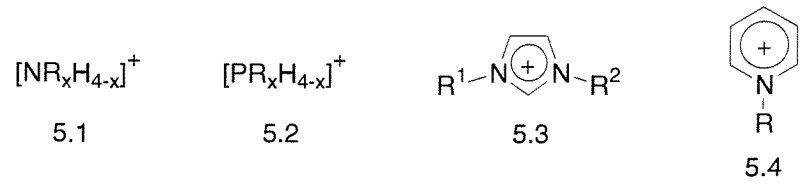
In our sequence, the imine **4.42** is formed overnight, and the subsequent cyclisation reaction combines the Pictet-Spengler and acylation steps in only 2 hours. Of particular interest is the finding that chloroacetyl chloride is a good acylating reagent for the *N*-Acyliminium Pictet-Spengler reactions, as the halide functionality lends itself to further transformations of the resulting tetrahydro-β-carboline products. These results have now been published by ourselves.[245]

Ionic Liquid Acceleration of Solid-Phase Suzuki-Miyaura Cross-Coupling Reactions

Chapter V

5.1 Introduction to Ionic Liquids

Room temperature ionic liquids are fluid materials consisting solely of ions, and are usually salts of quaternary ammonium species. Unlike conventional ionic compounds, organic ionic liquids (OIL's) comprise charged organic species with poorly coordinating and often bulky asymmetric counterions.



5.1 5.2 5.3 5.4

Figure 5.1 Four commonly encountered cationic species employed as ionic liquids

The most common salts used as ionic liquids may be broadly classified into one of four different structural groups (figure 5.1). Collectively these classes embrace *N*-alkylammonium **5.1**, *N*-alkylphosphonium **5.2**, *N,N*-dialkylimidazolium **5.3** and *N*-alkylpyridinium **5.4** cations. Although there is significant order in the fluid state of these materials, the steric demands of the ion-pairs prevents regular packing into stable lattices. As a result, the melting points of such substances are often below room temperature, permitting the use of ionic liquids as solvents for many reactions. The potential for OIL's to become new, more environmentally friendly 'green' replacements for conventional solvents, many of which are toxic, flammable and ozone depleting has become an exciting and heavily researched area of modern chemistry, especially with regard to catalysis.[1,2,3] The ionic nature of these materials often results in modified chemical selectivity and reactivity when compared to reactions performed in conventional solvents. Supporting their use in this area is the wide temperature range over which OIL's are fluid (>300 °C), and their almost insignificant vapour pressure over this range. This thermal stability, and lack of volatile organic components, coupled with good solubility properties allows the employment of small reactor volumes, and high concentrations of reactive solutes.

The largest class of ionic liquids is based around the 1*N*-alkyl-3*N*-methylimidazolium [mim] cation **5.3**, in conjunction with weakly nucleophilic anions such as [BF_4^-], [PF_6^-], [$CF_3CO_2^-$] or [$CF_3SO_3^-$].

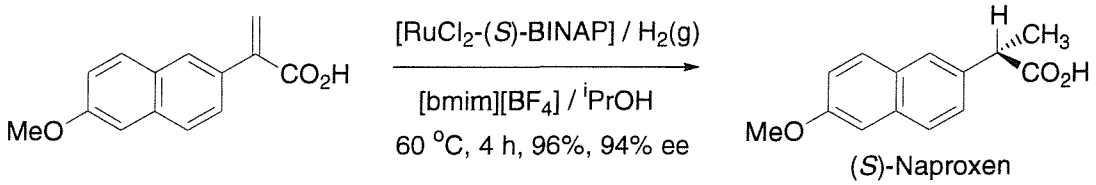
Many of these materials exhibit excellent air and moisture stability, and physical attributes such as viscosity, hydrophobicity, density and solvation properties are to a large extent determined by the identity of the 1*N*-alkyl substituent and nature of the counterion. The highly polar nature of ionic liquids ensures immiscibility with many organic solvents, offering unique opportunities for recycling and phase-switching techniques.

Many recent applications have focussed upon the isolation of reaction products by direct low-pressure distillation from OIL's, rendering the ionic liquid clean of volatile organic compounds. On the catalyst front, many reactions ranging from transition-metal mediated processes to Friedel-Crafts reactions, C-C bond-forming condensations, and cycloadditions are dramatically accelerated in ionic liquids.[1,2,3]

Also a fashionable subject of recent research, the heating of reaction media by focussed microwave irradiation, has been exploited in conjunction with OIL's. The ionic composition and thermal properties of such solvents makes them an obvious choice for use with this technique, and there have been a significant number of publications detailing vastly increased reaction rates and yields as a result.

5.2 Reactions conducted in ionic liquids

Ionic liquids are excellent solvents for many organometallic species, and have become valuable as reaction media for numerous transition-metal mediated processes. In particular, rhodium(0) and cobalt(0) catalysed hydrogenations conducted in OIL's have proven noteworthy.[4]



5.5 5.6

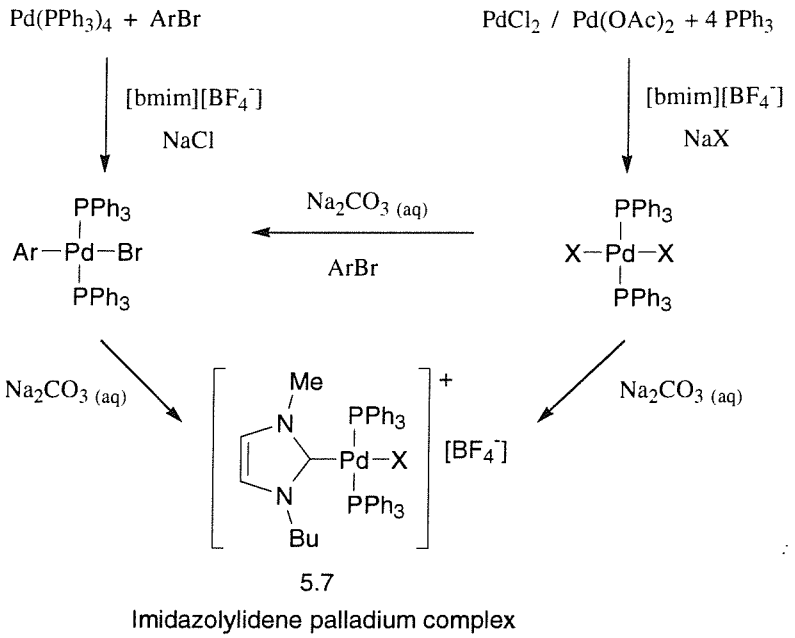
Scheme 5.1 Asymmetric hydrogenation using [$RuCl_2$-(*S*)-BINAP] in [bmim][BF_4]

Scheme 5.1 shows the highly selective asymmetric hydrogenation of 2-(6-methoxy-2-naphthyl)acrylic acid **5.5** to the pharmaceutically important drug compound Naproxen™ **5.6**. The reduction is conducted in 1*N*-butyl-3*N*-methylimidazolium tetrafluoroborate ([bmim][BF_4^-]), and was shown by Monteiro, Zinn, de Souza and Dupont to give both excellent yields and enantioselectivities using [$RuCl_2$-(*S*)-BINAP] as the catalyst.

In 2002, Berthold *et al.* demonstrated the rapid transfer hydrogenation of a wide variety of unsaturated substrates in ionic liquids.[5]

However, the authors exploited the polar nature of the reaction medium, facilitating the reduction process still further with the aid of microwave irradiation. The combination of palladium on charcoal (10% w/w, Pd/C), and either ammonium formate or triethylammonium formate in [bmim][BF_4^-], led to extremely good yields of cleanly reduced products in under 1 hour.

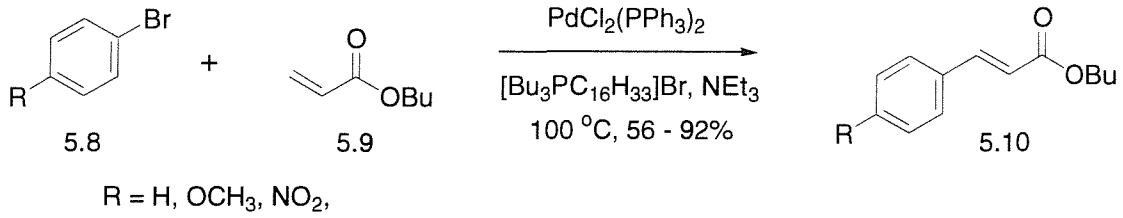
Palladium(0) catalysed cross-coupling reactions such as the Suzuki-Miyaura, Heck and Sonagashira reaction have also proven highly successful in OIL's. The nature of ionic liquid catalysis is likely to be twofold. Besides solvent effects due to the dissolving power of this polar medium, the formation of *N*-heterocyclic carbene complexes by active participation of the ionic liquid with the transition metal has been suggested, and experimentally demonstrated for Pd(0) catalysed reactions.[6] In 2001, Welton *et al.* published evidence for the increased catalytic activity of palladium(0) species solvated in ionic liquids. Welton *et al.* attributed this joint catalytic effect to the *in situ* formation of palladium imidazolylidene complexes, which was first observed by Xiao *et al.*



Scheme 5.2 The *in situ* formation of a phosphine-imidazolylidene-palladium complex

Welton's preliminary results indicated that the imidazolylidene palladium complex **5.7**, which may be formed from a number of palladium and halide sources (scheme 5.2), is extremely active in the catalytic cycle of the Suzuki-Miyaura cross-coupling reaction.

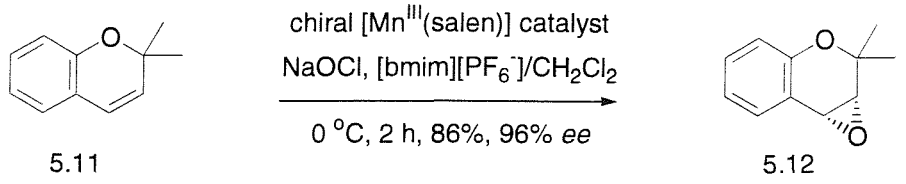
Welton concluded that although ionic liquids may generally be considered as 'innocent' non-interactive solvents in reactions not involving transition-metal complexes, OIL's certainly play a very active role in the chemistry of metal-catalysed processes.[7] The use of ionic liquids as reaction media for the Heck cross-coupling reaction was first described by Kaufmann *et al.* in 1996.[8]



Scheme 5.3 Heck cross-coupling of aryl bromides and butyl acrylate conducted in an ionic liquid

Kaufmann *et al.* employed a tetraalkylphosphonium bromide ionic liquid as the solvent in which to carry out the coupling reaction between a short series of 4-substituted arylbromides **5.8**, and butyl acrylate **5.9**, in the presence of triethylamine and catalytic palladium(0). The coupling was shown to proceed in good to excellent yield depending upon the electronic properties of the 4-substituent, to provide good to excellent yields of unsaturated butyl esters **5.10**. The high stability of imidazolylidene-palladium complexes implicated in such palladium-catalysed processes has often allowed multiple recycling of reaction media, and indeed Kaufmann was able to take advantage of this feature. Reaction products were isolated by fractional distillation from the crude reaction mixture, and the catalytic ionic liquid solvent mixture was recycled three times without loss of activity.

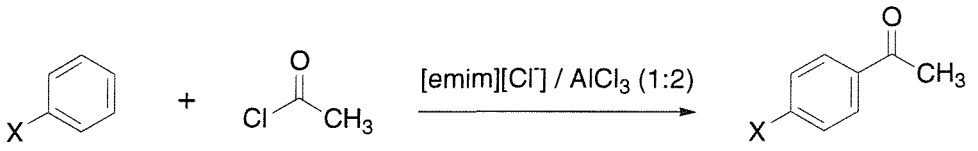
The use of ionic liquids has also proven advantageous as a solvent in which to conduct selective oxidation reactions. In 2000, Song and Roh published details of the epoxidation of a short series of chromenes using the chiral Mn^{III}[salen] complex ([*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)manganese^{III} chloride in a mixture of [bmim][PF_6^-] and CH_2Cl_2 (1:4 v/v), (scheme 5.4).[9] The addition of the ionic liquid to the reaction mixture was shown to greatly enhance the catalytic activity of the salen complex, allowing 86% epoxidation of 2,2-dimethylchromene **5.11** to **5.12**, after only 2 hours. In the absence of the ionic liquid, the same conversion was observed only after 6 hours. In both cases, the enantiomeric excess was as high as 96%.



5.11 5.12

Scheme 5.4 Accelerated epoxidation of 2,2-dimethylchromene through the use of ionic liquids

Seddon *et al.* studied the Friedel-Crafts acylation of several aromatic compounds **5.13**, using acetyl chloride (scheme 5.5).[10] The reactions were conducted in the ionic liquid 1*N*-ethyl-3*N*-methylimidazolium chloride ([emim][Cl$^-$]) in conjunction with the powerful Lewis acid $AlCl_3$. Reaction conditions were optimised such that the mole ratio of ionic liquid to Lewis acid was 1:2 ([emim][Cl$^-$]:$AlCl_3$). In all cases studied, excellent regioselectivities were observed, and substitution occurred exclusively in the 4-position, providing excellent yields of aryl methyl ketones **5.14**.



5.13 5.14

X	Temp (°C)	Time (h)	Yield (%)
CH_3O	-10	0.25	99
CH_3	20	1	98
Cl	20	24	97

Scheme 5.5 Ionic liquid-promoted Friedel-Crafts acylation reactions

5.3 Results and Discussion

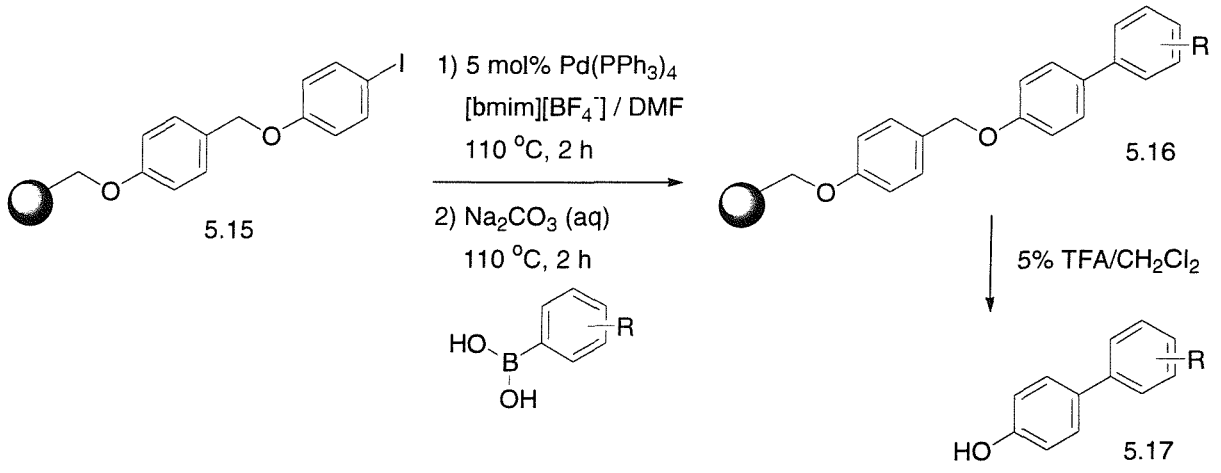
Unaware of any previous reports combining the potential of ionic liquids and solid-phase synthesis, we set out to examine whether the beneficial catalytic effects of ionic liquids were translatable to solid-phase reactions. Initial studies were focussed on the Suzuki-Miyaura palladium coupling of aryl or alkenyl boronic acids with aryl or alkenyl halides. Because of its efficiency and functional group tolerance, this cross-coupling reaction has been intensively employed in the solution-phase, and there are also numerous examples of solid-phase applications.

Furthermore, a solution-phase precedent reporting increased turnover frequency in Suzuki-Miyaura reactions carried out in the ionic liquid 1*N*-butyl-3*N*-methylimidazolium tetrafluoroborate ([bmim][BF_4^-]), prompted our interest in this reaction.[11]

Given the hydrophobicity of cross-linked polystyrene resins used in solid-phase synthesis, we anticipated the need for a co-solvent to ensure swelling of the beads to the gel-phase. The ionic liquid ([bmim][BF_4^-]) was mixed with four test solvents: dichloromethane, DME, DMF, and dimethyl acetamide.

The mixture with dichloromethane rapidly became cloudy, while those with DME and dimethyl acetamide gradually separated. Only DMF remained miscible with [bmim][BF_4^-] as a homogeneous translucent liquid upon overnight standing and was hence chosen as the co-solvent.

For our solid-phase reactions, 4-iodophenol was immobilised on polystyrene Wang resin according to the trichloroacetimidate procedure of Hanessian and Xie.[12] The aryl iodide resin **5.15** was then swollen in 1:1 [bmim][BF_4^-]/DMF, followed by addition of $Pd(PPh_3)_4$, and the catalyst was activated by heating to 110 °C for 2 hours. The resulting orange-red suspension was heated at 110 °C for a further 2 hours after addition of phenylboronic acid and aqueous Na_2CO_3. Upon cooling, workup, and resin cleavage, we were pleased to obtain ~70% isolated yield of 4-phenylphenol (Scheme 5.6, R = H).



Scheme 5.6 Ionic liquid-accelerated Suzuki-Miyaura reactions of immobilised 4-iodophenol

Two control experiments served to highlight the importance of both ionic liquid and co-solvent. Thus, under identical reaction conditions with neat DMF in the absence of any ionic liquid, only 46% of the biaryl product was isolated. However, when the solid-phase reaction was carried out with neat ionic liquid in the absence of any DMF, no biaryl was detected.

Presumably, this is due to poor penetration of the active catalyst into the unswollen resin beads. A time course of the extent of reaction with 1:1 [bmim][BF_4^-]/DMF versus DMF alone (Table 5.1) confirms significant rate acceleration in the former case.

Reaction Time	**Yield (%) DMF solvent**	**Yield (%) 1:1 [bmim][BF_4^-] / DMF solvent**
30 minutes	19	48
60 minutes	31	59
90 minutes	38	67
120 minutes	46	74
48 h	80	84

Table 5.1 Rate acceleration of the solid-phase Suzuki-Miyaura reaction by [bmim][BF_4^-]

The scope of the ionic liquid accelerated process was investigated through the parallel reactions of the resin-bound aryl iodide with a set of ten arylboronic acids bearing a range of electron donating or withdrawing substituents (Table 5.2).

Entry	**R**	**Yield (%)[a] 1:1 conditions**	**Yield (%)[a] 1:9 conditions**
1	H	74	70
2	4-CHO	72	68
3	3-CHO	70	64
4	4-OPh	61	64
5	3-NHAc	40	44
6	4-OCF_3	45	40
7	3,5-diCF_3	42	37
8	4-OEt	65	67
9	3,4-OCH_2O-	60	63
10	4-*t*-Bu	73	70

Table 5.2 Examples of ionic liquid promoted Suzuki-Miyaura cross-coupling reactions

[a] Isolated yield after silica chromatography, average of 3 experiments.

These reactions were carried out in both 1:1 as well as 1:9 [bmim][BF_4^-]/DMF. As can be seen, the ionic liquid efficiently promotes the Suzuki-Miyaura coupling of a variety of arylboronic acids. Furthermore, the isolated yields are very similar whether the ionic liquid is present as 10% or 50% of the solvent volume.

In all reactions we found that yields are very similar when the ionic liquid concentration is only 10% of the total solvent volume (Table 5.2, column 4). Further reduction to 5:95 [bmim][BF_4^-]/DMF led to a partial increase in yield compared to the ionic liquid-free conditions, while 1:99 [bmim][BF_4^-]/DMF resulted in practically no acceleration over the control.

We have attempted recycling of the ionic liquid, which should also contain the catalytically active species, after the solid-phase reaction. The supernatant was filtered and DMF evaporated from the solvent mixture, followed by aqueous washing to remove excess boronic acid and inorganic salts. When the resulting ionic liquid was recycled without addition of Pd(0), the cross-coupling of immobilised 4-iodophenol and phenylboronic acid proceeded in 29% yield. In these solid-phase reactions, we observe deposition of palladium black suggesting a significant loss of the metal. Repeating the cross-coupling with recycled ionic liquid and fresh addition of 5 mol% Pd(0) catalyst afforded 4-phenylphenol in 69%, virtually indistinguishable from the optimized yield in Table 5.2.

5.4 Conclusions

In summary, we have shown that the rate accelerating properties of ionic liquids observed in solution-phase Suzuki-Miyaura reactions can be extended to solid-phase conditions with standard hydrophobic crosslinked resins. The ionic liquid can be recovered and recycled after the reaction, and gives almost identical yields in further catalytic runs, on addition of fresh catalyst.[243]

Experimental

Chapter VI

6.1 General Experimental

All reactions were conducted under an inert atmosphere of dry nitrogen unless otherwise stated. Reactions requiring anhydrous conditions were carried out using oven-dried glassware (overnight at 110 °C), which was assembled hot and cooled under argon. All reactions were stirred magnetically and followed by TLC where appropriate, using aluminium-backed Silica Gel 60 (Mackeray Nagel: 0.25 mm layer). TLC visualisation was performed using short wavelength UV light (254 nm), and/or acidified aqueous potassium permanganate solution (0.1 mol dm^{-3}). Column chromatography was performed using a slight positive pressure with flash silica (Merck, 0.04 - 0.06 mm particle size).

Tetrahydrofuran was dried by distillation over sodium and benzophenone under nitrogen. Diethyl ether was distilled directly from a stirred suspension with lithium aluminium tetrahydride. Yields given are based upon chromatographically and spectroscopically (^1H and ^{13}C NMR) pure materials, unless otherwise stated.

^1H, ^{13}C and DEPT NMR spectra were recorded using a Bruker AM 300 spectrometer at 300 MHz and 75.5 MHz respectively using deuterated chloroform as the solvent and $CHCl_3$ as the lock signal (DMSO-D_6 was also used as stated). All chemical shift values are given on the δ scale relative to tetramethylsilane, where $\delta_H = 0$ ppm and $\delta_C = 0$ ppm.

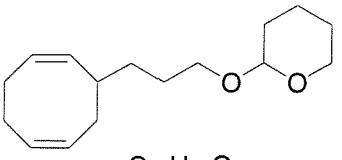
Mass spectra were recorded on a Micromass Platform quadrupole mass analyser with an electrospray ion source using atmospheric pressure chemical ionisation (APCI) and electrospray (ES) techniques. Analytical grade acetonitrile was used as the solvent, with samples prepared to a concentration of between 1-10 $\mu g\ mL^{-1}$. Electron impact (EI) mass spectra were recorded on a VG analytical 70-250-SE normal geometry double focussing mass spectrometer using an ionisation energy of 70 eV and a 200 °C source temperature. All melting points are uncorrected and were recorded on a Reichert melting point apparatus using a Comark digital temperature probe.

6.2 Chapter II experimental procedures and spectroscopic data

General procedure for LICKOR lithiation and alkylation of cycloocta-1,5-diene

tert-Butyllithium (3.5-6 mmol in pentanes, 1.0 equiv) was transferred to a Schlenk vessel by cannula under argon atmosphere, and the solvent was cautiously removed *in vacuo*. The resulting white powder was redissolved in anhydrous THF (30-50 mL) precooled to -78 °C. To the resulting yellow solution was added an anhydrous THF solution of t-BuOK (1 equiv) at -95 °C, followed by the dropwise addition of 1,5-cyclooctadiene (1.01 mol eq). The reaction mixture was stirred gently for 2 h, maintaining the reaction temperature between -78 and -95 °C, to give an orange/red suspension. The alkyl halide or ethylene oxide (1.1 equiv) was then added dropwise with stirring, and the reaction mixture was maintained at -95 °C for a further 1 h before warming to ambient temperature over 1 h. The reaction mixture was quenched by transfer to a stirred solution of saturated aq NH_4Cl, and the phases were separated. The aqueous-phase was extracted with diethyl ether, and the combined extracts were dried over $MgSO_4$, concentrated, and purified by column chromatography on silica.

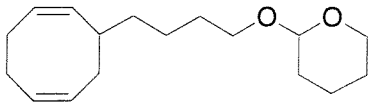
2-{[3-(2,6-cyclooctadienyl)propyl]oxy}tetrahydro-2*H*-pyran (2.117)



$C_{16}H_{26}O_2$
Mol. Wt.: 250.38

Obtained in 62% yield (3.8 mmol scale) as a colorless oil from the alkylation of lithiated cyclooctadiene with 2-(3-bromopropyloxy)-tetrahydropyran **2.112**. Chromatography eluent 5% ethyl acetate in hexane, R_f 0.3. FTIR (neat) ν_{max} = 1079, 1034 cm^{-1}; ^1H NMR δ 5.55 (3H, m), 5.25 (1H, dd, J= 6.8, 11.5 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.72 (1H, dd, J = 6.7, 13.6 Hz), 3.49 (1H, m), 3.38 (1H, dd, J = 6.7, 13.6 Hz), 2.75 (1H, m), 2.52 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.75-1.30 (8H, m); ^{13}C NMR δ 134.3, 128.7, 128.6, 127.7, 98.9, 67.8, 62.4, 38.8, 34.96, 33.9, 30.8, 28.1, 28.0, 27.8, 25.6, 19.8; MS 250 (M^+, 1%), 107 (23%), 85 (100%).

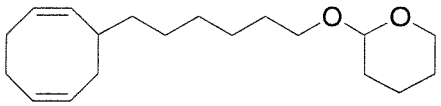
2-{[4-(2,6-cyclooctadienyl)butyl]oxy}tetrahydro-2*H*-pyran (2.119)



$C_{17}H_{28}O_2$
Mol. Wt.: 264.40

Obtained in 74% yield (3.8 mmol scale) as a colorless oil from the alkylation of lithiated cyclooctadiene with 2-(4-iodobutyloxy)-tetrahydropyran. Chromatography eluent 4% ethyl acetate in hexane, R_f 0.25-0.3. FTIR (neat) ν_{max} = 1080, 1035 cm^{-1}; ^1H NMR δ 5.5 (3H, m), 5.30 (1H, dd, J= 6.9, 11.3 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.7 (1H, m), 3.45 (1H, m), 3.35 (1H, m), 2.7 (1H, m), 2.55 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.7-1.25 (10H, m); ^{13}C NMR δ 134.4, 128.6, 128.4, 127.4, 98.8, 67.6, 62.3, 38.7, 37.1, 34.9, 30.8, 29.9, 28.02, 27.96, 25.5, 24.2, 19.7; MS 264 (M^+, 12%), 107 (93%), 85 (100%). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.26; H, 10.64.

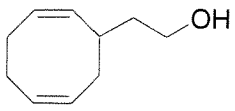
2-{[6-(2,6-cyclooctadienyl)hexyl]oxy}tetrahydro-2*H*-pyran (2.116)



$C_{19}H_{32}O_2$
Mol. Wt.: 292.46

Obtained in 78% yield (3.5 mmol scale) as a colorless oil from the alkylation of lithiated cyclooctadiene with 2-(6-iodohexyloxy)-tetrahydropyran **2.115**. Chromatography eluent 3% ethyl acetate in hexane, R_f 0.25. FTIR (neat) ν_{max} = 1079, 1034 cm^{-1}; ^1H NMR δ 5.53 (3H, m), 5.30 (1H, dd, J= 6.8, 11.5 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.71 (1H, ddd, J = 2.9, 6.8, 13.4 Hz), 3.48 (1H, m), 3.36 (1H, ddd, J = 2.9, 6.8, 13.4 Hz), 2.7 (1H, m), 2.55 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.65 (2H, m), 1.65-1.25 (12H, m); ^{13}C NMR δ 134.6, 128.8, 128.5, 127.4, 98.9, 67.7, 62.4, 38.9, 37.4, 35.0, 30.9, 29.8, 29.7, 28.1, 27.5, 26.3, 25.6, 19.8, 19.7; MS 292 (M^+, 2%), 107 (93%), 94 (94%), 80 (100%). Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.82; H, 11.34.

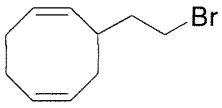
2-(2,6-cyclooctadienyl)-1-ethanol (2.90)



$C_{10}H_{16}O$
Mol. Wt.: 152.23

Obtained in 62% yield (6.0 mmol scale) as a colorless oil from the alkylation of lithiated cyclooctadiene with ethylene oxide. Chromatography eluent 20% ethyl acetate in hexane, R_f 0.3. FTIR (neat) ν_{max} = 3305, 3005 cm^{-1}; ^1H NMR δ 5.55 (3H, m), 5.35 (1H, dd, J= 6.9, 11.5 Hz), 3.68 (2H, t, J= 6.6 Hz), 2.92 (1H, dd, J = 5.8, 11.9 Hz), 2.53 (1H, m), 2.33 (4H, m), 2.2 (2H, m), 1.64 (2H, m); ^{13}C NMR δ 133.7, 128.8, 128.4 (2C), 61.3, 40.1, 35.5, 35.1, 28.1, 28.0; MS 152 (M^+, 10%), 91 (39%), 67 (100%).

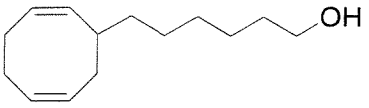
2-(2,6-cyclooctadienyl)-1-bromoethane (2.91)



$C_{10}H_{15}Br$
Mol. Wt.: 215.13

To a stirred and cooled (salt/ice-water bath) solution of 2-(2,6-cyclooctadienyl)-1-ethanol **2.90** (400 mg, 2.63 mmol) in anhyd diethyl ether (20 mL) was added phosphorus tribromide (175 µL, 1.84 mmol, 0.7 equiv) at a rate such that the internal reaction temperature was maintained as closely as possible to 0 °C. The reaction mixture was maintained at this temperature for 1 h under nitrogen, and then quenched rapidly whilst cold by cautious addition to ice-water. The aqueous layer was extracted, and the combined organic extracts washed (H_2O, saturated aq $NaHCO_3$, and brine), dried, and concentrated. The crude bromide was applied to a short silica plug and rapidly eluted with neat hexanes, R_f 0.7-0.9 to afford **5** as a light yellow oil (373 mg, 1.73 mmol, 66%). FTIR (neat) ν_{max} = 3002, 2945, 1061 cm^{-1}; ^1H NMR δ 5.6 (3H, m), 5.30 (1H, dd, J= 11.5, 7.0 Hz), 3.45 (2H, m), 3.0 (1H, m), 2.55 (1H, m), 2.35 (4H, m), 2.2 (2H, m), 1.91 (2H, dt, J = 6.8, 13.5 Hz); ^{13}C NMR δ 132.3, 129.2, 129.0, 127.9, 40.1, 37.4, 34.5, 32.1, 28.1, 28.0; MS 216 (M^++1, 10%), 107 (45%), 79 (100%).

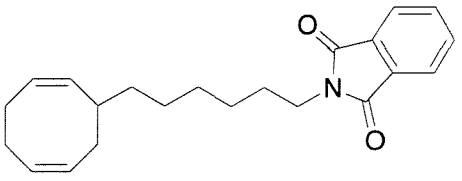
6-(2,6-cyclooctadienyl)-1-hexanol (2.120)



$C_{14}H_{24}O$
Mol. Wt.: 208.34

To a stirred solution of **2.116** (600 mg, 2.05 mmol) in MeOH (10 mL) was added PPTS (52 mg, 0.205 mmol, 0.1 equiv). After 6 h, the mixture was washed (saturated aq $NaHCO_3$), diluted with 9:1 hexane/EtOAc, and the aqueous-phase extracted with hexane. The combined extracts were washed with brine, dried, and concentrated. Chromatography on silica (eluent 20% ethyl acetate in hexane, R_f 0.25-0.35) yielded **2.120** as a colorless oil (397 mg, 1.91mmol, 93%). FTIR (neat) ν_{max} = 3357 cm^{-1}; ^1H NMR δ 5.53 (3H, m), 5.31 (1H, dd, J= 6.8, 11.6 Hz), 3.59 (2H, t, J= 6.6 Hz), 2.69 (1H, m), 2.53 (1H, m), 2.30 (4H, m), 2.12 (2H, m), 1.5 (2H, m), 1.30 (8H, m); ^{13}C NMR δ 134.5, 128.7, 128.5, 127.4, 62.9, 38.8, 37.3, 35.0, 32.8, 29.7, 28.0, 27.5, 25.8; MS 208 (M^+, 7%), 94 (78%), 80 (100%).

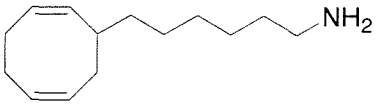
6-(2,6-cyclooctadienyl)-1-phthalimide (2.121)



$C_{22}H_{27}NO_2$
Mol. Wt.: 337.46

To a stirred solution of **2.120** (350 mg, 1.68 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (10 mL) was added triphenylphosphine (572 mg, 2.18 mmol, 1.3 equiv), and phthalimide (321 mg, 2.18 mmol, 1.3 equiv), followed by dropwise addition of diisopropyl azodicarboxylate (441 mg, 2.18 mmol, 1.3 equiv) with cooling (ice/water bath) over 5 min. The yellow reaction mixture was stirred under nitrogen for 16 h, after which the solvent was removed *in vacuo*. The resulting oil was triturated with *n*-pentanes, filtered, concentrated and chromatographed on silica (eluent 1:1 CH_2Cl_2/hexanes, R_f 0.3-0.35) to furnish **2.121** as a colorless oil (526 mg, 1.56 mmol, 93%). FTIR (neat) ν_{max} = 3003, 1707 cm^{-1}; ^1H NMR δ 7.83 (2H, dd, J = 3.0, 5.4 Hz), 7.7 (2H, dd, J = 3.0, 5.4 Hz), 5.53 (3H, m), 5.3 (1H, dd, 6.8, 11.6 Hz), 3.66 (2H, t, 7.3 Hz), 2.7 (1H, m), 2.52 (1H, m), 2.3 (2H, m), 2.13 (2H, m), 1.68 (2H m), 1.3 (10H, m); ^{13}C NMR δ 168.5, 134.6, 133.9, 128.8, 128.5, 127.5, 123.2, 38.8, 38.1, 37.3, 35.0, 29.5, 28.7, 28.1, 28.0, 27.5, 26.9; MS 337 (M^+, 71%), 160 (100%), 107 (78%).

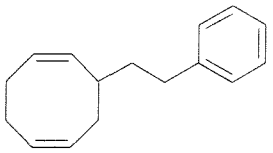
6-(2,6-cyclooctadienyl)-1-hexylamine (2.122)



$C_{14}H_{25}N$
Mol. Wt.: 207.36

To a stirred solution of **2.121** (500 mg, 1.48 mmol) in ethanol (10 mL) was added hydrazine hydrate (185 μL, 5.95 mmol, 4 equiv). The reaction mixture was refluxed under nitrogen for 18 h. After cooling, the phthalhydrazide precipitate was removed by filtration, and the filtrate concentrated. To the residue was added aq 1 M NaOH, and the resulting emulsion extracted with CH_2Cl_2. The combined organic extracts were dried (K_2CO_3), filtered, concentrated, and chromatographed on silica (eluent 9:1 CH_2Cl_2/MeOH saturated with ammonia, R_f 0.2-0.25) to afford **2.122** as a colorless oil (242 mg, 1.17mmol, 79%). FTIR (neat) ν_{max} = 3373, 3290 cm^{-1}; ^1H NMR δ 5.41 (3H, m), 5.21 (1H, dd, J= 11.4, 6.8 Hz), 2.56 (2H, t, J= 6.8 Hz), 2.43 (1H, m), 2.2 (2H, m), 2.0 (2H, m), 1.3 (2H, m), 1.2 (10H, m); ^{13}C NMR δ 134.3, 128.5, 128.2, 127.1, 42.1, 38.6, 37.1, 34.8, 33.7, 29.5, 27.8, 27.3, 26.7; MS 208 (M^+, 55%), 107 (61%), 79 (100%).

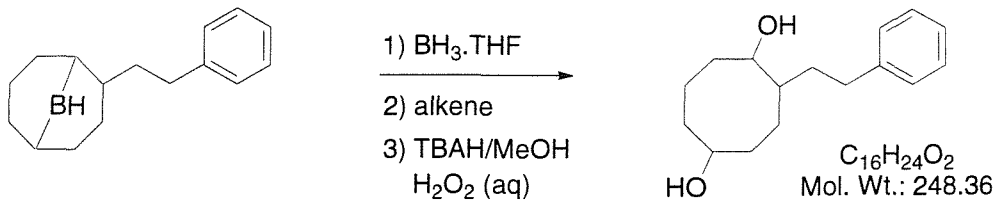
3-phenethyl-cycloocta-1,5-diene (2.130)



$C_{16}H_{20}$
Mol. Wt.: 212.33

To a stirring solution of KO^{t}Bu (4.61 g, 41.1 mmol, 1.01 equiv) in THF (100 mL) under argon at –78 °C, was added dropwise over 10 minutes, n-BuLi in hexanes (16.40 mL, 41.1 mmol, 2.5 mol dm^{-3}, 1.01 equiv). The yellow solution was stirred at low temperature for a further 30 minutes, and cycloocta-1,5-diene (5.00 mL, 40.7 mmol, 1.0 equiv) was added. The bright orange reaction mixture was stirred at –78 °C for 4 hours then allowed to warm to –25 °C and immediately recooled to –78 °C. To the stirring mixture at low temperature was added dropwise over 10 minutes, phenethyl bromide (5.56 mL, 40.7 mmol,1.0 equiv), and the resulting cream-coloured suspension was stirred for a further 1 hour before warming to room temperature. The reaction mixture was canulated into saturated aqueous NH_4Cl (100 mL), and extracted with EtOAc/hexanes (1:1, 10 x 30 mL). Combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to a light straw-coloured oil, which was chromatographed on $AgNO_3$ doped SiO_2 (10% w/w, 100 g) eluting with EtOAc/hexanes (10-30% v/v). Appropriate fractions were combined and concentrated *in vacuo* to afford the title compound as a light colourless oil (6.22 g, 29.3 mmol, 72%). FTIR (neat) ν_{max} = 2934, 2887, 1495, 1454 cm^{-1}; ^{1}H NMR δ 7.24 (2H, d, *J* = 7.0 Hz), 7.16 (2H, d, *J* = 7.0 Hz), 5.56 (3H, m), 5.39 (1H, dd, *J* = 7.0, 11.5 Hz), 2.8 (1H, m), 2.67 (2H, m), 2.52 (1H, m), 2.35 (3H, dd, *J* = 8.3, 13.1 Hz), 2.15 (2H, m), 1.64 (2H, ddd, *J* = 6.5, 14.3, 22.3 Hz); ^{13}C NMR δ 142.9, 134.3, 128.9, 128.8 (2C), 128.7 (2C), 128.6, 128.3, 126.0, 39.5, 38.4, 35.4, 34.1, 28.4, 28.1, 27.2; MS 212 (M^+, 48%), 158 (56%), 143 (67%), 121 (64%), 91 (100%), 67 (62%).

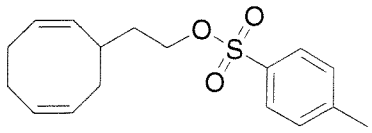
Hydroboration/oxidation of 3-phenethyl-cycloocta-1,5-diene (2.130)



To a stirring solution of 3-phenethyl-cycloocta-1,5-diene **2.130** (1.51 g, 7.11 mmol, 1 equiv) in THF (40 mL) at 0 °C, was added dropwise, a solution of borane in THF (28.5 mL, 28.5 mmol, 4.0 equiv, 1 mol dm^{-3}), over 30 minutes. The reaction was stirred at room temperature for 1 hour, then heated to 50 °C for a further 4 hours. The solution was concentrated *in vacuo* under argon, and volatiles were removed under high vacuum overnight to afford the hydroborated compound 2-phenethyl-9-bora-bicyclo[3.3.1]nonane as a heavy colourless oil which was not characterised due to its air sensitivity.

To a stirring solution of the hydroborated compound in THF (40 mL) under argon at 0 °C, was added a solution of the alkene (8.89 mmol, 1.25 equiv), and the resulting solution was stirred at room temperature for 24 hours. To the stirring solution at 0 °C was added dropwise over 10 minutes, TBAH in MeOH (21.3 mL, 21.3 mmol, 3 equiv, 1 mol dm^{-3}), followed by cautious dropwise addition of H_2O_2 (3.45 mL, 35.6 mmol, 5 equiv, 35 vol %). The oxidation mixture was stirred at 50 °C for 4 hours, cooled to room temperature and poured into water (50 mL), extracting with EtOAc/hexanes (1:1, 5 x 25 mL). Combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to a heavy straw-coloured oil, which was chromatographed on SiO_2 (100 g) eluting with 20-40% EtOAc/hexanes. 2-Phenethyl-cyclooctane-1,5-diol **2.132** was isolated as a heavy colourless oil (1.63 g, 6.54 mmol, 92%). FTIR (neat) ν_{max} = 3351, 2926, 2857, 1453, 996 cm^{-1}; ^1H NMR δ 7.25 (2H, d, *J* = 7.3 Hz), 7.17 (3H, dd, *J* = 5.0, 8.8 Hz), 3.86 (1H, m), 3.70 (1H, dd, *J* = 8.5, 7.5 Hz), 3.38 (1H, m), 2.79-2.67 (1H, m), 2.64 (1H, dd, *J* = 7.8, 8.3 Hz), 2.60-2.48 (1H, m), 2.0, (2H, m), 1.9-1.4 (11H, br m); ^{13}C NMR δ 142.9, 128.62 (2C), 128.59 (2C), 126.0, 76.2, 71.9, 69.9, 45.1, 42.0, 36.5, 36.4, 35.4, 33.8, 24.5; MS 231 (68%), 213 (28%), 117 (50%), 104 (84%), 91 (100%).

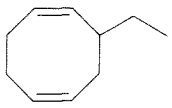
Toluene-4-sulfonic acid 2-cycloocta-2,6-dienyl-ethyl ester (2.126)



$C_{17}H_{22}O_3S$
Mol. Wt.: 306.42

To a stirring solution of 2-(2,6-cyclooctadienyl)-1-ethanol **2.90** (10.0 g, 65.7 mmol, 1 equiv) in CH_2Cl_2 (150 mL) was added TsCl (12.5 g, 65.7 mmol, 1.0 equiv). To the solution cooled to 0 °C, was added dropwise with stirring, a solution of freshly distilled pyridine (5.84 mL, 72.3 mmol, 1.1 equiv) in CH_2Cl_2 (100 mL), and the slightly pink reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into water (200 mL), adjusted to pH 5 by dropwise addition of conc. HCl, and extracted with EtOAc/hexanes (1:1, 5 x 30 mL). Combined extracts were dried over $MgSO_4$, filtered, and chromatographed on SiO_2, eluting with EtOAc/hexanes (10% v/v). Appropriate fractions were combined and concentrated *in vacuo* to afford the title compound as a colourless mobile oil (17.9 g, 58.4 mmol, 89%). FTIR (neat) ν_{max} = 3004, 2888, 1357, 1173 cm^{-1}; ^1H NMR δ 7.74 (2H, d, *J* = 8.15 Hz), 7.31 (2H, d, *J* = 8.15 Hz), 5.46 (3H, m), 5.12 (1H, dd, *J* = 6.9, 11.4 Hz), 4.04 (2H, ddd, *J* = 3.5, 9.7, 16.2 Hz), 2.80 (1H, m), 2.45 (1H, m), 2.40 (3H, s), 2.20 (3H, m), 2.05 (2H, m), 1.63 (2H, m); ^{13}C NMR δ 144.8, 132.2, 130.0 (2C), 129.1, 128.9, 127.9 (2C), 127.8, 69.0, 36.0, 34.9, 34.7, 28.0, 27.8, 21.7; MS 324 ($M^+ + NH_3$, 35%), 155 (18%), 134 (74%), 106 (38%), 91 (92%), 80 (100%).

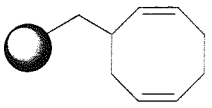
3-ethyl-cycloocta-1,5-diene (2.127)



$C_{10}H_{16}$
Mol. Wt.: 136.23

To a stirring slurry of $LiAlH_4$ (1.40 g, 36.8 mmol, 1.5 equiv) in Et_2O (50 mL) at 0 °C under argon, was added dropwise a solution of tosylate **2.126** (7.51 g, 24.5 mmol, 1 equiv) in Et_2O (50 mL) over 30 minutes. The reaction mixture was stirred for 30 minutes at room temperature, then heated to reflux (using a CO_2 cooled reflux condenser) for 4 hours. To the light yellow suspension, cooled to 0 °C, was added sequentially dropwise with caution, water (1.40 mL), 15% NaOH (1.40 mL), and water (4.20 mL) with rapid stirring over 10 minutes. Solidified salts were removed by filtration, and the filtrate dried over $MgSO_4$, concentrated *in vacuo* to a straw-coloured oil and eluted through a short pad of SiO_2 eluting with neat pentanes. Appropriate fractions were concentrated *in vacuo* and purified further by short-path distillation under high vacuum (120 °C, 15 mm Hg) to afford the title compound as a light colourless oil with a penetrating odour (2.30 g, 16.9 mmol, 69%). FTIR (neat) ν_{max} = 2959, 2875, 1462 cm^{-1}; ^1H NMR δ 5.56 (3H, m), 5.35 (1H, dd, J= 6.8, 11.6 Hz), 2.60 (2H, m), 2.35 (3H, m), 2.15 (2H, m), 1.38 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz); ^{13}C NMR δ 134.4, 128.8, 128.5, 127.6, 40.8, 34.7, 30.2, 28.24, 28.22, 12.1; MS 136 (M^+, 18%), 107 (36%), 91 (24%), 82 (98%), 67 (100%).

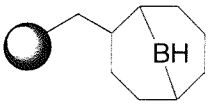
cycloocta-1,5-dienyl-2-methylene polystyrene (2.139)



To a stirring solution of KO^{t}Bu (50 mmol, 5.61 g) in THF (80 mL) cooled to -78 °C was added dropwise *n*-BuLi in hexanes (50 mmol, 2.5 mol dm^{-3}, 20 mL) under argon. The yellow solution was stirred for 10 minutes, and 1,5-cyclooctadiene (1.1 mol eq, 55 mmol, 6.75 mL) was added dropwise maintaining the reaction mixture at -78 °C.

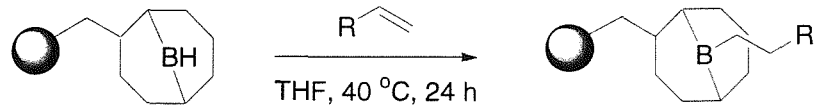
With stirring, the reaction mixture was allowed to warm to -25 °C, then re-cooled to -78 °C, and a slurry of chloromethyl polystyrene (0.5 mol eq, 25 mmol, 4.54 mmol g^{-1} Cl [Novabiochem EHL, 1% DVB, 150 mesh], 5.50 g) pre-swollen in anhydrous THF (100 mL) was added rapidly. Cooling was maintained for 2 hours, when the reaction mixture was allowed to warm to ambient temperature and stirring was continued for a further 24 hours. The dark orange reaction mixture was filtered, and the resin washed 3 times with a 1:1 v/v solution (50 mL) of THF in aqueous hydrochloric acid (1 mol dm^{-3}). Further washing was conducted with a 1:1 v/v solution of THF in water (3 x 50 mL), followed by ^{i}PrOH, EtOH, MeOH, THF, Et_2O (3 x 50 mL). The washing sequence was repeated 3 times before the resin was dried *in vacuo* over 24 hours to afford the title compound **2.139** (6.49 g). FTIR (neat) ν_{max} = 1640, 1508, 1448 cm^{-1}; Microanalysis: 0.45 mmol/g residual chloride, corresponding to 89% loading. New loading = 3.85 mmol g^{-1} COD.

9-borabicyclo[3.3.1]nonanyl-3-methylene polystyrene (2.140)



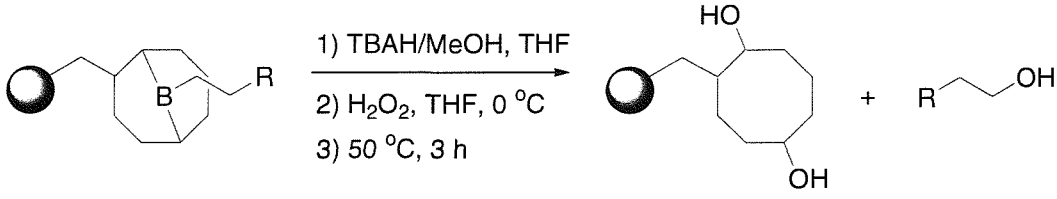
To a pre-swollen slurry of cycloocta-1,5-dienyl-2-methylene polystyrene **2.139** (3.00 g, 3.85 mmol g^{-1} COD, 11.6 mmol) in anhydrous THF (30 mL) was added dropwise under argon at 0 °C a solution of borane in THF (100 mL, 100 mmol, 8.6 equiv). The reaction mixture was warmed to 40 °C with stirring for 4 hours. A reflux condenser was fitted, and the reaction mixture was heated to 65 °C with stirring under argon for 1 hour. The white slurry was rapidly filtered under argon over a dry glass sinter, and the resin was alternatively washed with anhydrous THF and hexanes (10 x 30 mL each). The filtered resin was dried *in vacuo* over 4 hours to afford the title compound **2.140** (3.16 g). FTIR (neat) ν_{max} = 1562, 1368 cm^{-1}; Microanalysis: 3.24 mmol/g boron = 89% loading.

Representative procedure for hydroboration of alkenes



To a stiring slurry of hydroborated COD polystyrene **2.140** (1.0 g, 3.25 mmol g^{-1}, 3.25 mmol) in anhydrous THF (10 mL) was added a solution of the alkene (3 mol eq, 9.75 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at 40 °C under argon for 24 hours when the resin slurry was filtered and washed alternatively with anhydrous THF and hexanes (10 x 10 mL each). The filtered resin was dried *in vacuo* over 4 hours. A list of hydroborated alkene substrates is given in Table 6.1.

Representative procedure for oxidation of trialkylborane resin



To a stiring slurry of the trialkylborane resin in THF (20 mL/g^{-1}) was added dropwise a solution of TBAH (3 mol eq, 10 mmol, 10 mL in MeOH). The stirring slurry was cooled to 0 °C and hydrogen peroxide solution (1.62 mL, 10.0 mmol, 5 equiv, 35% v/v) was added dropwise resulting in an exothermic reaction. The reaction mixture was stirred for 1 hour, then heated to 50 °C with stirring for a further 3 hours. The reaction mixture was then filtered, the resin washed with THF (5 x 15 mL) and hexanes (5 x 15 mL) and the combined supernatant and washings were concentrated *in vacuo*. The concentrate was partitioned between water and hexanes, and extracted with a solution of ethyl acetate in hexanes (1:9 v/v). Combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*, then applied to a thin pad of silica eluting with ethyl acetate in hexanes (1:9 v/v). Appropriate fractions were combined and concentrated *in vacuo* to yield the oxidised product. A list of the alcohol products of oxidation is given in Table 6.1.

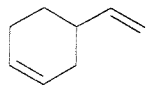
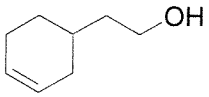
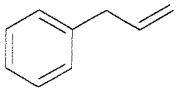
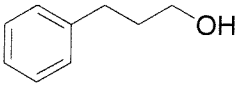
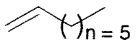
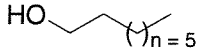
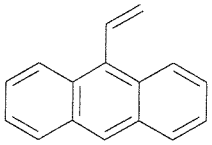
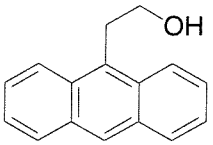
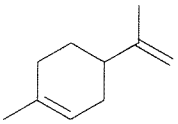
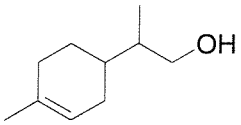
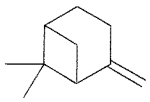
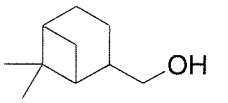
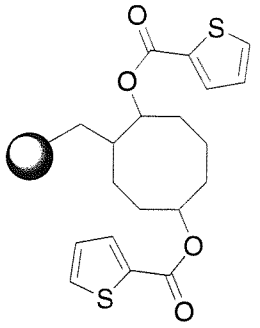
Alkene Substrate of hydroboration	Product Alcohol from oxidation	Isolated Yield (%)	Literature [ref] Yield (%)
		60	89
		53	91
		56	86
		35	45
		61	69
		59	78

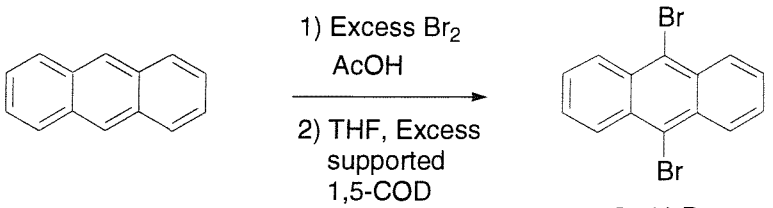
Table 6.1 Hydroborated/oxidised alkene substrates from solid-phase 9-BBN

1,5-dithiophenecarboxycyclooctane-2-methylene polystyrene (2.145)



To a stirring slurry of 1,5-dihydroxycyclooctane-2-methylene polystyrene **2.142** (315 mg, 2.05 mmol/g) in anhydrous CH_2Cl_2 (5.0 mL) was added thiophene-2-carboxylic acid (5 mol eq, 10.25 mmol, 1.31 g), DMAP (0.4 mol eq, 0.82 mmol, 0.1 g) and DCC (2 mol eq, 4.1 mmol, 0.85 g). The reaction mixture was stirred at room temperature under nitrogen for 24 hours. The resin was filtered and washed with the following solvents: CH_2Cl_2, $^{i}PrOH$, EtOH, MeOH, H_2O, THF, Et_2O (3 x 100 mL). The washing sequence was performed 3 times before the resin was dried *in vacuo* over 24 hours to afford the title solid (560 mg). FTIR (neat) ν_{max} = 2924, 2856, 1703 cm^{-1}; Microanalysis: 4.05 mmol/g sulfur.

Representative procedure scavenging of bromine using supported COD

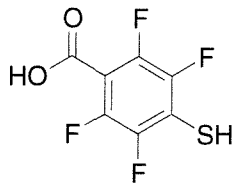


$C_{14}H_8Br_2$
Mol. Wt.: 336.02

To a stirring solution of anthracene (890 mg, 5.0 mmol, 1.0 equiv) in AcOH (glacial, 20.0 mL) at 0 °C was added dropwise with stirring, bromine (0.77 mL, 15.0 mmol, 3.0 equiv) with provision for release of HBr (g). The reaction mixture was stirred at room temperature for 2 hours, then diluted with THF (80 mL). To the mixture was added PS-supported COD (2 mol equiv, 10 mmol COD, 3.85 mmol g^{-1} COD, 2.60 g), and the dark red mixture was stirred for a further 2 hours at room temperature. The bright yellow mixture was filtered and the resin washed with THF (3 x 10 mL). Combined filtrates were concentrated *in vacuo* to afford pure 9,10-dibromoanthracene as a yellow crystalline solid (1.51 g, 4.5 mmol, 90%). M.p. = 224 °C (lit = 222-223 °C).[114]

6.3 Chapter III experimental procedures and spectroscopic data

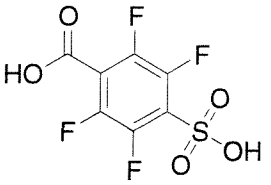
4-mercapto-2,3,5,6-tetrafluorobenzoic acid [3.56][164]



$C_7H_2F_4O_2S$
Mol. Wt.: 226.15

To a solution of pentafluorobenzoic acid (50.0 g, 236 mmol) in aqueous sodium hydroxide (1 mol equiv, 236 mmol, 9.44 g in 130 mL water), was added dropwise with rapid stirring, a solution of sodium hydrosulfide (1.25 mol equiv, 295 mmol, 16.5 g) in aqueous sodium hydroxide (1 mol equiv, 236 mmol, 9.44 g in 100 mL water). The mixture was stirred at 70 °C for 3 hours, cooled to 0 °C, and acidified to pH 1 (conc. HCl). The precipitated acid was extracted into diethyl ether (5 x 75 mL) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The light yellow solid was recrystallised from 10% (v/v) ethyl acetate/hexanes (1 L) to afford the title compound as a buff coloured crystalline solid, (44.8 g, 198 mmol, 84%) M.p. 151-152 °C. LRMS (ES^+) 226 (100%). FTIR (neat) ν_{max} = 3082, 1700, 1637, 1475 cm^{-1}.

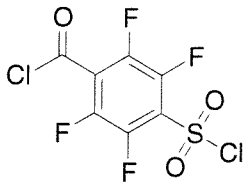
4-sulfo-2,3,5,6-tetrafluorobenzoic acid [3.57][164]



$C_7H_2F_4O_5S$
Mol. Wt.: 274.15

To a stirred solution of 4-mercapto-2,3,5,6-tetrafluorobenzoic acid **3.56** (40.0 g, 177 mmol) in glacial acetic acid (180 mL) at 65 °C, was added dropwise a solution of hydrogen peroxide (30% (v/v), 3 mol equiv, 620 mmol, 70 mL), maintaining the reaction temperature between 65-70 °C. The reaction mixture was heated at 70 °C with stirring for a further 3 hours then cooled to ambient temperature. Excess oxidant was destroyed by careful addition of $Na_2S_2O_5$ (30.0 g), and the resulting solution was concentrated almost to dryness. The resulting slurry was extracted into ethyl acetate (5 x 75 mL), from which a water-soluble fraction was back-extracted into water (5 x 75 mL). The water-soluble extracts were combined and concentrated *in vacuo* to a solid white residue, which was dried under high vacuum at 90 °C overnight. Complete removal of traces of water was achieved by desiccation over P_2O_5 for a further 24 hours to give the title compound as a pure white solid (34.9 g, 127 mmol, 72%). LRMS (ES^+) 274 (100%). FTIR (neat) ν_{max} = 3500-2400, 3408, 3043, 1707, 1630, 1465 cm^{-1}.

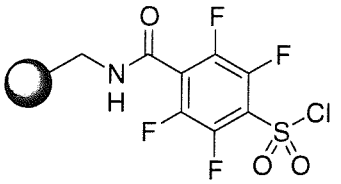
4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoyl chloride [3.58][164]



$C_7Cl_2F_4O_3S$
Mol. Wt.: 311.04

A mixture of 4-sulfo-2,3,5,6-tetrafluorobenzoic acid **3.57** (30.0 g, 109 mmol), phosphorus pentachloride (2.5 mol equiv, 274 mmol, 57.0 g), and phosphoryl chloride (1.5 mol equiv. 164 mmol, 25.2 g, 15.0 mL) was heated at 60 °C under nitrogen for 4 hours with provision for HCl (g) release. To the cooled mixture at 0 °C, was added freshly distilled pentanes (50 mL), and the precipitated phosphorus salts were removed by filtration under nitrogen. The filtrate was concentrated *in vacuo* to a straw-coloured oil, and fractionally distilled to give the title compound as a colourless oil which crystallised on standing (23.5 g, 75.5 mmol, 69%). (b.p. 101-102 °C / 0.2 mbar). M.p. 57-59 °C (previously unreported as a solid).[164] ^{13}C NMR ($CDCl_3$) δ 158.0, 145.6, 142.1, 126.3, 122.8. ^{19}F NMR ($CDCl_3$) δ -134.8 (s, 2 F), -131.9 (s, 2 F). CIMS 275 (100%), 310 (9%), 312 (7%). FTIR ν_{max} = 1793, 1767, 1489, 1404, 1294, 994 cm^{-1}.

2,3,5,6-tetrafluoro-4-methylcarbamoyl-benzenesulfonyl chloride polystyrene-supported [3.60]



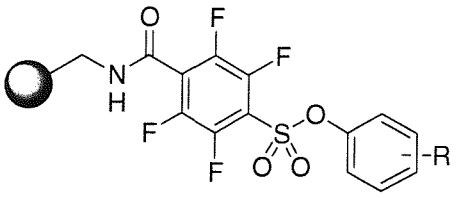
To 1.00 g of aminomethyl polystyrene[a] (Polymer Laboratories, 1% DVB, 1.10 mmol g^{-1} NH_2) pre-swelled in anhydrous CH_2Cl_2 (20 mL) at 0 °C, was added dropwise over 30 minutes with agitation 4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoyl chloride **3.58** (1.10 mol equiv, 0.34 g) and agitation was continued for 1 hour at this temperature under argon. *N,N*-diisopropylethylamine[b] (1.15 mol equiv, 1.15 mmol, 0.20 mL) was added as a dilute solution in CH_2Cl_2 (10% v/v, 1.8 mL) dropwise with agitation over 30 minutes, maintaining the reaction temperature at 0 °C.[c] The reaction mixture was then allowed to warm to ambient temperature and agitation was continued for a further 12 hours. The resin was filtered and washed with anhydrous CH_2Cl_2, and diethyl ether under argon, then dried *in vacuo* at room temperature over 12 hours under high vacuum to give the title compound (1.33 g, 0.85 mmol g^{-1} Cl). Gel-phase ^{19}F NMR ($CDCl_3$) δ -136.6 (s, 2 F), -133.6 (s, 2 F). FTIR (neat) ν_{max} = 2923, 1695, 1483, 1452, 990 cm^{-1}.

[a] Aminomethyl polystyrene was washed thoroughly prior to use with a solution of ammonia saturated methanol in CH_2Cl_2 (10% v/v, $MeOH.NH_3/CH_2Cl_2$). The resin was finally washed with anhydrous THF, hexanes and diethyl ether, and dried *in vacuo* over 12 hours prior to its use.

[b] *N,N*-diisopropylethylamine was distilled from CaH_2 immediately prior to its use.

[c] The slow rate of addition of the base, and temperature regulation are critical, as deviation invariably leads to highly coloured resin of poor substitution.

Representative preparation of immobilised sulfonates.



To a slurry of freshly prepared polystyrene-supported sulfonyl chloride[a] (0.85 mmol g^{-1}) pre-swollen in CH_2Cl_2[b] (20 mL/g^{-1}) under argon, was added a mixture of the phenol (3 mol equiv, 2.54 mmol) and *N,N*-diisopropylethylamine[c] (3 mol equiv, 2.54 mmol, 0.44 mL) in CH_2Cl_2.[d] The reaction mixture was shaken under argon for 18 hours at room temperature, the resin was filtered and washed thoroughly with DMF, THF, CH_2Cl_2, and Et_2O and dried *in vacuo* for 12 hours to give the resin bound sulfonate (typical loading 0.75 mmol g^{-1}).

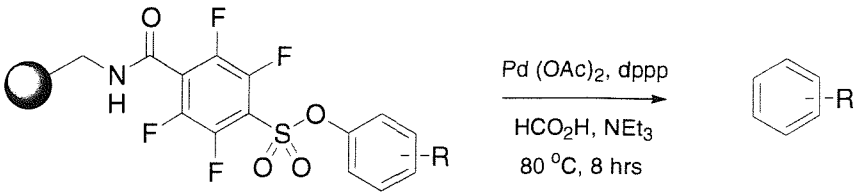
[a] A qualitative test for reactivity may be performed prior to sulfonate formation. Sulfonyl chloride resin was shaken with a solution of ethylenediamine in DMF (5% v/v) for 5 minutes at room temperature then washed thoroughly with DMF, THF and Et_2O. The resin was then shaken with a solution of bromophenol blue in *N,N*-dimethylacetamide (1% w/v) at room temperature for 1 minute. The resin was washed thoroughly with DMF, THF, CH_2Cl_2 and Et_2O. Persistent dark blue colouration of the resin indicates appropriate reactivity of the sulfonyl chloride resin.

[b] CH_2Cl_2 was distilled from CaH_2 immediately prior to use.

[c] *N,N*-diisopropylethylamine was distilled from CaH_2 immediately prior to use.

[d] To ensure complete dissolution of the phenol, addition of DMF may be required.

Representative procedure for reductive cleavage of the sulfonate linker.



To arylsulfonate resin (1.00 g, 0.75 mmol/g^{-1} typical sulfonate loading) swollen in DMF[a] (20.0 mL/g^{-1}) was added $Pd(OAc)_2$ (10 mol%, 0.075 mmol, 17.0 mg), 1,3-bis(diphenylphosphino)propane (15 mol %, 0.11 mmol, 45.0 mg) and a mixture of HCO_2H (18 mol equiv, 13.5 mmol, 510 μL) and NEt_3 (13 mol equiv, 9.75 mmol, 1.36 mL).[b] The mixture was shaken at 80 °C for 8 hrs, filtered, and the resin washed alternately with Et_2O and THF.[c] Combined washings were gently concentrated *in vacuo* to remove Et_2O, CH_2Cl_2, and excess NEt_3. To the remaining DMF mixture was added an equal volume of water, and the mixture was extracted with Et_2O (6 x 10 mL). Combined ether extracts were concentrated *in vacuo* to a small volume (2-4 mL), and eluted (Et_2O) through a short silica pad.[c] Appropriate fractions were collected and concentrated *in vacuo*, and purified by preparative TLC (1 mm SiO_2), eluting with 5% v/v ethyl acetate/hexanes. Appropriate regions were removed, the silica extracted with ethyl acetate (6 x 10 mL), and combined extracts were concentrated *in vacuo* to give the desired deoxygenated products (66-89% yield). A list of phenolic substrates and deoxygenated products of transfer hydrogenation is given in Table 6.2.

[a] Anhydrous *N,N*-dimethylformamide was degassed by sparging with argon over 2 hours at room temperature immediately prior to its use.

[b] A mixture of triethylammonium formate in formic acid was prepared by dropwise addition with cooling, of 98% formic acid to triethylamine (freshly distilled from CaH_2).

[c] Careful washing of the reacted resin is required to achieve the tabulated yields of desired products; in all examples, 5 washing cycles each of sufficient volume to slurry the resin was sufficient.

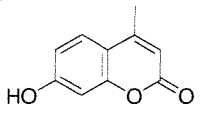
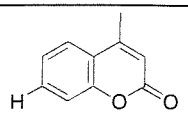
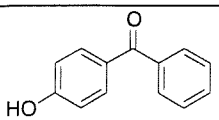
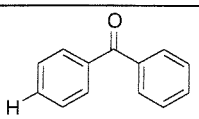
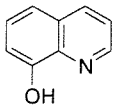
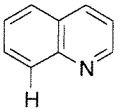
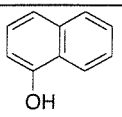
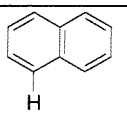
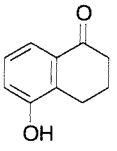
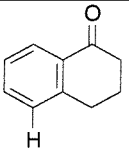
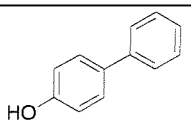
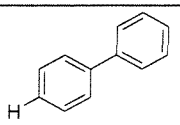
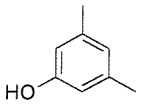
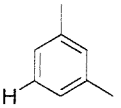
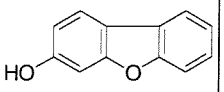
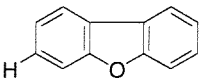
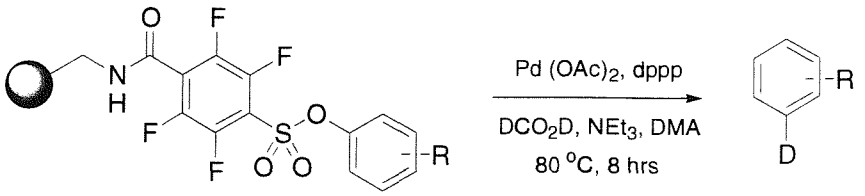
Substrate	Reductive cleavage product	Entry	Yield (%)
		**3.65a**	82
		**3.65b**	89
		**3.65c**	76
		**3.65d**	80
		**3.65e**	66
		**3.65f**	79
		**3.65g**	72
		**3.65h**	81

Table 6.2 Isolated yields for transfer hydrogenation of sulfonate esters on aminomethylpolystyrene (AMP)
For all entries, spectroscopic data was identical to that obtained from commercially available compounds

Representative procedure for deuterative cleavage of the sulfonate linker.



To arylsulfonate resin (1.00 g, 0.75 mmol/g^{-1} typical sulfonate loading) swollen in DMA[a] (20.0 mL/g^{-1}) was added $Pd(OAc)_2$ (10 mol%, 0.075 mmol, 17.0 mg), 1,3-bis(diphenylphosphino)propane (15 mol %, 0.11 mmol, 45.0 mg) and a mixture of DCO_2D (18 mol equiv, 13.5 mmol, 510 μL) and NEt_3 (13 mol equiv, 9.75 mmol, 1.36 mL).[b] The mixture was shaken at 80 °C for 8 hrs, filtered, and the resin washed alternately with Et_2O and THF.[c] Combined washings were gently concentrated *in vacuo* to remove Et_2O, THF, and excess NEt_3. To the remaining DMA mixture was added an equal volume of water, and the mixture was extracted with Et_2O (6 x 10 mL). Combined ether extracts were concentrated *in vacuo* to a small volume (2-4 mL), and eluted (Et_2O) through a short silica pad.[c] Appropriate fractions were collected and concentrated *in vacuo*, and purified by preparative TLC (1 mm SiO_2), eluting with 5% v/v ethyl acetate/hexanes. Appropriate regions were removed, the silica extracted with ethyl acetate (6 x 10 mL), and combined extracts were concentrated *in vacuo* to give the deuterated products (76-84 % yield). A list of phenolic substrates and deoxygenated products of transfer deuteration is given in Table 6.3.

[a] Anhydrous *N,N*-dimethylacetamide was degassed by sparging with argon over 2 hours at room temperature immediately prior to its use.

[b] A mixture of triethylammonium deuterate in deuterated formic acid was prepared by dropwise addition with cooling, of 99% deuterated formic acid to triethylamine (freshly distilled from CaH_2).

[c] Careful washing of the reacted resin is required to achieve the tabulated yields of desired products; in all examples, 5 washing cycles each of sufficient volume to slurry the resin was sufficient.

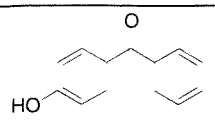
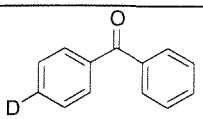
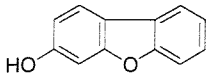
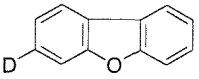
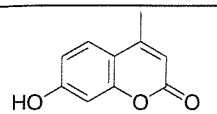
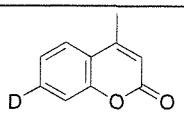
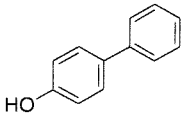
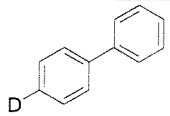
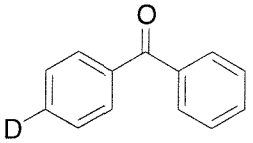
Substrate	Reductive deuteration product	Entry	Yield (%)
		**3.67a**	84
		**3.67b**	76
		**3.67c**	80
		**3.67d**	77

Table 6.3 Transfer deuteration cleavage products

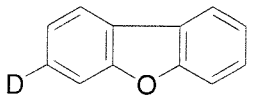
(4-deuterio-phenyl)-phenyl-methanone [3.67a]



$C_{13}H_9DO$
Mol. Wt.: 183.22

Obtained in 84% yield (1.0 mmol scale) as a colourless oil from the transfer deuteration of sulfonate immobilised 4-hydroxy-benzophenone. ^{1}H NMR δ 7.80 (4H, d, *J* = 7.7 Hz), 7.58 (1H, dd, *J* = 7.35), 7.47 (4H, m); ^{13}C NMR δ 197.0, 137.8, 132.7, 130.3, 128.5, 128.4; CIMS 183 (100%), 153 (34%), 105 (92%), 77 (82%), 51 (60%); FTIR (neat) ν_{max} = 3059, 1657, 1275 cm^{-1}.

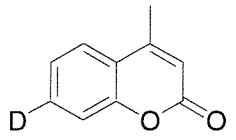
3-deuterio-dibenzofuran [3.67b]



$C_{12}H_7DO$
Mol. Wt.: 169.20

Obtained in 76% yield (1.0 mmol scale) as a colourless crystaline solid from the transfer deuteration of sulfonate immobilised 2-hydroxy-dibenzofuran. M.p 83-84 °C; ^{1}H NMR δ 7.97 (2H, m), 7.60 (2H, d, *J* = 8.3 Hz), 7.47 (2H, m), 7.36 (1H, dd, *J* = 7.4 Hz); ^{13}C NMR δ 156.5, 127.5, 127.3, 124.6, 123.0, 121.0, 120.9, 112.0; CIMS 169 (100%), 140 (73%), 114 (36%); FTIR (neat) ν_{max} = 3045, 1592, 1439, 1189 cm^{-1}.

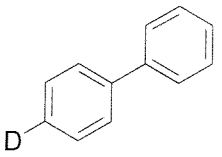
7-deuterio-4-methyl-chromen-2-one [3.67c]



$C_{10}H_7DO_2$
Mol. Wt.: 161.18

Obtained in 80% yield (1.0 mmol scale) as a colourless crystaline solid from the transfer deuteration of sulfonate immobilised 7-hydroxy-4-methyl-coumarin. M.p 91-93 °C; ^{1}H NMR δ 7.60 (2H, d, *J* = 8.09 Hz), 7.31(1H, s), 6.26 (1H, s), 2.42(3H, s); ^{13}C NMR δ 160.9, 153.5, 152.6, 131.9, 131.6, 131.3, 124.7, 124.3, 120.0, 116.9, 115.1, 18.8, 18.5, 18.2; CIMS 163 (96%), 134 (100%), 105 (28%); FTIR (neat) ν_{max} = 3063, 1708, 1601, 1168 cm^{-1}.

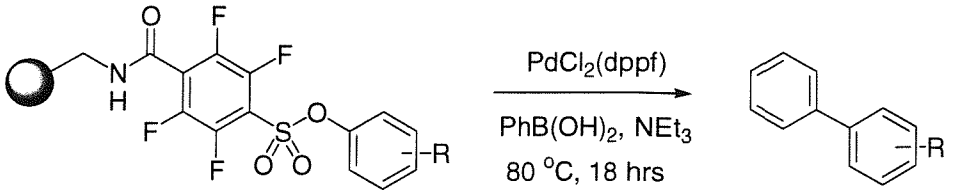
4-deuterio-biphenyl [3.67d]



$C_{12}H_9D$
Mol. Wt.: 155.21

Obtained in 77% yield (1.0 mmol scale) as a colourless crystaline solid from the transfer deuteration of sulfonate immobilised 4-hydroxy-biphenyl. M.p 69-71 °C; ^{1}H NMR δ 7.65 (4H, d, *J* = 7.8 Hz), 7.49 (4H, m), 7.40 (1H, dd, J = 7.4 Hz); ^{13}C NMR δ 141.6, 129.1, 129.0, 127.6, 127.5; CIMS 155 (100%), 127 (18%), 77 (23%); FTIR (neat) ν_{max} = 3060, 3031, 1473, 1402 cm^{-1}.

Representative procedure for the Suzuki-Miyaura cross-coupling of immobilised sulfonates.



To the arylsulfonate resin (1.00 g, 0.75 mmol/g^{-1} typical sulfonate loading) swollen in DMF[a] (20 mL/g^{-1}) was added $PdCl_2(dppf)$ (10 mol%, 0.075 mmol, 65.0 mg), phenylboronic acid (3 mol equiv, 2.25 mmol, 274.0 mg) and NEt_3 (6 mol equiv, 4.5 mmol, 630 μL). The mixture was shaken at 80 °C for 18 hrs, filtered, and the resin washed alternately with Et_2O and CH_2Cl_2. Combined washings were gently concentrated *in vacuo* to remove Et_2O, CH_2Cl_2, and excess NEt_3. To the remaining DMF mixture was added an equal volume of water, and the mixture was extracted with Et_2O (6 x 10 mL). Combined ether extracts were concentrated *in vacuo* to a small volume (2-4 mL), and eluted (Et_2O) through a short silica pad. Appropriate fractions were collected and concentrated *in vacuo*, and purified by preparative TLC (1 mm SiO_2), eluting with 5% v/v ethyl acetate/hexanes. Appropriate regions were removed, the silica extracted with ethyl acetate (6 x 10 mL), and combined extracts were concentrated *in vacuo* to give the desired biaryl products (67-86% yield). A list of phenolic substrates and products of Suzuki-Miyaura cross-coupling is given in Table 6.4.

[a] Anhydrous *N*,*N*-dimethylformamide was degassed by sparging with argon over 2 hours at room temperature immediately prior to its use.

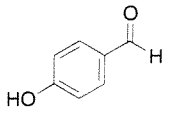
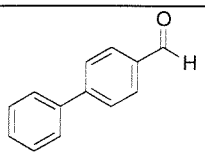
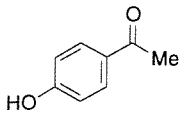
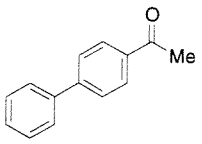
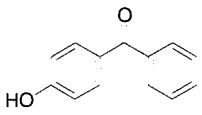
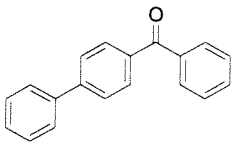
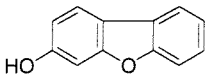
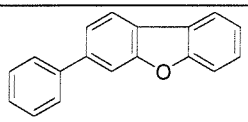
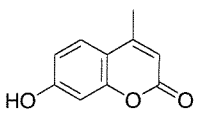
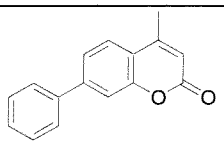
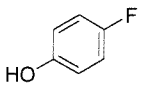
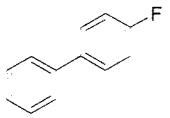
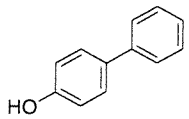
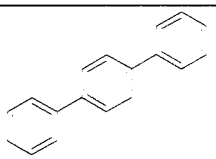
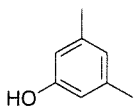
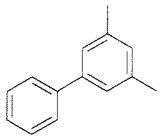
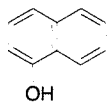
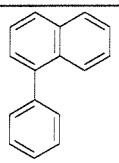
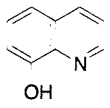
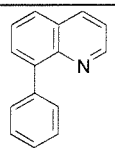
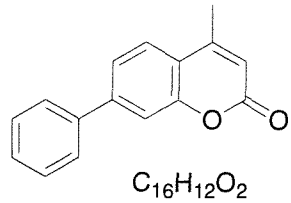
Substrate	Suzuki Cross-coupling product	Entry[ref]	Yield (%)
		**3.66a**[166]	80
		**3.66b**[167]	78
		**3.66c**[166]	86
		**3.66d**[168]	82
		**3.66e**	76
		**3.66f**[169]	71
		**3.66g**[170]	77
		**3.66h**[171]	76
		**3.66i**[172]	79
		**3.66j**[173]	0, 69*

Table 6.4 Suzuki- Miyaura cross-coupling products. Reactions were conducted using 10 mol % $PdCl_2(dppf)$. *Reaction was conducted using 10 mol % $Pd(OAc)_2$ in conjunction with Xphos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl).

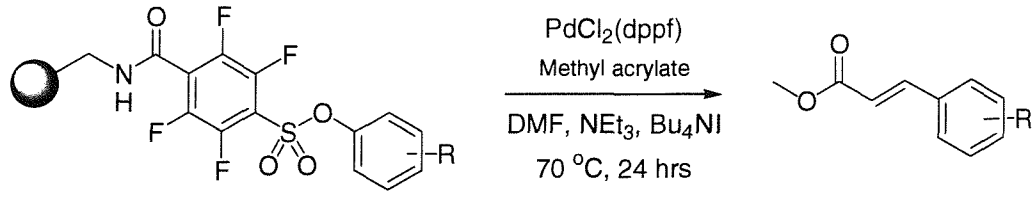
4-methyl-7-phenyl-chromen-2-one [3.66e]



$C_{16}H_{12}O_2$
Mol. Wt.: 236.27

Obtained in 76% yield (0.75 mmol scale) as a colourless crystaline solid from the Suzuki-Miyaura cross-coupling reaction of sulfonate immobilised 7-hydroxy-4-methylcoumarin. M.p 149-150 °C; ^{1}H NMR δ 7.68-7.60 (3H, m), 7.57-7.38 (5H, m), 6.29 (1H, s), 2.46 (3H, s); ^{13}C NMR δ 161.2, 154.2, 152.5, 145.2, 139.4, 129.4, 128.8, 127.5, 125.3, 123.3, 119.2, 115.4, 115.1, 19.0; CIMS 236 (100%), 208 (57%), 178 (27%), 152 (12%); FTIR (neat) ν_{max} = 3055, 1710, 1612, 1506, 1386 cm^{-1}.

Representative procedure for Heck cross-coupling of immobilised sulfonates with methyl acrylate.



To the arylsulfonate resin (1.00 g, 0.75 mmol/g^{-1} typical sulfonate loading) swollen in DMF[a] (20 mL/g) was added $PdCl_2$(dppf) (10 mol%, 0.075 mmol, 65.0 mg), methyl acrylate (10 mol equiv, 7.5 mmol, 0.68 mL), Bu_4NI (2 mol equiv, 1.5 mmol, 554.0 mg) and NEt_3 (6 mol equiv, 4.5 mmol, 630 μL). The mixture was shaken at 70 °C for 24 hrs and the resin was filtered and washed alternately with Et_2O and CH_2Cl_2.[b] Combined washings were gently concentrated *in vacuo* to remove excess methyl acrylate and triethylamine. To the remaining DMF mixture was added an equal volume of water, and the mixture was extracted with Et_2O (6 x 10 mL). Combined ether extracts were concentrated *in vacuo* to a small volume (2-4 mL), and eluted (Et_2O) through a short silica pad. Appropriate fractions were collected and concentrated *in vacuo*, and purified by preparative TLC (1 mm SiO_2), eluting with 5% v/v ethyl acetate/hexanes. Appropriate regions were removed, the silica extracted with ethyl acetate (6 x 10 mL), and combined extracts were concentrated *in vacuo* to give the desired product (64-81% yield). A list of phenolic substrates and products of Heck cross-coupling with methyl acrylate is given in Table 6.5.

[a] Anhydrous *N,N*-dimethylformamide was degassed by sparging with argon over 2 hours at room temperature immediately prior to its use.

[b] Careful washing of the reacted resin is required to achieve the tabulated yields of desired products; in all examples, 5 washing cycles each of sufficient volume to slurry the resin was sufficient.

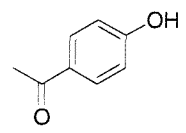
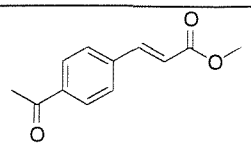
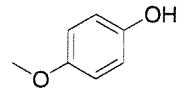
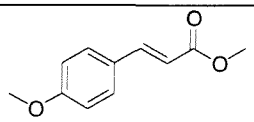
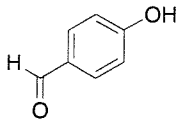
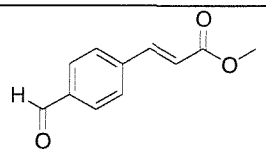
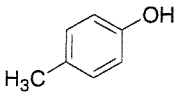
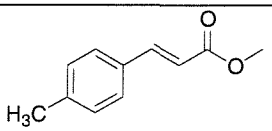
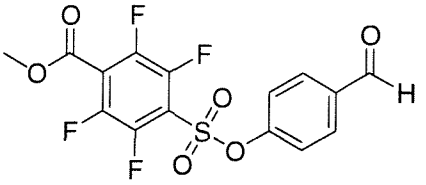
Substrate	Heck cross-coupling	Entry[ref]	Yield (%)
		**3.68a**[177]	81
		**3.68b**[178]	64
		**3.68c**[179]	69
		**3.68d**[178]	72

Table 6.5 Products of Heck cross-coupling with methyl acrylate

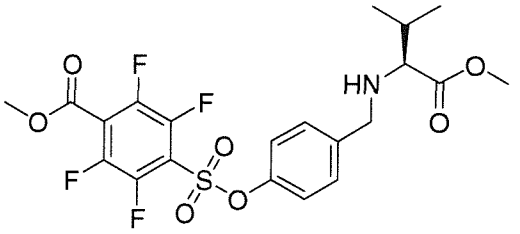
2,3,5,6-tetrafluoro-4-(4-formyl-phenoxysulfonyl)-benzoic acid methyl ester [3.112]



$C_{15}H_8F_4O_6S$
Mol. Wt.: 392.28

To a rapidly stirred solution of methyl 4-chlorosulfonyl-2,3,5,6-tetrafluorobenzoate **3.111**[51] (3.22 g, 10.5 mmol, 1 mol equiv) and 4-hydroxybenzaldehyde (1.34 g, 11.0 mmol, 1.05 mol equiv) in anhydrous CH_2Cl_2 (50.0 mL) under argon at 0 °C was added dropwise NEt_3 (1.17 g, 1.62 mL, 11.6 mmol, 1.1 mol equiv) over 30 minutes. The mixture was allowed to warm to room temperature and stirring was continued for a further 6 hours. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (5 x 25 mL). Combined extracts were dried over $MgSO_4$ and concentrated to a light orange oil which was chromatographed on SiO_2 (50 g) eluting with neat $CHCl_3$ (Rf = 0.3). Clean fractions were collected and concentrated *in vacuo* to a colourless oil which solidified on standing (3.79 g, 9.7 mmol, 92%). ^{1}H NMR δ 10.00 (s, 1 H), 7.94 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 4.02 (s, 3 H). ^{13}C NMR δ 190.6, 158.7, 153.0, 146.6, 143.1, 136.0, 132.1, 122.6, 118.9, 118.1, 54.4. ^{19}F NMR δ -132.70 (s, 2 F), -135.19 (s, 2F). LRMS (ES^+), 392 (94%). FTIR (neat) ν_{max} = 2961, 1738, 1700, 1483, 1314 cm^{-1}.

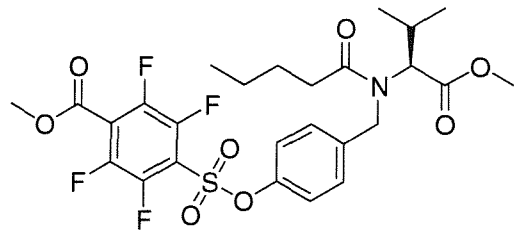
2,3,5,6-tetrafluoro-4-{4-[((*S*)-1-methoxycarbonyl-2-methyl-propylamino)-methyl]-phenoxysulfonyl}-benzoic acid methyl ester [3.113]



$C_{21}H_{21}F_4NO_7S$
Mol. Wt.: 507.45

To a rapidly stirred solution of the aldehyde **3.112** (2.05 g, 5.2 mmol, 1 mol equiv) in methanol (50.0 mL) at 0 °C was added $NaBH(OAc)_3$ (3.32 g, 15.7 mmol, 3 mol equiv). The stirred reaction mixture became turbid over 3 minutes, when L-valine methyl ester hydrochloride (2.63 g, 15.7 mmol, 3 mol equiv) was added in one portion with rapid stirring. Cooling of the reaction mixture was continued for a further hour after which the mixture was allowed to warm to room temperature and stirring was continued for a further 12 hours. The reaction mixture was concentrated *in vacuo* to a small volume, poured into water (100 mL) and extracted with EtOAc (10 x 20 mL). Combined extracts were dried over K_2CO_3 and concentrated to a heavy translucent oil which was chromatographed on SiO_2 (40 g) eluting with $CHCl_3$/EtOAc/MeOH/NEt_3 (70 : 25 : 4 : 1) (Rf = 0.3). Clean fractions were collected and concentrated *in vacuo* to a heavy colourless oil (2.24 g, 4.4 mmol, 84%). ^{1}H NMR ($CDCl_3$) δ 7.35 (aryl, d, J = 8.6 Hz, 2 H), 7.09 (aryl, d, J = 8.6 Hz, 2 H), 4.00 (methyl, s, 3 H), 3.81 and 3.53 (benzylic, AM d, J = 13.7 Hz, 2 H), 3.69 (methyl, s, 3 H), 2.94 (methine, d, J = 5.9 Hz, 1 H), 1.89 (methine, m, 1 H), 1.78 (NH, s, 1 H), 0.90 (^{i}Pr, dd, J = 3.7, 6.8 Hz, 6 H). ^{13}C NMR δ 175.9, 158.8, 148.0, 146.4, 143.1, 140.9, 130.2, 121.5, 118.3, 66.8, 54.3, 51.8, 31.9, 19.6, 18.8. ^{19}F NMR δ -132.56 (s, 2 F), -135.56 (s, 2 F). LRMS (ES^+), 508 (96%). FTIR (neat) ν_{max} = 2961, 1732, 1482, 1309 cm^{-1}; $[\alpha]^{25}$ –32.1 (c=3.5, $CDCl_3$).

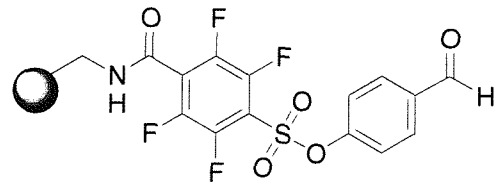
2,3,5,6-tetrafluoro-4-(-4-{[((*S*)-1-methoxycarbonyl-2-methyl-propyl)-pentanoyl-amino]-methyl}-phenoxysulfonyl)-benzoic acid methyl ester [3.114]



$C_{26}H_{29}F_4NO_8S$
Mol. Wt.: 591.57

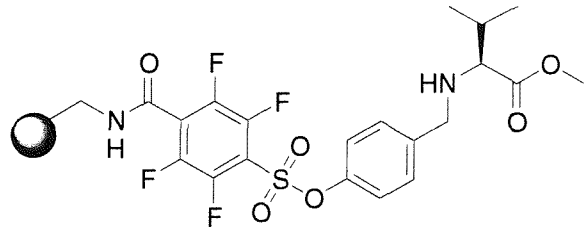
To a rapidly stirring solution of the secondary amine **3.113** (2.10 g, 4.14 mmol, 1 mol equiv) and NEt_3 (0.46 g, 0.63 mL, 4.55 mmol, 1.1 mol equiv) in anhydrous CH_2Cl_2 (30 mL) under argon at 0 °C was added dropwise n-valeryl chloride (0.55 g, 0.55 mL, 4.55 mmol, 1.1 mol equiv) over 30 minutes. The mixture was allowed to warm to room temperature and stirring was continued for a further 6 hours. The resulting slurry was poured into water (100.0 mL) and extracted with CH_2Cl_2 (5 x 20 mL). Combined extracts were dried over $MgSO_4$ and concentrated to a light yellow oil which was chromatographed on silica (40 g) eluting with neat $CHCl_3$ (Rf = 0.3). Clean fractions were combined and concentrated *in vacuo* to a colourless oil (2.23 g, 3.77 mmol, 91%). ^{1}H NMR ($CDCl_3$) δ 7.22 (aryl, d, *J* = 8.4 Hz, 2 H + 2 H), 7.15 (aryl, d, *J* = 8.6 Hz, 1 H + 1 H), 7.06 (aryl, d, *J* = 8.6 Hz, 1 H + 1 H), 4.92 and 4.23 (benzylic rotamer, AM d, *J* = 15.5 Hz, 2 H), 4.85 and 4.03 (methine rotamer, d, *J* = 10.5 Hz, 1 H + 1 H), 4.63 (benzylic rotamer, s, 2 H), 4.01 (methyl, s, 3 H + 3 H), 3.39 (methyl, s, 3 H), 3.32 (methyl, s, 3 H), 2.63-2.08 (m, 3 H + 3 H), 1.77-1.49 (m, 2 H + 2 H), 1.39 (ddd, *J* = 7.4, 14.7, 22.2 Hz, 1 H + 1 H), 1.25 (ddd, *J* = 7.4, 14.7, 22.1 Hz, 1 H + 1 H), 1.00-0.76 (m, 9 H + 9 H). ^{13}C NMR δ 175.6, 174.4, 171.1, 170.3, 158.5, 147.9, 147.8, 147.6, 146.3, 142.8, 140.7, 138.8, 138.0, 130.0, 129.7, 128.0, 121.9, 121.3, 121.2, 118.2, 77.6, 66.6, 65.8, 61.9, 54.1, 54.0, 53.7, 51.8, 51.6, 47.9, 44.9, 33.4, 33.3, 31.7, 27.9, 27.6, 27.4, 27.4, 27.1, 22.6, 22.4, 19.9, 19.8, 19.4, 18.7, 18.6, 14.0, 13.8. ^{19}F NMR δ -132.23 (s, 2 F), -135.98 (s, 2 F). LRMS (ES^+), 592 (87%). FTIR (neat) ν_{max} = 2961, 1742, 1650, 1483, 1309 cm^{-1}; $[\alpha]^{25}$ –29.2 (c=3.5, $CDCl_3$).

2,3,5,6-tetrafluoro-4-methylcarbamoyl-benzenesulfonic acid 4-formyl-phenyl ester polystyrene-supported [3.104]



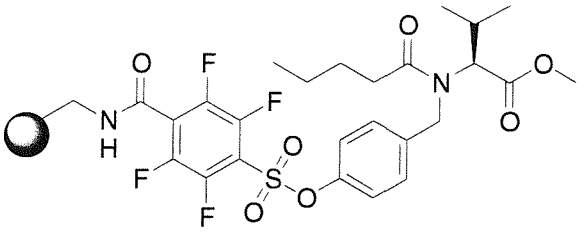
To a slurry of freshly prepared polystyrene-supported sulfonyl chloride **3.60** (5.05 g, 0.85 mmol g^{-1}, 4.27 mmol) pre-swelled in anhydrous CH_2Cl_2 (80 mL) was added 4-hydroxybenzaldehyde (5 mol equiv, 21.34 mmol, 2.61 g). The reaction vessel was purged with argon and shaken for 30 minutes to ensure dissolution of the aldehyde. *N,N*-diisopropylethylamine (6 mol equiv, 25.62 mmol, 4.43 mL) was added dropwise over 30 minutes with constant agitation. The reaction mixture was shaken under argon for a further 18 hrs at room temperature, the resin was filtered and washed with DMF, THF, CH_2Cl_2, Et_2O and MeOH and dried *in vacuo* for 12 hours to give the immobilised aldehyde (5.51 g, 0.77 mmol g^{-1}). FTIR (neat) ν_{max} = 2926, 1693, 1481, 1453 cm^{-1}.

3-methyl-2-[4-(2,3,5,6-tetrafluoro-4-methylcarbamoyl-benzenesulfonyloxy)-benzylamino]-butyric acid methyl ester polystyrene-supported [3.105]



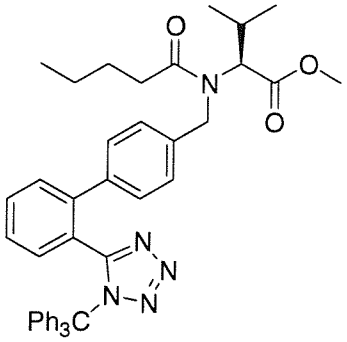
To a slurry of the sulfonate linked aldehyde on polystyrene **3.104** (4.50 g, 0.77 mmol g^{-1}, 3.49 mmol) swollen in a mixture of AcOH in DMF (1% v/v, 60 mL) was added $NaBH(OAc)_3$ (5 mol equiv, 17.43 mmol, 3.69 g) and the reaction vessel was purged with argon and shaken for 30 minutes to ensure dissolution of the reducing agent. To the cloudy slurry was added L-valine methyl ester hydrochloride (5 mol equiv, 17.43 mmol, 2.92 g) in one portion. The reaction mixture was shaken under argon for a further 18 hrs at room temperature, the resin was filtered and washed with DMF, THF, CH_2Cl_2, Et_2O and MeOH and dried *in vacuo* for 12 hours to give the immobilised secondary amine (4.99 g, 0.70 mmol g^{-1}). FTIR (neat) ν_{max} = 2925, 1732, 1693, 1480, 1453 cm^{-1}.

3-methyl-2-{pentanoyl-[4-(2,3,5,6-tetrafluoro-4-methylcarbamoyl-benzenesulfonyloxy)-benzyl]-amino}-butyric acid methyl ester polystyrene-supported [3.106]



To a slurried mixture of the supported secondary amine **3.105** (4.00g, 0.70 mmol g^{-1}, 2.80 mmol) and NEt_3 (5 mol equiv, 14 mmol, 1.95 mL) in CH_2Cl_2 (60 mL) under argon at 0 °C was added dropwise n-valeryl chloride (5 mol equiv, 14 mmol, 1.66 mL) over 30 minutes with constant agitation. The reaction mixture was allowed to warm to room temperature and agitation was continued for a further 12 hours. The resin was filtered and washed with DMF, THF, CH_2Cl_2, Et_2O and MeOH and dried *in vacuo* for 12 hours to give the sulfonate linked immobilised amide (4.28 g, 0.65 mmol g^{-1}). FTIR (neat) ν_{max} = 2928, 1724, 1691, 1662, 1493 cm^{-1}.

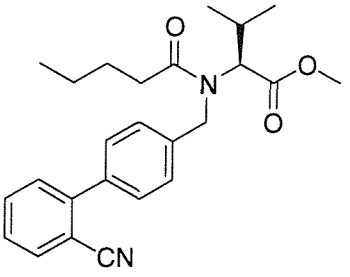
(*S*)-3-methyl-2-{pentanoyl-[2'-(1-trityl-tetrazolidin-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid methyl ester [3.108]



$C_{44}H_{45}N_5O_3$
Mol. Wt.: 691.86

To a slurry of the sulfonate linked amide **3.106** (2.00 g, 0.65 mmol g^{-1}, 1.30 mmol) in degassed DME (20 mL) was added $Pd(OAc)_2$ (3 mol%, 0.039 mmol, 8.75 mg), Xphos (10 mol %, 0.13 mmol, 62.0 mg) and NEt_3 (10 mol equiv, 13.0 mmol, 1.81 mL). The reaction vessel was purged with argon, and the mixture was agitated for 30 minutes, prior to the addition of a degassed solution of the trityltetrazolylphenyl boronic acid (3 mol equiv, 3.90 mmol, 1.69 g) in DME (10 mL). The reaction mixture was heated to 80 °C and agitated for a further 18 hrs at this temperature. The cooled reaction mixture was filtered and the resin washed alternately with Et_2O and CH_2Cl_2 (6 x 20 mL). Combined washings were concentrated *in vacuo* and the residue purified by silica chromatography, eluting with 10% ethyl acetate/hexanes. Appropriate fractions were combined and concentrated *in vacuo* to give the desired product as a light yellow solid (350 mg, 0.506 mmol, 39%). M.p = 132-133 °C; ^{1}H NMR ($CDCl_3$, two rotamers, 2:1) δ 7.90-7.81 (m, 1 H), 7.54-7.24 (m, 11 H), 7.17-6.95 (m, 11 H), 4.90 and 4.21 (minor benzylic rotamer, AM d, J = 15.3 Hz, 2 H), 4.85 (major) and 4.02 (minor methine rotamer, d, J = 10.6 Hz, 1 H + 1 H), 4.58 and 4.51 (major benzylic rotamer, d, J = 21.0 Hz, 2 H), 3.37 (major methyl rotamer, s, 3 H), 3.29 (minor methyl rotamer, s, 3 H), 2.67-2.10 (m, 3 H + 3 H), 1.85-1.10 (m, 4 H + 4 H), 1.05-0.95 (m, 9 H + 9 H). ^{13}C NMR δ 174.8, 174.5, 171.3, 170.6, 164.5, 142.3, 141.8, 141.6, 140.4, 139.8, 137.0, 136.0, 131.0, 130.8, 130.5, 130.3, 130.1, 129.7, 129.2, 128.5, 128.0, 127.8, 127.6, 126.7, 126.6, 125.9, 83.1, 77.6, 66.1, 62.2, 60.7, 52.1, 51.9, 48.7, 45.7, 33.8, 33.6, 28.0, 27.8, 27.7, 22.9, 22.7, 21.3, 20.3, 19.1, 19.0, 14.5, 14.2. LRMS (ES^+), 692 (100%); FTIR (neat) ν_{max} = 2962, 1739, 1649, 1447, 1202 cm^{-1}; $[\alpha]^{25}$ –31.6 (c=3.5, $CDCl_3$).

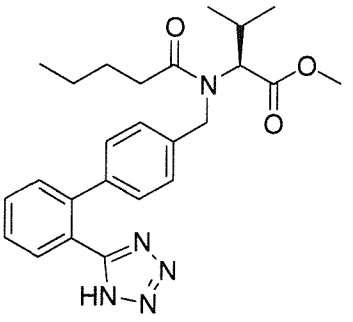
(*S*)-2-[(2'-cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid methyl ester [3.116]



$C_{25}H_{30}N_2O_3$
Mol. Wt.: 406.52

To a slurry of the sulfonate linked amide **3.106** (2.00 g, 0.65 mmol g^{-1}, 1.30 mmol) in degassed DME (20 mL) was added $PdCl_2$(dppf) (5 mol%, 0.07 mmol, 53.0 mg), Xphos (10 mol %, 0.13 mmol, 62.0 mg), finely ground K_3PO_4 (2 mol equiv, 2.6 mmol, 550 mg), NEt_3 (10 mol equiv, 13 mmol, 1.81 mL). The reaction vessel was purged thoroughly with argon, and the reaction mixture was agitated for 30 minutes, prior to the addition of a degassed solution of 2-cyanophenyl boronic acid (3 mol equiv, 3.90 mmol, 570.0 mg) in DME (10 mL). The reaction mixture was heated to 80 °C and agitated for a further 18 hrs at this temperature. The cooled reaction mixture was filtered and the resin washed alternately with Et_2O and CH_2Cl_2 (6 x 20 mL). Combined washings were concentrated *in vacuo* and the residue purified by silica chromatography, eluting with 30% ethyl acetate/hexanes. Appropriate fractions were combined and concentrated *in vacuo* to give the desired product as a colourless oil (310 mg, 0.76 mmol, 59%). ^{1}H NMR ($CDCl_3$, two rotamers, 1.8:1) δ 7.62 (aryl, app t, *J* = 7.5, Hz, 1 H + 1 H), 7.52 (aryl, d, *J* = 7.5, 1 H), 7.50 (aryl, d, *J* = 7.5, 1 H), 7.47-7.17 (aryl, m, 6 H + 6 H), 5.00 and 4.16 (minor benzylic rotamer, AM d, *J* = 15.6 Hz, 2 H), 4.87 (major) and 3.99 (minor methine rotamer, d, *J* = 10.3 Hz, 1 H + 1 H), 4.65 and 4.57 (major benzylic rotamer, d, *J* = 18.4 Hz, 2 H), 3.34 (major methyl rotamer, s, 3 H), 3.25 (minor methyl rotamer, s, 3 H), 2.61-2.12 (m, 3 H + 3 H), 1.73-1.47 (m, 2 H + 2 H), 1.34 (dd, *J* = 7.4, 14.8 Hz, 1 H + 1 H), 1.17 (ddd, *J* = 7.5, 14.9, 23.3Hz, 1 H + 1 H), 0.96-0.70 (m, 9 H + 9 H). ^{13}C NMR δ 174.4, 174.1, 170.9, 170.1, 145.1, 144.6, 138.7, 137.9, 137.0, 136.5, 133.7, 133.6, 132.9, 132.8, 129.9, 128.9, 128.4, 127.9, 127.7, 127.5, 126.2, 118.6, 118.5, 111.00, 65.6, 61.6, 60.2, 51.9, 51.6, 48.0, 45.1, 33.3, 33.2, 31.5, 27.7, 27.4, 27.3, 27.3, 22.6, 22.5, 22.3, 20.9, 19.8, 18.6, 18.5, 14.12, 14.07, 13.9, 13.8. CIMS, 407 (100%), 321 (56%), 192 (52%); FTIR (neat) ν_{max} = 2959, 2224, 1738, 1649, 1202 cm^{-1}; $[\alpha]^{25}$ –38.0 (c=3.5, $CDCl_3$).

(*S*)-3-methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid methyl ester (Valsartan methyl ester) [3.83]

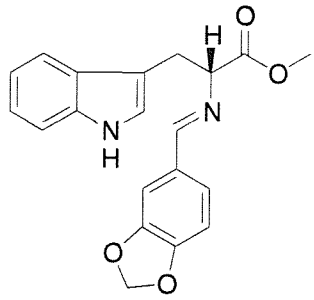


$C_{25}H_{31}N_5O_3$
Mol. Wt.: 449.55

To a stirring solution of the nitrile **3.116** (250.0 mg, 0.61 mmol) in dry toluene (3.0 mL) was added trimethylsilylazide (5 mol equiv, 3.07 mmol, 0.41 mL) and di-n-butyltin oxide (10 mol%, 0.06 mmol, 15.0 mg). The reaction mixture was heated to 100 °C and stirred under Ar (g) for 48 hrs. Upon cooling, the crude reaction mixture was evaporated *in vacuo* to a light brown gum which was chromatographed (eluting with 30% ethyl acetate/hexanes) on silica to give the desired tetrazole as a colourless amorphous glass (239.0 mg, 0.53 mmol, 87%). M.p = 129-130 °C; ^{1}H NMR ($CDCl_3$, two rotamers, 1:1) δ 7.85 (d, J = 7.5 Hz, 1 H), 7.77 (d, J = 7.4 Hz, 1 H), 7.54 (m, 1 H + 1 H), 7.41 (m, 2 H + 2 H), 7.03 (m, 4 H + 4 H), 4.89 and 4.17 (benzylic rotamer, AM d, J = 15.6 Hz, 2 H), 4.77 and 4.00 (methine rotamer, d, J = 10.6 Hz, 1 H + 1 H), 4.61 and 4.53 (benzylic rotamer, d, J = 17.8 Hz, 2 H), 3.36 (methyl rotamer, s, 3 H), 3.33 (methyl rotamer, s, 3 H), 2.60-2.10 (m, 1 H + 2 H), 1.65-1.40 (m, 1 H + 1 H), 1.38-1.15 (m, 1 H + 1 H), 0.95-0.75 (m, 9 H + 9 H). ^{13}C NMR δ 175.4, 174.6, 171.3, 170.4, 155.8, 155.4, 141.5, 139.0, 138.2, 137.8, 136.9, 131.4, 131.3, 131.0, 130.9, 129.6, 129.1, 128.2, 128.2, 128.0, 126.5, 123.5, 123.1, 66.2, 62.2, 52.4, 52.1, 48.6, 45.7, 33.7, 31.9, 27.9, 27.8, 27.8, 27.6, 23.0, 22.7, 20.2, 20.1, 19.0, 18.9, 14.4, 14.1. LRMS (ES^-), 448 (98%). FTIR (neat) ν_{max} = 2962, 1737, 1606, 1459, 1205 cm^{-1}; $[\alpha]^{25}$ –28.8 (c=3.5, $CDCl_3$).

6.4 Chapter IV experimental procedures and spectroscopic data

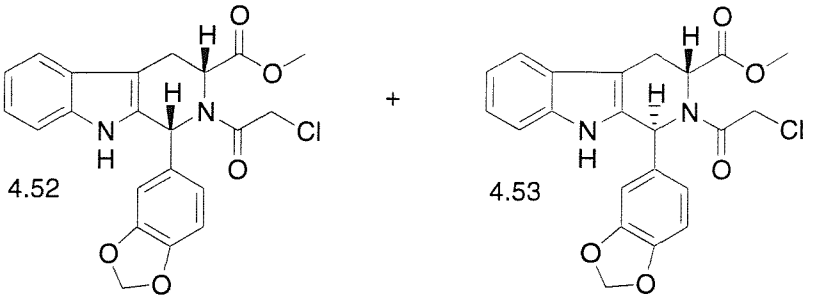
2-[(Benzo[1,3]dioxol-5-ylmethylene)-amino]-3-(1*H*-indol-3-yl)-propionic acid methyl ester (4.42)



$C_{20}H_{18}N_2O_4$
Mol. Wt.: 350.37

To a solution of D-Tryptophan methyl ester hydrochloride (2.3 g, 10.5 mmol, 1 mol equiv) and piperonal (1.05 mol equiv, 11.0 mmol, 1.66 g) in CH_2Cl_2 (25 mL) were added anhydrous magnesium sulfate (5 mol equiv, 52.7 mmol, 6.34g) and triethylamine (1.01 mol equiv, 10.64 mmol, 1.48 mL) added in one portion with rapid stirring under nitrogen for 24 h. The reaction mixture was filtered and evaporated to dryness *in vacuo*, then under high vacuum (4 h). Trituration with pentane (3 x 50 mL), and recrystallisation from 10 % v/v CH_2Cl_2 / hexanes afforded a white powder (3.51 g, 10.01 mmol, 95 %). ^{1}H NMR ($CDCl_3$) δ 9.08 (s, 1H, indole NH), 7.67 (s, 1H), 7.51 (d, 1H, *J* = 7.5 Hz), 7.29 (d, 1H, *J* = 7.7 Hz), 7.23 (s, 1H), 6.99 (ddd, 2H, *J* = 7.2, 6.8, 4.0 Hz), 6.86 (d, 1H, *J* = 7.7 Hz), 6.85 (s, 1H), 6.64 (d, 1H, *J* = 8.1 Hz), 5.87 (s, 2H), 4.12 (dd, 1H, J = 5.2, 2.9 Hz), 3.62 (s, 3H), 3.41 (dd, 1H, *J* = 9.4, 5.1 Hz), 3.09 (dd, 1H, *J* = 8.5, 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 162.7, 150.2, 148.2, 136.4, 130.5, 127.4, 125.1, 123.7, 121.6, 119.1, 118.7, 111.6, 110.8, 108.0, 106.9, 101.6, 73.7, 52.2, 29.8; MS (ES+) *m/z* 351.0 ($[M + H]^+$). FTIR ν_{max} 3284, 1734, 1447, 1253, 1036 cm^{-1}.

1-Benzo[1,3]dioxol-5-yl-2-(2-chloro-acetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester (4.52 and 4.53)



4.52 + 4.53

cis-D-isomer $C_{22}H_{19}ClN_2O_5$ *trans*-D-isomer

Mol. Wt.: 426.85

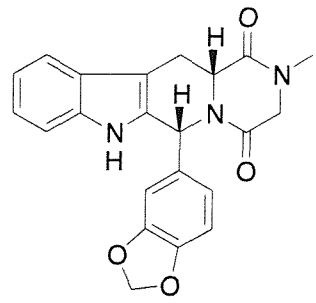
To a stirring solution of D-tryptophan imine (1.09 g, 3.11 mmol, 1.0 equiv) in dry CH_2Cl_2 (50 mL) under argon, was added DMAP (1.14 g, 3.0 equiv, 9.34 mmol) and the mixture was cooled to -25 °C. To the cooled solution was added dropwise over 10 minutes, a solution of chloroacetyl chloride (0.74 mL, 3.0 equiv, 9.29 mmol) in CH_2Cl_2 (10 mL). The yellow reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was washed successively with saturated aq. KH_2PO_4 (2 x 50 mL), brine (2 x 50 mL) and water (2 x 50 mL), then dried over $MgSO_4$. The filtrate was evaporated *in vacuo* to a yellow foam which was chromatographed on deactivated alumina (80 g), eluting with EtOAc/hexanes (30% v/v) to afford the *cis*-tetrahydro-β-carboline as a white solid, M.p. = 233-234 °C, (*Rf* = 0.3) (577 mg, 1.35 mmol, 44 %) and the *trans*-tetrahydro-β-carboline as a white solid, M.p. = 210-211 °C, (*Rf* = 0.2) (453 mg, 1.06 mmol, 34%). Total mass = 1.03 g, 2.41 mmol, 78%).

D-tryptophan *cis*-isomer (top TLC spot)

^{1}H NMR (DMSO-D_6) δ 10.91 (s, 1H, indole NH), 7.60 (d, 1H, *J* = 7.5 Hz), 7.34 (d, 1H, *J* = 7.8 Hz), 7.15 (app t, 1H, *J* = 7.3, 7.8 Hz), 7.08 (app t, 1H, *J* = 7.3 Hz), 6.85 (d, 1H, *J* = 8.0 Hz), 6.82 (s, 1H), 6.70 (s, 1H), 6.52 (d, 1H, *J* = 7.8 Hz), 6.02 (d, 2H, *J* = 7.3 Hz), 5.25 (d, 1H, *J* = 6.5 Hz), 4.85 (d, 1H, *J* = 13.8 Hz), 4.46 (d, 1H, *J* = 13.8 Hz), 3.49 (d, 1H, *J* = 16.0 Hz), 3.14 (dd, 1H, *J* = 6.5, 16.0 Hz), 3.09 (s, 3H); ^{13}C NMR (DMSO-D_6) δ 170.9 (CO), 167.3 (CO), 147.5 (Ar), 147.2 (Ar), 137.0 (Ar), 134.0 (Ar), 130.5 (Ar), 126.4 (Ar), 122.9 (ArH), 122.0 (ArH), 119.2 (ArH), 118.5 (ArH), 111.7 (ArH), 109.6 (ArH), 108.0 (ArH), 106.7 (Ar), 101.5 (CH_2), 52.9 (CH), 52.2 (CH_3), 51.9 (CH), 43.4 (CH_2), 21.7 (CH_2). MS (ES^+) 427 (100 %); FT IR (neat) ν_{max} = 3243, 1732, 1655, 1036 cm^{-1}.

D-tryptophan *trans*-isomer (lower TLC spot) exhibits broad duplicated rotameric signals ^{1}H NMR (DMSO-D6) δ 10.82 (s, 1H, indole NH), 7.45 (d, 1H, *J* = 7.8 Hz), 7.27 (d, 1H, *J* = 7.9 Hz), 7.04 (app t, 1H, *J* = 7.2, 7.6 Hz), 6.97 (app t, 1H, *J* = 7.0 Hz), 6.93 (d, 2H, *J* = 8.0 Hz), 6.82 (s, 1H), 6.11 (s, 1H), 5.94 (d, 2H, *J* = 5.5 Hz), 4.63 (d, 1H, *J* = 13.9 Hz), 4.26 (s, 1H), 3.52 (s, 3H), 3.42 (s, 1H), 3.32 (s, 2H); ^{13}C NMR (DMSO-D_6) δ 171.8 (CO), 170.9 (CO), 167.8 (CO), 147.8 (Ar), 147.1 (Ar), 145.9 (Ar), 137.9 (Ar), 136.4 (Ar), 134.7 (Ar), 133.3 (Ar), 125.8 (Ar), 121.3 (Ar), 120.3 (ArH), 118.9 (ArH), 118.1 (ArH), 111.4 (ArH), 108.5 (ArH), 108.0, 107.4, 106.6, 105.0, 103.3, 101.3, 100.9, 56.7, 55.9, 54.1, 52.8, 52.1, 43.6, 43.0, 23.5, 22.2; MS (ES^+) 427 (100 %); FT IR (neat) ν_{max} = 3338, 1725, 1642, 1238 cm^{-1}.

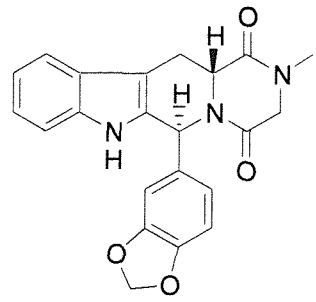
6-Benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (*cis R, R*-diastereoisomer) (Cialis™) (4.39)



$C_{22}H_{19}N_3O_4$
Mol. Wt.: 389.40

To a solution of the *cis*-tetrahydro-β-carboline chloride **4.46** (500 mg, 1.17 mmol, 1 mol equiv) dissolved in MeOH (5 mL) was added $MeNH_2$ in MeOH (2 mol dm^{-3}, 20 mol equiv, 23.4 mmol, 11.7 mL), and the reaction mixture was stirred at 50 °C under argon for 16 h, then evaporated *in vacuo* to an off-white solid. The residue was dissolved in CH_2Cl_2 (5 mL) and chromatographed on deactivated neutral alumina, eluting with EtOAc/Hexanes/CH_2Cl_2 (1:1.5:2 v/v) to afford after recrystallisation from ethanol, the *cis* title compound as a colourless crystalline solid (421 mg, 1.08 mmol, 92%). mp 299-301 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.13 (br s, 1H, indole NH), 7.6 (dd, 1H, *J* = 6.2, 2.2 Hz), 7.26 (m, 1H), 7.18 (m, 2H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.73 (s, 1H), 6.68 (d, 1H, J = 8.0 Hz), 6.13 (s, 1H), 5.84 (d, 2H, *J* = 5.1 Hz), 4.3 (dd, 1H, *J* = 7.3, 4.1 Hz), 4.1 (d, 1H, *J* = 18 Hz), 3.92 (d, 1H, *J* = 18 Hz), 3.79 (dd, 1H, *J* = 11.5, 4.5 Hz), 3.21 (dd, 1H, *J* = 12.2, 3.7 Hz), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 166.5, 136.7, 135.5, 132.9, 126.3, 122.6, 120.8, 120.2, 118.7, 111.3, 108.4, 107.6, 101.3, 56.8, 56.3, 52.2, 33.7, 24.0; MS (ESI) *m/z* 391.1 ($[M + H]^+$); FT IR (neat) ν_{max} = 3314, 1643, 1435, 1241 cm^{-1}.

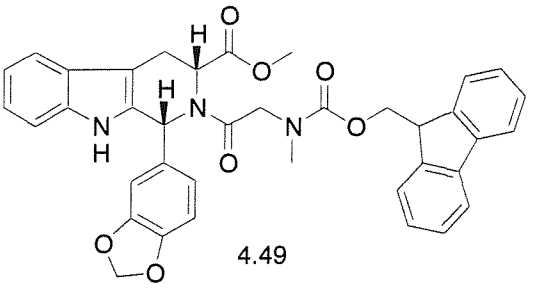
6-Benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (*trans R, S*-diastereoisomer) (epi-Cialis™) (4.51)



$C_{22}H_{19}N_3O_4$
Mol. Wt.: 389.40

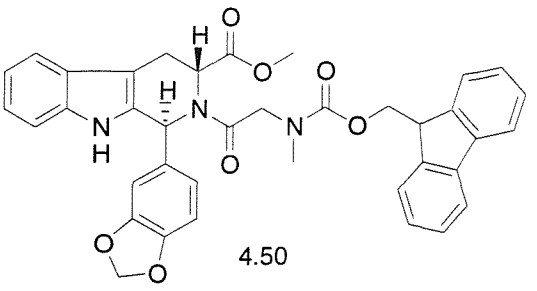
To a solution of the *trans*-tetrahydro-β-carboline chloride **4.47** (400 mg, 0.94 mmol, 1 mol equiv) dissolved in MeOH (4 mL) was added $MeNH_2$ in MeOH (2 mol dm^{-3}, 20 mol equiv, 18.8 mmol, 9.4 mL), and the reaction mixture was stirred at 50 °C under argon for 24 h, then evaporated *in vacuo* to an off-white solid. The residue was dissolved in CH_2Cl_2 (5 mL) and chromatographed on deactivated neutral alumina, eluting with EtOAc/Hexanes/CH_2Cl_2 (1:1.5:2 v/v) to afford the *trans* title compound as a white foam (327 mg, 0.84 mmol, 89%). mp 297-298 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H, indole NH), 7.52 (d, 1H, J = 7.4 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.18 (ddd, 2H, J = 9.2, 6.2, 4.8 Hz), 7.0 (s, 1H), 6.79 (s, 1H), 6.67 (s, 2H), 5.90 (d, 2H, J = 4.0 Hz), 4.32 (dd, 1H, J = 7.8, 4.0 Hz), 4.13 (d, 1H, J = 17.8 Hz), 3.95 (d, 1H, J = 17.8 Hz), 3.52 (dd, 1H, J = 11.3, 4.2 Hz), 2.98 (s, 3H), 2.92 (dd, 1H, J = 14.1, 8.3 Hz); MS (ESI) *m/z* 390.1 ($[M]^+$); FT IR (neat) ν_{max} = 3356, 1659, 1453, 1235 cm^{-1}.

1-Benzo[1,3]dioxol-5-yl-2-{2-[(9*H*-fluoren-9-ylmethoxycarbonyl)-methyl-amino]-acetyl}-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylic acid methyl ester



4.49

cis-D-isomer



4.50

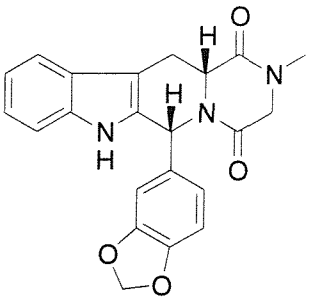
trans-D-isomer

$C_{38}H_{33}N_3O_7$
Mol. Wt.: 643.68

To a stirring solution of D-tryptophan imine **4.42** (355 mg, 1.01 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) under argon, was added DMAP (3 equiv, 3.03 mmol, 372 mg) and the mixture was cooled to -25 °C. To this cooled solution was added dropwise over 10 minutes, a solution of Fmoc-Sar-Cl (3 equiv, 3.03 mmol, 1.0 g) in CH_2Cl_2 (10 mL). The yellow reaction mixture was allowed to warm to ambient temperature and stirred for 2 h. The reaction mixture was washed successively with saturated aq KH_2PO_4 (2 x 50 mL), brine (2 x 50 mL) and water (2 x 50 mL), then dried over $MgSO_4$. The filtered solution was evaporated *in vacuo* to a yellow foam which was chromatographed on deactivated alumina eluting with EtOAc/hexanes (30% v/v) to afford the *cis*-tetrahydro-β-carboline as a white solid, M.p. > 250 °C (dec), (*Rf* = 0.3) (218 mg, 0.339 mmol, 34%) and the *trans*-tetrahydro-β-carboline as a white solid, M.p > 250 °C (dec), (*Rf* = 0.2) (198.1 mg, 0.308 mmol, 30%). Total mass = 416.1 mg, 0.646 mmol, 64%). *Cis*-tetrahydro-β-carboline, ^{1}H NMR ($CDCl_3$, exhibits broad duplicated rotameric signals) δ 9.26 (s, 1H, indole NH), 7.68 (d, 2H, *J* = 7.1 Hz), 7.54 (d, 1H, *J* = 6.8 Hz), 7.40 (d, 1H, *J* = 7.2 Hz), 7.33-7.19 (m, 5H), 7.15-7.05 (m, 3H), 6.86 (s, 1H), 6.64 (s, 1H), 6.45 (d, 1H, *J* = 7.3 Hz), 6.21 (d, 1H, *J* = 7.9 Hz), 5.68 (d, 1H, *J* = 15.9 Hz), 5.41 (s, 2H), 4.58 (d, 1H, *J* = 16.1 Hz), 4.41 (d, 1H, *J* = 5.5 Hz), 4.27 (d, 1H, *J* = 6.45 Hz), 4.18 (dd, 1H, *J* = 3.6, 10.9 Hz), 3.98 (d, 1H, *J* = 10.7 Hz), 3.92 (d, 1H, *J* = 6.7 Hz), 3.72 (d, 1H, *J* = 16.3 Hz), 3.01 (s, 3H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 167.9, 157.8, 147.4, 147.0, 144.6, 144.1, 141.5, 136.9, 133.9, 129.8, 127.9, 127.9, 127.4, 127.3, 126.7, 125.8, 125.4, 125.0, 123.1, 122.9, 122.3, 120.2, 120.2, 119.4, 119.1, 118.8, 111.5, 111.1, 109.9, 107.6, 107.0, 101.3, 101.1, 68.5, 67.3, 52.4, 52.0, 51.9, 51.4, 47.6, 47.2, 36.0, 22.6, 20.8, 14.4; MS (ES^+) = 645, ($[M + H]^+$); FT IR (neat) ν_{max} = 3279, 1740, 1660, 1449 cm^{-1}.

Trans-tetrahydro-β-carboline, ^{1}H NMR ($CDCl_3$, exhibits broad duplicated rotameric signals) δ 8.07 (br s, 1H, indole NH), 7.66 (d, 2H, *J* = 7.4 Hz), 7.42 (dd, 3H, *J* = 7.7, 8.1 Hz), 7.29 (t, 3H, *J* = 7.4 Hz), 7.18 (t, 3H, *J* = 7.4 Hz), 7.11 (d, 1H, *J* = 8.1 Hz), 7.01 (m, 3H), 6.74 (dd, 2H, *J* = 1.6, 8.1 Hz), 6.56 (d, 1H, *J* = 7.8 Hz), 5.98 (s, 1H), 5.71 (s, 2H), 4.28-3.95 (br m, 3H), 3.90 (br s, 1H), 3.46 (s, 3H), 3.19 (br s, 1H), 2.90 + 2.85 (methyl rotamer, s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 144.3, 144.2, 141.5, 137.0, 128.0, 127.4, 125.4, 122.6, 120.2, 120.1, 118.7, 111.5, 108.9, 107.1, 106.8, 101.6, 68.3, 68.0, 57.4, 52.9, 52.4, 47.4, 36.4, 35.6, 22.7, 14.4; MS (ES^+) = 645, ($[M + H]^+$); FT IR (neat) ν_{max} = 3322, 1738, 1674, 1214 cm^{-1}.

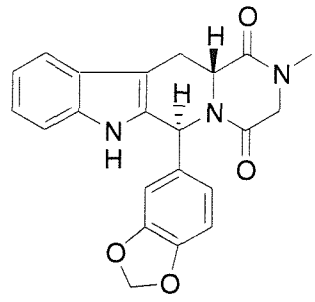
6-Benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (*cis R, R*-diastereoisomer) (Cialis™) (4.39)



$C_{22}H_{19}N_3O_4$
Mol. Wt.: 389.40

To a solution of the Fmoc-protected *cis*-tetrahydro-β-carboline (218 mg, 0.339 mmol) dissolved in DMF (4 mL) was added piperidine (1 mL), and the reaction mixture was stirred under argon for 1 h, the evaporated to dryness *in vacuo* to an off white solid. The residue was dissolved in CH_2Cl_2 (500 mL) and chromatographed on deactivated neutral alumina, eluting with EtOAc/Hexanes/CH_2Cl_2 (1:1.5:2 v/v) to afford after recrystallisation from ethanol, the *cis* title compound as a flocculent white powder (121.4 mg, 0.312 mmol, 92%). mp 299-301 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.13 (br s, 1H, indole NH), 7.6 (dd, 1H, *J* = 6.2, 2.2 Hz), 7.26 (m, 1H), 7.18 (m, 2H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.73 (s, 1H), 6.68 (d, 1H, J = 8.0 Hz), 6.13 (s, 1H), 5.84 (d, 2H, *J* = 5.1 Hz), 4.3 (dd, 1H, *J* = 7.3, 4.1 Hz), 4.1 (d, 1H, *J* = 18 Hz), 3.92 (d, 1H, *J* = 18 Hz), 3.79 (dd, 1H, *J* = 11.5, 4.5 Hz), 3.21 (dd, 1H, *J* = 12.2, 3.7 Hz), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 166.5, 136.7, 135.5, 132.9, 126.3, 122.6, 120.8, 120.2, 118.7, 111.3, 108.4, 107.6, 101.3, 56.8, 56.3, 52.2, 33.7, 24.0; MS (ESI) *m/z* 391.1 ($[M + H]^+$); FT IR (neat) ν_{max} = 3314, 1643, 1435, 1241 cm^{-1}.

6-Benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (*trans R, S*-diastereoisomer) (epi-Cialis™) (4.51)



$C_{22}H_{19}N_3O_4$
Mol. Wt.: 389.40

To a solution of the Fmoc-protected *trans*-tetrahydro-β-carboline (218 mg, 0.339 mmol) dissolved in DMF (4 mL) was added piperidine (1 mL), and the reaction mixture was stirred under argon for 1 h, the evaporated to dryness *in vacuo* to an off white solid. The residue was dissolved in CH_2Cl_2 (500 mL) and chromatographed on deactivated neutral alumina, eluting with EtOAc/Hexanes/CH_2Cl_2 (1:1.5:2 v/v) to afford after recrystallisation from ethanol, the *cis* title compound as a flocculent white powder (121.4 mg, 0.312 mmol, 86%). M.p. 297-299 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H, indole NH), 7.52 (d, 1H, J = 7.4 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.18 (ddd, 2H, J = 9.2, 6.2, 4.8 Hz), 7.0 (s, 1H), 6.79 (s, 1H), 6.67 (s, 2H), 5.90 (d, 2H, J = 4.0 Hz), 4.32 (dd, 1H, J = 7.8, 4.0 Hz), 4.13 (d, 1H, J = 17.8 Hz), 3.95 (d, 1H, J = 17.8 Hz), 3.52 (dd, 1H, J = 11.3, 4.2 Hz), 2.98 (s, 3H), 2.92 (dd, 1H, J = 14.1, 8.3 Hz); MS (ES^+) *m/z* 390.1 ($[M]^+$); FT IR (neat) ν_{max} = 3356, 1659, 1453, 1235 cm^{-1}.

6.5 Chapter V experimental procedure

General procedure for ionic liquid promoted solid-phase Suzuki-Miyaura reactions

The aryl iodide resin **5.15** (1.00 g, 0.68 mmol) was partially swollen in a degassed mixture of [bmim][BF_4^-] and DMF (either 1:1 or 1:9, total 6 mL). Tetrakis(triphenylphosphine)palladium(0) (5.0 mol %, 0.034 mmol, 39 mg) was added with rapid stirring under argon, and the catalytic reaction mixture heated to 110 °C (oil-bath temperature) with rapid stirring for 2 h. After cooling to ambient temperature, to the orange/red suspension was added with stirring the arylboronic acid (2.5 mol equiv, 1.7 mmol) followed by aq 1M Na_2CO_3 (2 mol equiv, 1.36 mmol). The reaction mixture was again heated to 110 °C with rapid stirring for 2 h. After cooling, the resulting black suspension was filtered. For recycling of the ionic liquid, the supernatant was washed with DMF (2 x 5 mL) and the combined washings filtered through celite. The DMF was evaporated *in vacuo*, and the orange/red ionic liquid washed with water (5 x 20 mL), ether (3 x 20 mL), and dried under vacuum for 2 h. The biaryl resin **5.16** was washed with water (1 x 10 mL), diethyl ether (5 x 10 mL), and THF (5 x 20 mL), and dried. The resin was then suspended in 5% TFA/CH_2Cl_2 (15 mL) with agitation for 1 h. The supernatant was neutralised with excess solid K_2CO_3 (~500 mg), and the resulting dark-coloured mixture was filtered concentrated, and dried. The crude product was taken up in 15 mL 1:1 EtOAc/hexanes, adsorbed onto silica (2 g), loaded on a short silica plug (2 g) and pure product fractions collected by chromatography. All biaryl compounds prepared are known, and their identity was confirmed by comparison with the literature.

The chosen set of ten arylboronic acids bearing a range of electron donating or withdrawing substituents 'R' and respective yields of isolated cross-coupling products under 2 different mole fractions of [bmim][BF_4^-] : DMF (either 1:1 or 1:9) is given in Table 6.6.

Entry	R	Yield (%)[a] 1:1 conditions	Yield (%)[a] 1:9 conditions
1	H	74	70
2	4-CHO	72	68
3	3-CHO	70	64
4	4-OPh	61	64
5	3-NHAc	40	44
6	4-OCF_3	45	40
7	3,5-diCF_3	42	37
8	4-OEt	65	67
9	3,4-OCH_2O-	60	63
10	4-*t*-Bu	73	70

Table 6.6 Examples of ionic liquid promoted Suzuki-Miyaura cross-coupling reactions;

[a] Isolated yield after silica chromatography, average of 3 experiments

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