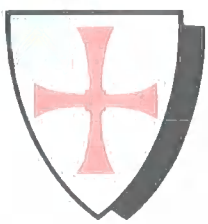
Perfluoroalkanesulfonyl linker units for solid phase organic synthesis

Scott, Peter J. H.

PERFLUOROALKANESULFONYL LINKER UNITS for SOLID PHASE ORGANIC SYNTHESIS



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Ph.D Thesis

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ABSTRACT

Perfluoroalkanesulfonyl Linker Units for Solid Phase Organic Synthesis

Peter J. H. Scott

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Diversity linker units exploit the cleavage step in solid phase synthesis for the incorporation of further diversity into target molecules. A solid-supported perfluorosulfonyl linker unit would allow cleavage of substrates using transition-metal-catalysed cross-coupling reactions. This thesis describes several approaches towards a perfluoroalkanesulfonyl diversity linker from diiodoperfluoroalkanes.

Early work concentrated on the reaction of diiodoperfluoroalkanes with eugenol. The resulting perfluoroalkyliodides were attached to Wang resin using Mitsunobu chemistry. However, stability problems prevented the generation of resin bound perfluoroalkanesulfonic acids and the route was abandoned.

A bis-perfluoroalkanesulfonyl chloride linker unit was prepared from diiodoperfluoroalkanes by generation of the bis-sodium sulfite salt and subsequent chlorination. Optimisation studies using design software allowed preparation of multigram quantities in 60 – 70% yield. Model solution phase synthesis of bis-perfluoroalkanesulfonamides and bis-perfluoroalkanesulfonate esters showed the feasibility of attaching the bis-sulfonyl chloride to amino resins and loading phenols. Diversity cleavage was demonstrated using Suzuki and Stille reactions and optimised by screening parallel arrays of reaction conditions. Loading the bis-sulfonyl chloride onto TentaGel® gave access to solid supported perfluorosulfonate esters and diversity cleavage was shown using Suzuki reactions. However, the linkage to solid supports proved to be unstable and an additional spacer unit was required if the linker was to find widespread use. To this end, a second generation perfluoroalkanesulfonyl linker unit was developed from allyl alcohol and diiodoperfluoroalkanes. Oxidation to a perfluoroalkanesulfonyl chloride was achieved using a novel reaction employing *N*-chlorosuccinimide. Several methods for loading this linker unit onto a solid support were investigated but none were successful and this chemistry requires further development before it offers a practical perfluoroalkanesulfonyl diversity linker.

CONTENTS

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Thank you, I couldn't have done it without all of you.

DECLARATION

The work contained in this thesis was carried out in the Department of Chemistry, University of Durham between October 2001 and October 2004. All the work is my own unless otherwise indicated. It has not previously been submitted for a degree at this or any other university.

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ABBREVIATIONS

The following abbreviations appear in this thesis:

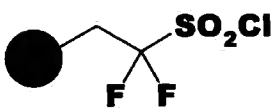
Ac	Acetate
ADDP	1,1'-(Azodicarbonyl) dipiperidine
AIBN	Azo-bis-*iso*butyronitrile
Ar	Aryl group
ATR	Attenuated total reflection
BEMP	2-*t*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
BuLi	*n*-Butyllithium
Cbz	Benzyloxycarbonyl
CPG	Controlled pore glass
d	Doublet
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	Dichloromethane
DIAD	Di*iso*propyl azodicarboxylate
DIC	*N,N'*-Di*iso*propylcarbodiimide
DIPEA	Di*iso*propylethyl amine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*'-Dimethylformamide
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane

EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionisation
ES	Electrospray
Et	Ethyl
Ether	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Fmoc	9-Fluorenylmethyloxycarbonyl
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
h	Hours
HOBt	1-Hydroxybenzotriazole hydrate
HRMS	High resolution mass spectrometry
Hz	Hertz
IMES	1,3-Bis-(2,4,6-trimethylphenyl) imidazolium chloride
IR	Infra red
m	Multiplet
M	Molar
MAS-NMR	Magic angle spinning nuclear magnetic resonance
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
min	Minutes
mmol	Millimole
mol	Mole
m.p	Melting point
NCS	*N*-Chlorosuccinimide
NfO	Nonaflate (Nonafluorobutanesulfonate O-$SO_2C_4F_9$)
nm	Nanometre
NMR	Nuclear magnetic resonance
o/n	Over night

PEG	Polyethylene glycol
Ph	Phenyl
PMB	*para*-Methoxy benzyl
ppm	Parts per million
PS	Polystyrene
psi	Pounds *per* square inch
q	Quartet
quint	Quintet
rt	Room temperature
s	Singlet
sept	Septet
t	Triplet
TBDMS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TfO	Triflate (Trifluoromethanesulfonate, O-SO_2CF_3)
TG	Amino TentaGel®
THF	Tetrahydrofuran
TLC	Thin layer chromatography
W	Watts
µl	Microlitres

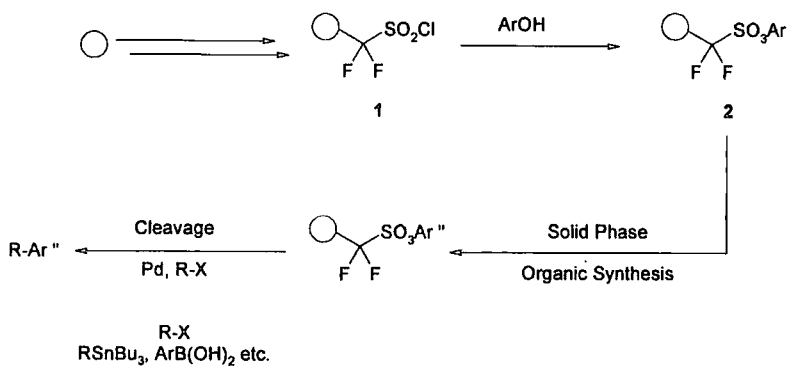
CHAPTER 1

GENERAL INTRODUCTION



1 General Introduction

This thesis describes research concerning the synthesis of a novel perfluoroalkanesulfonyl diversity linker unit based upon the triflate group for use in solid phase organic synthesis. Aryl perfluoroalkanesulfonate esters have received much attention in the literature following the discovery that they undergo transition-metal-catalysed cross-coupling reactions and therefore represent a desirable linker motif.[1-6] A solid-supported perfluoroalkanesulfonyl linker unit 1 would allow for the attachment of phenols to give solid-supported analogues of aryl perfluoroalkanesulfonate esters 2. After solid phase synthesis, cleavage of substrates could be envisaged by exploiting the reactivity of aryl perfluoroalkanesulfonate esters under transition-metal-catalysed cross-coupling conditions to leave a wide variety of groups at the cleavage site of the molecule, Scheme 1.1. This chapter will introduce the concept of solid phase organic synthesis, describe the general synthesis and reactivity of perfluoroalkanesulfonyl groups and finally outline the aims of the current research. The results obtained are discussed in Chapters 2 to 4, Chapter 5 concludes and experimental procedures are reported in Chapter 6.

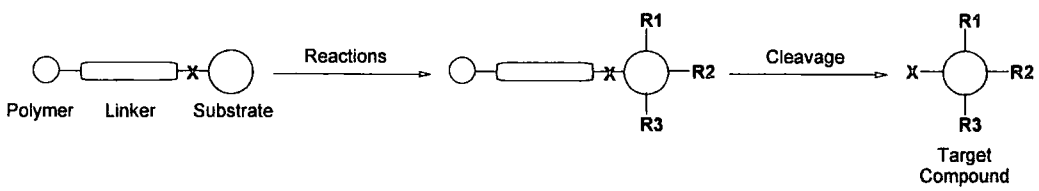


Scheme 1.1

1.1 Solid Phase Organic Synthesis

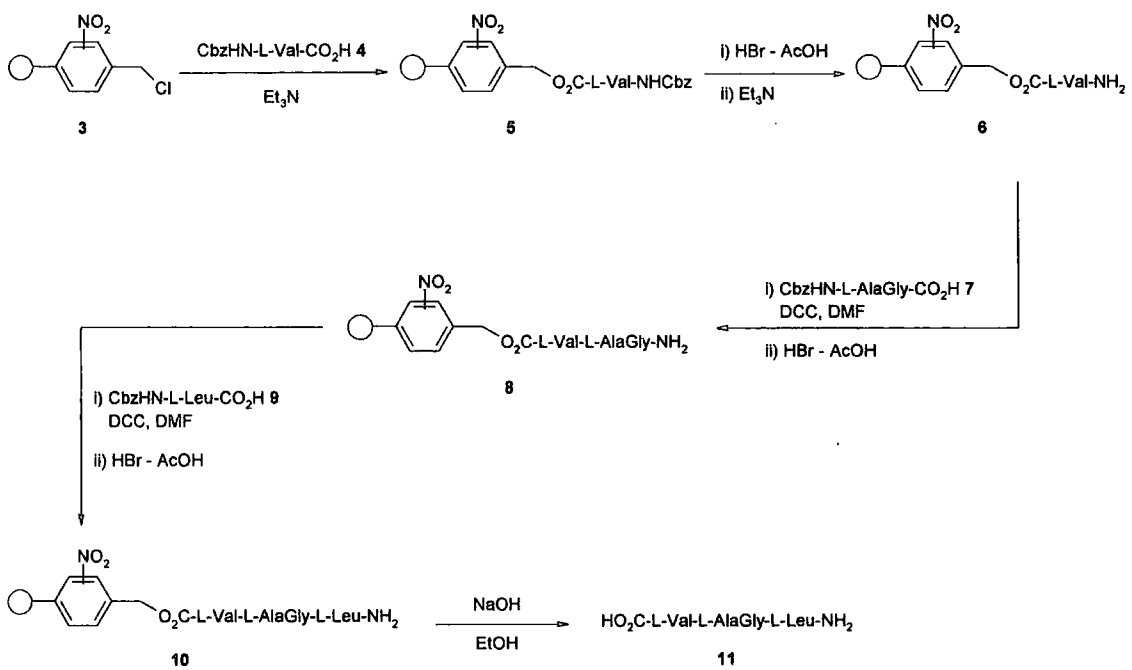
Solid phase organic synthesis is a simple and attractive synthetic technique. Reactions occur while one of the reagents is immobilised on an insoluble

polymer support, typically a polystyrene bead, *via* a suitable linker unit, Scheme 1.2.[7,8] These solid-supported reagents are suspended in solvents and shaken with the necessary reactants. As intermediates cannot be purified in solid phase chemistry, it is important that reactions are driven to completion and high yields so that the final product is not contaminated. In order to achieve this, it is not uncommon to use large excesses of reagents which would never be considered in conventional solution phase synthesis. For example, the use of 5 or 10 equivalents of reagents is not uncommon. Purification can then be achieved by collecting the solid supported species by filtration and washing away unreacted reagents and by-products with large amounts of solvent. A typical washing procedure is 5 – 10 washings with DCM to remove unreacted organic materials followed by 5 – 10 washings with methanol to remove any inorganic by-products. This is followed by further washings with DCM or ether and the resin can then be used without drying in the next step.[7] After the desired reactions have been completed, the target compound is detached from the linker unit in a final cleavage step. The basic cleavage protocol is to shake the resin with a solution of cleavage reagents. When cleavage is complete, the resin is filtered and the filtrate is kept as this contains the target molecule. If the cleavage reagent is an organic acid such as trifluoroacetic acid then this can simply be evaporated under reduced pressure to yield the product. However, some recent diversity linkers use more sophisticated reagents for cleavage. For example, if cleavage is achieved using a palladium-catalysed cross-coupling reaction then further purification of the target molecule is required. This can be achieved using conventional methods of purification such as flash chromatography.



Scheme 1.2

Solid phase chemistry was originally developed for peptide synthesis by Merrifield and reported in a seminal paper of 1963.[9] It was employed in the synthesis of a tetrapeptide, L-leucyl-L-alanylglycyl-L-valine 11, Scheme 1.3. Merrifield used a nitrated chloromethylpolystyrene-based resin 3 as the solid support. Cbz-protected L-valine was attached 5 by treating the resin with the triethylammonium salt 4. The Cbz group was removed under acidic conditions to give 6. The nitro groups on the resin were sufficiently deactivating to prevent unwanted acid mediated cleavage of compounds from the solid support at this stage. Cbz-protected L-alanylglycine 7 was then coupled using *N,N'*-dicyclohexylcarbodiimide (DCC) to yield resin-bound tripeptide 8. The Cbz deprotection was repeated and a further coupling step using L-leucine 9 gave tetrapeptide 10. Cleavage from the solid support was achieved by saponification using sodium hydroxide to yield tetrapeptide 11 which was purified using a Dowex ion exchange column.



Scheme 1.3

In recent years automated combinatorial chemistry and high throughput screening methods have revolutionised organic chemistry and the processes by which novel compounds are synthesised and screened for biological activity. Consequently, solid phase organic synthesis has become much more common and is no longer confined to peptide and oligonucleotide chemistry. A wide range of standard solution phase organic chemistry has now been adapted for solid-supported synthesis. To accommodate the growing number of reactions carried out using solid-supported reagents, large numbers of sophisticated solid supports and linker units have been developed. Therefore this section will discuss a representative system employed in solid phase organic synthesis including supports employed, different classes of linker units and typical methods of analysing solid phase reactions. The vast range of reactions employed in solid phase synthesis is analogous to standard solution phase synthesis and is consequently beyond the scope of this thesis. However, solid phase reactions have been extensively reviewed.[2, 7, 10-12]

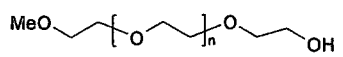
1.1.1 Supports for Solid Phase Organic Synthesis

A wide variety of chemically functionalised polymer supports have been utilised in solid phase chemistry. These include linear polymers, inorganic supports and insoluble polymer beads.[7, 8, 13] Solid supports must have high mechanical stability so that they are not broken down into smaller particles which could block filters. Furthermore, they need to be chemically inert to the large range of reaction conditions they will encounter and be stable at a range of temperatures.

1.1.1.1 Linear Polymer Supports

Polyethylene glycol, with a molecular weight of 5000, is a typical linear polymer support.[7, 8, 13] Usually the monomethyl ether 12 is used which possesses one hydroxyl group which can be functionalised, Scheme 1.4. PEG is soluble in water and most organic solvents but can be precipitated using hexane or diethyl ether. Once precipitated, substrates bonded to it are purified by filtering and washing away excess reagents. The main advantages of soluble polymer

supports are that insoluble reagents or catalysts can be used and NMR spectroscopy of substrates is possible. Disadvantages with linear polymers are that automation is difficult and loading of substrates is low. Despite these problems, they have been exploited in the synthesis of peptides and small organic molecules. Linear polymers have not been employed in the current research and so a detailed discussion is not relevant to this thesis but their use has been reviewed by Janda and Gravert.[14]



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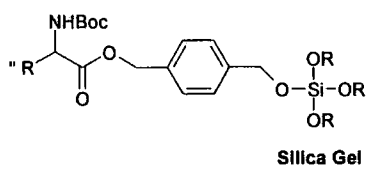
Scheme 1.4

1.1.1.2 Inorganic Polymer Supports

A typical inorganic polymer support is silicon dioxide which is commercially available as silica gel. The large surface area allows for the efficient transfer of reagents and it has become the support of choice for the synthesis of oligonucleotides.[7, 15] It was first used by Bayer who linked an amino acid to it as the ester of 1,4-bis(hydroxymethyl)benzene 13, Scheme 1.5.[16] Silica, with a larger pore size (25 – 300 nm), is commercially available as controlled pore glass (CPG) and has greater mechanical stability and a more regular particle size than regular silica gel.[7, 8] CPG is stable to any solvent and extremes of temperature and pressure. However, disadvantages are expense and very low loading (0.006 – 0.06 mmol / g). Furthermore, high hydrophilicity makes removal of water problematic.



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Scheme 1.5

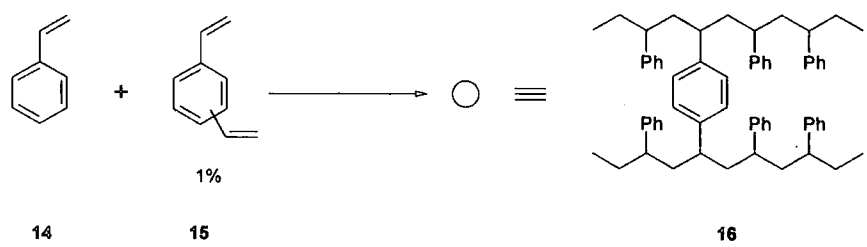
1.1.1.3 Insoluble Polymer Supports

The third and most common type of solid support is based on insoluble polymer beads which are easily filtered, dried and weighed.[7, 8] They have been extensively used in the current research and so will be discussed in detail. Insoluble polymer supports can be prepared in the laboratory but are more typically obtained from suppliers who prepare them on an industrial scale. Usually this involves the addition and dispersion of an organic phase of monomer and cross-linker in an aqueous phase. A free radical initiator is added and the temperature raised to promote polymerisation, converting the microdroplets into resin beads. This process is carefully monitored and the final size of the polymer bead is controlled by the degree of polymerisation. After completion the beads are filtered, washed to remove excess monomer and the aqueous phase, dried and finally sieved to ensure consistency of size.[7] A number of different types of resins are regularly employed in solid phase synthesis ranging from microporous gel-phase resins to insoluble macroporous resins. By far the most common are polystyrene beads which have been cross-linked with varying amounts of divinylbenzene and so these will be described initially.

1.1.1.4 Polystyrene Resins

Microporous Styrene – Divinylbenzene Copolymers

The resin bead first employed by Merrifield was a gel-type polymer prepared from microporous cross-linked polystyrene.[9] Divinylbenzene 15 (1%) was added to a suspension of undissolved styrene monomers 14 in water in order to cross-link the growing polystyrene chains 16 during the polymerisation process, Scheme 1.6. By far the most common resins in use today are still microporous polystyrene cross-linked with 1 – 2% divinylbenzene.[6, 16]

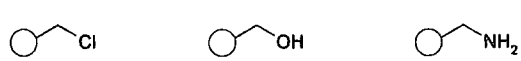


14 15 16

Scheme 1.6

The resulting cross-linked polystyrene bead can be considered as a single macromolecule. The cross-linking offers mechanical stability and insolubility (provided the degree of cross-linking exceeds 0.2%) but still allows swelling of the molecule in organic solvents.[7] Swelling is a characteristic of gel-type resins resulting from solvents penetrating the cross-linked polystyrene and causes the size of the beads to increase.[18] Polystyrene is hydrophobic and polarisable and so swelling is strongest in dipolar aprotic solvents and weakest in water, protic solvents and alkanes. As a result of this swelling property, reactions using lipophilic reagents proceed very quickly as penetration into the swollen polymer matrix is rapid whereas reactions involving ionic reagents tend to be slower due to the poor penetration of charged particles into the hydrophobic polymer.

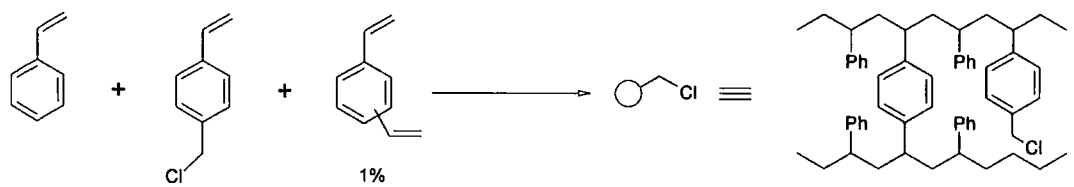
Microporous cross-linked polystyrene resins are mechanically stable allowing for reaction temperatures up to 130 °C and they tolerate a wide range of reaction conditions. However, the beads resulting from the polymerisation process described above do not allow for the covalent attachment of reactive substrates and so they require further functionalisation. The most common groups for the attachment of substrates are chloromethyl 17, originally employed by Merrifield, hydroxymethyl 18 and aminomethyl 19 groups, Scheme 1.7.[7, 8]



17 18 19

Scheme 1.7

Functionalised polystyrene resins can be prepared in two ways. The first is the copolymerisation of functionalised monomers such as 4-(chloromethyl)-styrene 20, Scheme 1.8.[17] However, this method is not ideal as styrene and 4-(chloromethyl)-styrene polymerise at different rates leading to uneven distribution of functional groups within the polymer.



14 20 15 17

Scheme 1.8

The second method is the chemical transformation of unfunctionalised polymers which may be achieved in many ways. A common approach is electrophilic aromatic substitution reactions and generally, reactions which can be carried out on *iso*-propylbenzene can also be performed on cross-linked polystyrene. Thus Friedel-Crafts alkylation and acylation, bromination, sulfonation and nitration reactions have all been employed to functionalise polystyrene.[19] Alternatively, polystyrene resins can also be functionalised using a metallation approach. Farrall and Fréchet showed that treatment of polystyrene resin with *n*-butyllithium and subsequent reaction with a range of electrophiles provided easy access to a range of functionalised resins.[20] For example, reaction with dry ice provided a carboxylic acid functionalised resin.

The number of reactive sites on a polymer support is termed the 'loading' and is expressed in mmol / g. This means that loading decreases with increasing weight of the compound attached to the polymer. Typical loadings of microporous polystyrene range from 0.5 to 1.5 mmol / g corresponding to approximately 20% derivatisation of the available phenyl groups. Higher loadings can be achieved but are less desirable as the high concentration of

resin-bound substrates in close proximity allows them to react with themselves leading to unwanted side reactions and contaminated products. Therefore, 0.5 – 1.5 mmol / g is a good compromise. An enormous number of functionalised microporous polystyrene resins are now commercially available and are routinely used in solid phase organic synthesis.[7, 8]

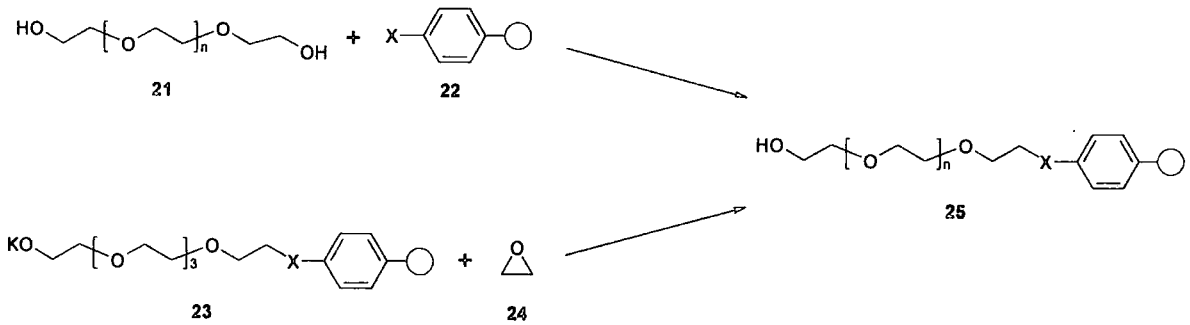
Macroporous Styrene – Divinylbenzene Copolymers

In the synthesis of microporous cross-linked polystyrene resins described above, an aqueous suspension of *undissolved* monomers was polymerised. However, if instead a solution of monomers *dissolved* in a solvent such as toluene is polymerised then it is possible to generate macroporous polystyrene. This is achieved by polymerising in the presence of a *porogen,* such as linear polystyrene, and a large amount of divinylbenzene (> 10%). The effect of this is to trap the porogen in the cross-linked polymer resulting in large pores and when polymerisation is complete the porogens are removed by washing. The macroporous polymers then remain stable in the absence of solvent and they have a large internal surface.[7] Typically, macroporous polystyrene divinylbenzene copolymers are used as ion exchange resins but more recently they have also found use in solid phase synthesis.[21] Typical loading for macroporous polystyrene is 0.8 – 1.0 mmol / g and they do not swell noticeably. Therefore the choice of solvent is less important and water and alcohols are suitable. The main advantage is that the macroporous nature means reagents do not need to penetrate a hydrophobic polystyrene matrix allowing for more rapid ionic reactions than if microporous resins were used.

1.1.1.5 PEG-grafted Polystyrene Resins

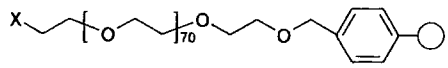
A modified form of cross-linked polystyrene which has had a large impact on solid phase organic synthesis is the polyethylene glycol grafted polystyrene family of resins **25**.[22] These can be prepared by linking PEG **21** on to functionalised polystyrene **22** but since PEG is bifunctional this can lead to high levels of cross-linking. Therefore, an alternative approach reported by a number

of groups is to polymerise oxirane 24 on to hydroxylated polystyrene 23, Scheme 1.9.



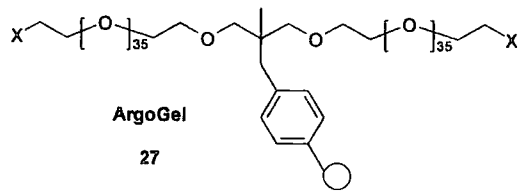
Scheme 1.9

TentaGel 26 is a commercially available PEG-grafted polystyrene resin. TentaGel consists of a 30% porous matrix of approximately 1% cross-linked polystyrene on to which 70% PEG with an average molecular weight of 3000 has been attached using the oxirane oligomerisation method.[7] Analogues of TentaGel are also available under the commercial name Argogel™ 27, Scheme 1.10.[7] TentaGel swells in a wide variety of organic solvents and typical loadings are 0.15 – 0.30 mmol / g. These resins have two main advantages. Firstly, resin-bound substrates exist in a pseudo solution-like environment comparable to THF and ether solvents which improves reactivity compared to basic microporous polystyrene. Secondly, the length and flexibility of the PEG chains makes it possible to record magic angle NMR spectra allowing for easy confirmation of resin-bound substrates at any given stage. Magic angle NMR spectroscopy will be discussed further in Section 1.1.3.3 as an analytical technique for solid phase chemistry. There are also some disadvantages to using TentaGel. The main disadvantage is the low loading of substrates although higher loading versions (~0.80 mmol / g) are available if required. Furthermore, they can release PEG upon treatment with trifluoroacetic acid, a common cleavage reagent, and the high PEG content also makes resins difficult to dry. Despite this, they have become very popular resins and find very wide use in solid phase synthesis.



TentaGel

26



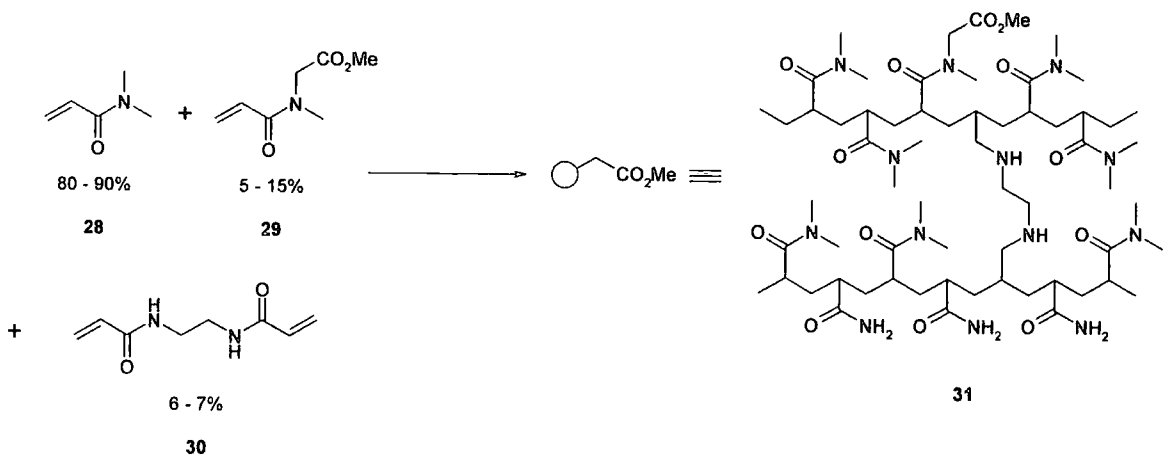
ArgoGel

27

Scheme 1.10

1.1.1.6 Polyacrylamide Resins

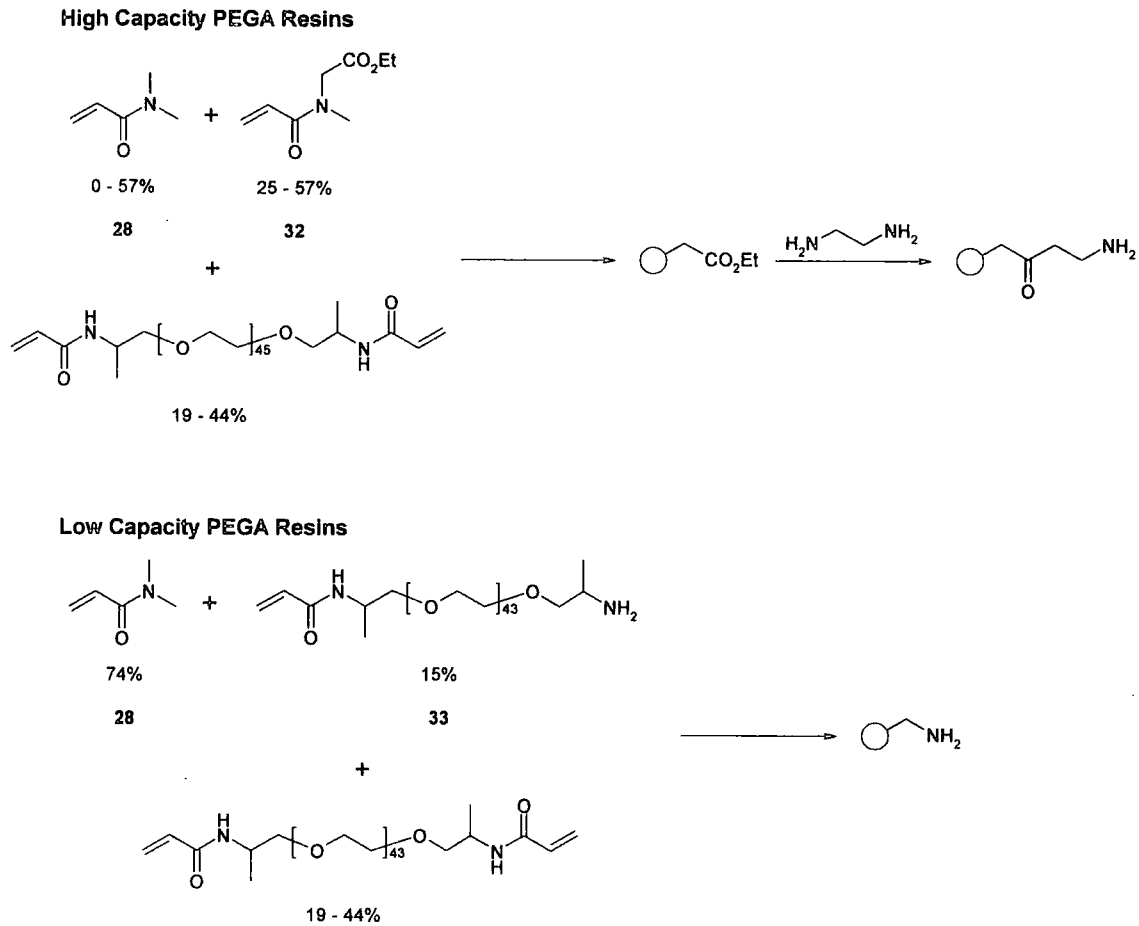
While the PEG-grafted polystyrene resins described above are quite hydrophilic, they are still based around a hydrophobic polystyrene core. Therefore, much research has been carried out to find a support more hydrophilic than polystyrene and this has led to the development of polyacrylamide supports.[7, 8, 22, 23] Similar to polystyrene, cross-linked polyacrylamides are insoluble and tend to gelate in organic solvents. However, as polyacrylamide is very hydrophilic, it is incompatible with most organic solvents and so derivatives of *N*,*N*-dimethylacrylamide 28 have been used as the basis for solid supports instead. For example, Pepsyn resin 31 is prepared by copolymerising *N*,*N*-dimethylacrylamide 28, *N*-acryloylsarcosine methyl ester 29 and *N*-(2-acryloylaminoethyl)acrylamide 30, Scheme 1.11. The ester functionality allows for the attachment of substrates or a linker unit. These polyacrylamide resins are chemically stable towards acids, bases and weak oxidising and reducing agents and are available in high loading of approximately 5.0 mmol / g.



Scheme 1.11

1.1.1.7 Polyacrylamide – PEG Copolymer Resins (PEGA Resins)

Medal has developed PEGA resins which are amino-functionalised polyacrylamide resins cross-linked with PEG.[24] PEGA resins can be obtained in two ways: either by copolymerisation with *N*-acryloylsarcosine ethyl ester 32 followed by aminolysis with ethylenediamine or by copolymerisation with an amino-group-containing monomer 33, Scheme 1.12. High capacity PEGA (0.8 mmol / g) and low capacity PEGA (0.2 – 0.4 mmol / g) resins have both been developed and their main advantages are acid stability and good swelling in a wide range of organic solvents. The major disadvantage is low mechanical stability which can lead to filtration problems. The main use of PEGA resins is in enzyme-mediated solid phase chemistry as enzymes are able to diffuse into the polymers.



Scheme 1.12

1.1.1.8 Magnetic Beads

A recent development in solid phase organic synthesis is the concept of magnetic beads. All resins described above are manipulated by manual methods and so in order to improve this Szymonifka and Chapman introduced magnetic beads.[8, 25] Polydivinylbenzene resin beads are initially nitrated. Reduction of the resulting nitro groups with ferrous sulfate hexahydrate produces ferrous and ferric ions that are trapped within the beads. These are then converted in to iron oxide crystals on heating with concentrated ammonium hydroxide solution and, after washing, the resulting beads contain 24 – 32% iron. These 'magnetic beads' can be manipulated using a simple bar magnet and have been exploited in peptide synthesis. Disadvantages lie in the fact that the highly

cross-linked polymer is intolerant of high levels of chemical functionality and that the iron in the bead is also reactive under some synthetic conditions.

This concludes a review of the most commonly used solid supports in solid phase chemistry. With the desired support in hand, the next step in a solid phase synthesis is to load the substrate on to the polymer. Typically, this is not done directly but rather a linker unit is loaded on first. Linker units possess some functionality which can be used for the subsequent loading of substrates and the wide range of available linker units is discussed below.

1.1.1.9 Conclusions

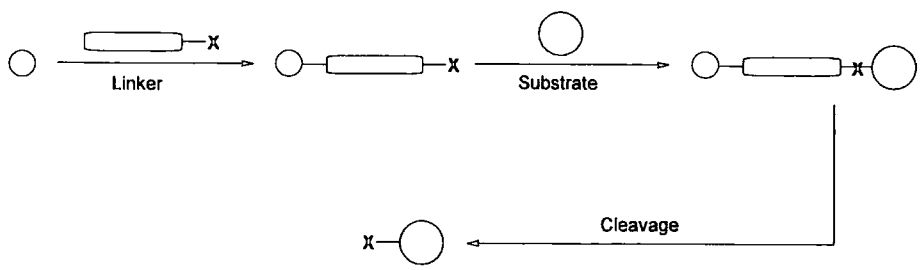
- A wide range of supports for solid phase organic synthesis have been developed including linear polymers, inorganic supports and insoluble polymer beads.

- The most popular are insoluble polymer beads based upon cross-linked polystyrene and PEG grafted polystyrene.

- More hydrophilic polymer supports have also been developed based upon polyacrylamide and polyacrylamide-PEG copolymers.

1.1.2 Linker Units in Solid Phase Organic Synthesis

The purpose of the linker unit in solid phase organic synthesis is twofold. Firstly linkers possess a functional group **X** which is used to attach reactive substrates to solid supports and which releases them at a later date under specific cleavage conditions, Scheme 1.13. Secondly, linker units tend to be long molecules which serve to hold reactive substrates away from the polymer matrix of the solid support in order to improve reactivity. This second function is less important in the case of PEG-grafted polymers.



Scheme 1.13

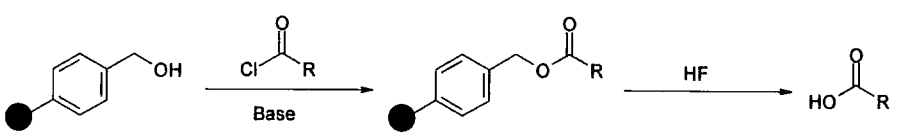
An ideal linker unit needs to be cheap to produce and it should be easily synthesised and loaded on to a solid support. As linker units will encounter a wide range of reactions, they also need to be stable to a huge range of synthetic conditions. Finally, if a linker unit is to be of practical use it should give quantitative attachment and cleavage of substrates. Many linker units do not fulfil all of these criteria but as the chemistry attempted on solid-supported substrates becomes ever more ambitious and diverse, more linker units are being developed all the time. Over 200 linkers have been developed in the last 20 years and consequently a comprehensive survey is beyond the scope of this thesis. However, they have been extensively reviewed and so this section will summarise the history of linkers giving representative examples to indicate key stages of development.[7, 8, 26-32] Linker units are broken down into three groups: traditional, traceless and diversity linker units. Traditional linker units possess some polar functionality X (*e.g.* OH, NH_2, CO_2H *etc.*) which is used to attach substrates to the solid support. However, one drawback of these early linker units is that this polar functional group is transferred to the target molecule upon cleavage as shown in Scheme 1.13. This can affect the biological activity of the target molecule and, if unwanted, these polar groups can be problematic to remove. In order to overcome this problem, traceless linker units and diversity linker units have been developed. There is a certain amount of ambiguity surrounding these terms and so, in this thesis, traceless linkers are defined as those which leave a hydrogen residue upon cleavage. Conversely, diversity linkers are more sophisticated and utilise the cleavage step for the incorporation of further diversity into target molecules and compound libraries.

1.1.2.1 Traditional Linker Units

Early linker units are classified according to the synthetic conditions required for cleavage. Typically, these conditions are simple acid- or base-induced cleavage and many of these linker units are still regularly employed in solid phase synthesis today.

Acid-labile Linker Units

Treatment with strong acid is one of the most common methods of cleavage used in solid phase organic synthesis. A significant advantage to acid cleavage is that once substrates have been removed from the solid support, they can be purified by simple evaporation of the acid. The lability of an acid-cleavable linker unit is dependent upon the stability of the protonated linker unit versus the cation formed upon cleavage. The more stable the cation, the more labile resin-bound substrates are to treatment with acid. The earliest example of an acid-labile linker unit is hydroxymethylpolystyrene **18**, known as the Merrifield linker unit. Substrates are attached through an ester linkage **34** and then cleaved as carboxylic acids **35** upon treatment with HF, Scheme 1.21.[7, 26, 29]

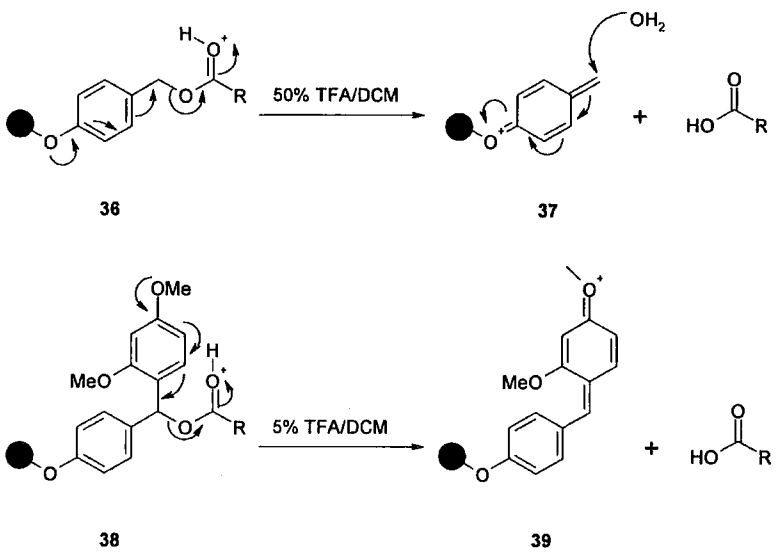


18 34 35

Scheme 1.14

While HF affords quantitative cleavage from the Merrifield linker, it is not an ideal acid to use in solid phase synthesis and so the Merrifield linker has evolved into linker units which can be cleaved using less harsh conditions. In order to achieve cleavage using milder conditions it is necessary to stabilise the resin-bound cation which is produced. To this end, two of the most commonly used linker units in solid phase organic synthesis are a hydroxymethylphenyl derivative developed by Wang[33] **36** and a hydroxymethylphenyl derivative stabilised by a

further anisole unit **38** reported by Rink.[34] The *para* oxygen in the Wang linker stabilises the resulting cation **37** so that cleavage can be achieved using 50% trifluoroacetic acid in DCM, Scheme 1.15. In comparison, greater stabilisation is afforded by the *ortho*- and *para*-methoxy groups of the Rink linker **39** and so cleavage can be carried out using just 5% trifluoroacetic acid (TFA). Trifluoroacetic acid is a milder acid than HF and a much preferred cleavage reagent in solid phase synthesis.

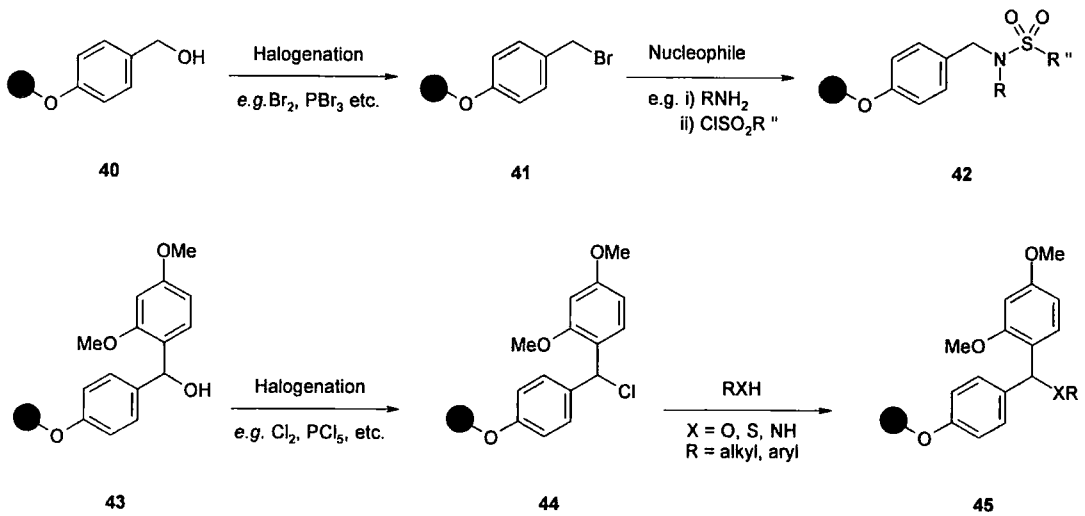


36 37 38 39

Scheme 1.15

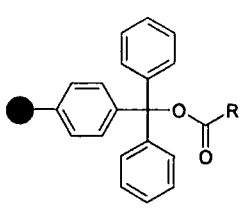
Initially substrates were attached to Wang and Rink linkers as carboxylic acids as shown in Scheme 1.15. Alternatively, substrates could be attached as ethers using Mitsunobu chemistry. However, significant advances were made in solid phase synthesis when the Wang linker **40** was converted into the bromo Wang linker **41** and the Rink linker **43** was converted into the chloro Rink linker **44**, Scheme 1.16.[29] These are both acid-cleavable linker units that a wide range of nucleophiles can be attached to using standard chemical reactions. For example, Ngu and Patel loaded an amine on to the bromo Wang linker. Subsequent sulfonation gave a resin-bound sulfonamide **42** which could be cleaved using 95% TFA / DCM.[35] Reacting amines with Rink chloride gives

access to the Rink amine linker to which substrates can be attached as amides, while Rink chloride **44** allows loading of substrates directly as thiols and alcohols **45**.



Scheme 1.16

One problem associated with the acid labile linkers described above is that the use of nucleophiles in synthetic steps can sometimes lead to unwanted cleavage of ester-linked substrates. To overcome this problem, the trityl linker unit **46** was introduced, Scheme 1.17.[29] The steric hindrance of the three phenyl groups prevents unwanted cleavage occurring even with reactive unhindered nucleophiles. Cleavage can still be achieved using TFA.

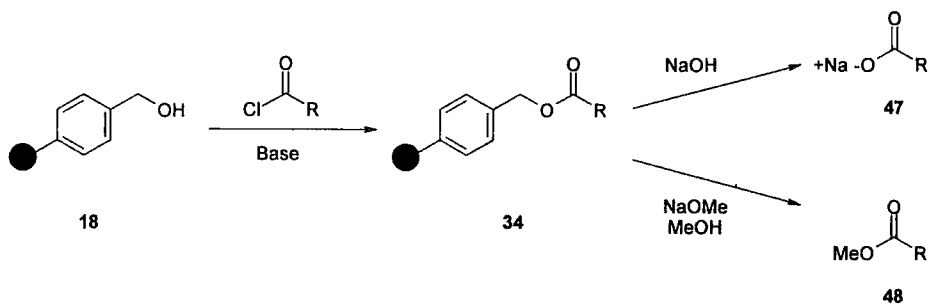


46

Scheme 1.17

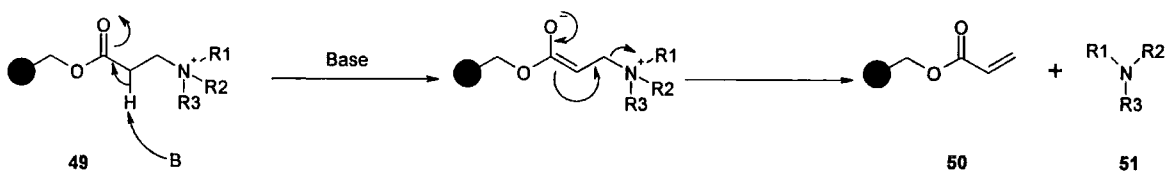
Base-labile Linker Units

There are two distinct types of base-labile cleavage in solid phase synthesis. The first involves nucleophilic addition elimination reactions, typically on a substrate attached to a linker unit through a carbonyl group, while the second is a base-catalysed reaction such as elimination or cyclisation. Hydroxymethylpolystyrene **18** was discussed above as an HF-cleavable linker unit but resin-bound substrates **34** are also labile under nucleophilic conditions. This was demonstrated in Merrifield's original work as the tetrapeptide was cleaved using sodium hydroxide.[9] Treatment with sodium hydroxide cleaves target molecules as the salt of the carboxylic acid derivative **47**. Alternatively, cleavage can be achieved using sodium methoxide in methanol to give the corresponding methyl ester **48**, Scheme 1.18.[29]



Scheme 1.18

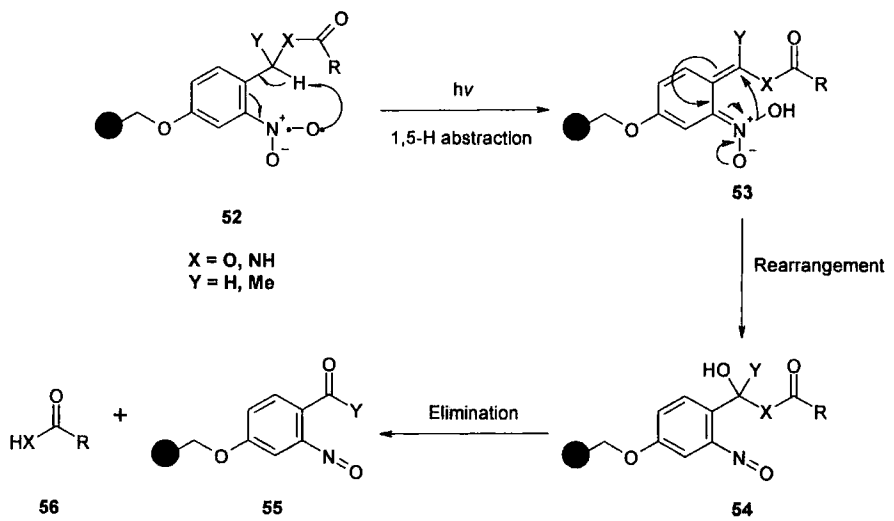
The second type of base-labile linker unit is typified by the tertiary amine linker **49**. Cleavage is the result of a Hofmann E1$_c$B elimination, Scheme 1.19, and so the lability of the linker unit is determined by the basicity of the cleavage reagent.[36] The target material is cleaved as a tertiary amine **51** to leave a resin-bound alkene **50**.



Scheme 1.19

Photocleavable Linker Units

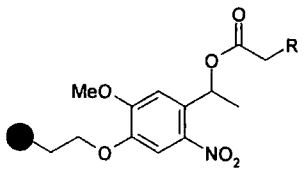
Photocleavable linker units can be stable to both acidic and basic conditions allowing for syntheses to be carried out without risk of unwanted cleavage.[7, 26, 29] A further major advantage is that target molecules cleaved from photocleavable linkers do not need to be purified from cleavage reagents. The first example was introduced by Rich and Gurwara in 1975 and is based upon the nitrobenzyl group.[37, 38] Substrates are attached through an ester or amide linkage **52** and on irradiation with UV light a 1,5-hydrogen abstraction occurs yielding **53**. However, this is unstable and undergoes a further rearrangement to yield acetal **54** which undergoes elimination to form a resin-bound aldehyde or ketone **55** and releases the product **56**, Scheme 1.20.



Scheme 1.20

There are some drawbacks to photocleavable linker units. Photocleavage reactions in solid phase synthesis are slow, often taking about 10 h, because of shadowing by the polymer matrix. Furthermore, they are complicated by UV absorbing by-products. For example, the resin-bound carbonyl **55** which is the by-product from the linker described above absorbs UV light strongly, making quantitative cleavage difficult to achieve. These problems have been in part overcome by Holmes who introduced the 4,5-dialkoxy-2-nitrobenzyl alcohol linker

unit **57**, Scheme 1.21.[7, 39] The deactivating nitro group makes the linker unit stable to TFA but the activating methoxy group allows for rapid cleavage of substrates in high purity using UV light in 2 h.



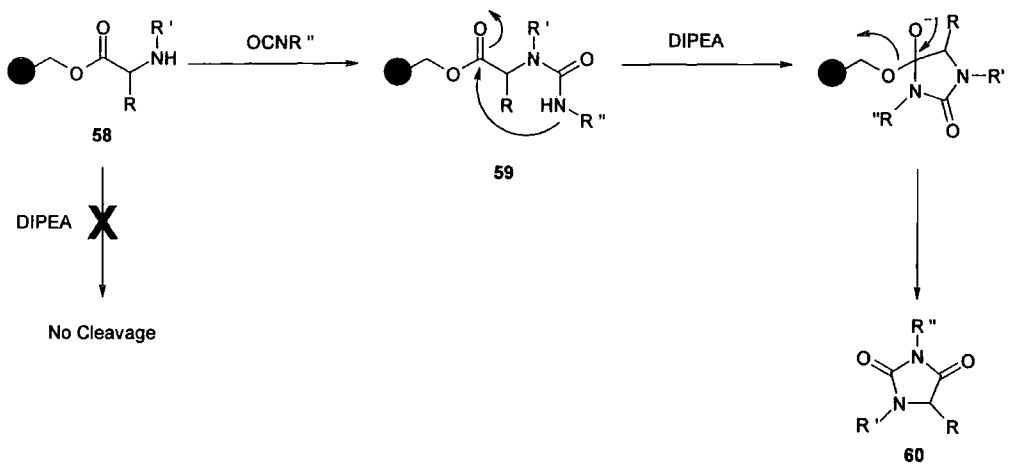
57

Scheme 1.21

Cyclo-cleavable Linker Units

Cyclo-cleavable linker units are those in which cyclisation and cleavage occur in the same step because the bond being broken in an intramolecular reaction is involved in attaching the substrate to the solid support. One of the principle advantages of cyclo-cleavable linker units is that only molecules containing the nucleophile will undergo cyclo-cleavage.[7, 26, 29] Therefore, if some synthetic steps have not gone to completion despite the use of excess reagents, only the target molecule will be cleaved. This gives rise to products of high purity which is one of the key aims of solid phase organic chemistry, especially in library synthesis.

A cyclo-cleavable linker unit was reported by Pavia *et al.* in 1993.[29] Treatment of an amino acid attached to hydroxymethylpolystyrene **58** with DIPEA does not result in cleavage, Scheme 1.22. However, reaction with an isocyanate results in urea **59** which on treatment with DIPEA cyclises to form hydantoin **60** and simultaneously breaks the carbon-oxygen bond to cleave the product. Any amino acid which did not react with the isocyanate remains bound to the solid support resulting in products of high purity.

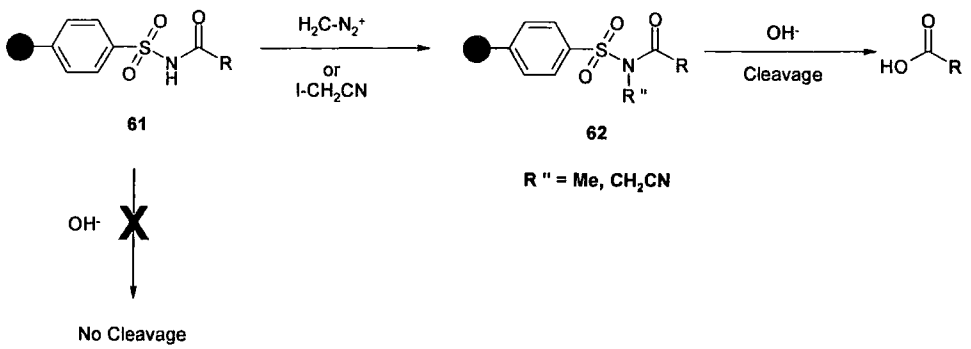


Scheme 1.22

Safety Catch Linker Units

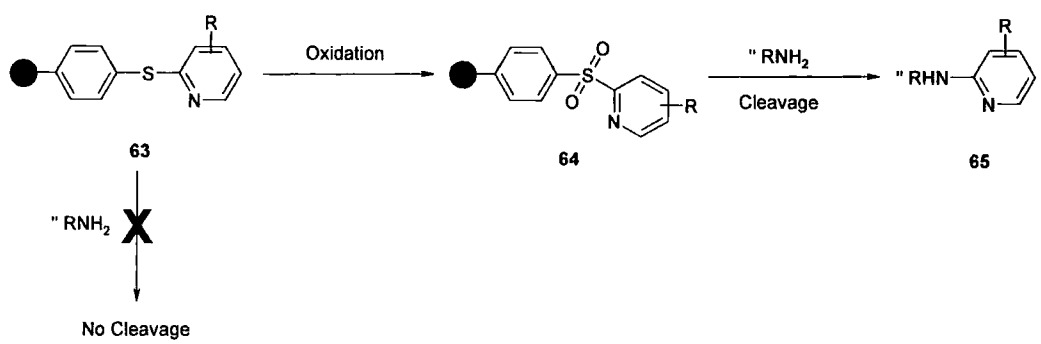
The final class of linker unit described in this section is the safety catch linkers. Cleavage from a safety catch linker is a 2-step process in which the first step activates the otherwise inert linker unit for cleavage and the second step cleaves the target molecule.[7, 29] The main advantage of safety catch linker units is that they are useful if conditions similar to the cleavage conditions are required during the solid phase synthesis. This would not be possible using traditional linker units described above, as cleavage of substrates would occur. However, in the case of safety catch linkers, no unwanted cleavage will occur without prior activation of the linker unit.

Kenner introduced a sulfonamide safety catch linker unit **61** in 1971.[40] It is stable to both acidic and basic conditions which is synthetically very useful. However, on alkylation of the nitrogen with diazomethane or iodoacetonitrile to give **62**, substrates can be cleaved under nucleophilic conditions, Scheme 1.23.



Scheme 1.23

Activation of safety catch linker units does not just have to occur by alkylation. For example, Gayo and Suto developed a pyridyl linker unit **63** containing a thioether linkage.[41] This thiol linkage is stable to a wide range of synthetic conditions but if it is oxidised to the corresponding sulfone **64** then cleavage of substrates can be achieved by aromatic nucleophilic substitution with an amine **65**, Scheme 1.24. As with all the linker units described so far, safety catch linker units also have some disadvantages associated with them. Primarily, while the linker units are stable to a range of synthetic conditions and cleavage occurs with mild reagents, conditions for activation are often quite extreme. In the two examples given above, substrates bound to the resin must be stable to either strong alkylation or oxidation conditions. While this is possible, it is often not the case and if a safety catch linker is to be used, activation *and* cleavage conditions need to be considered carefully.



Scheme 1.24

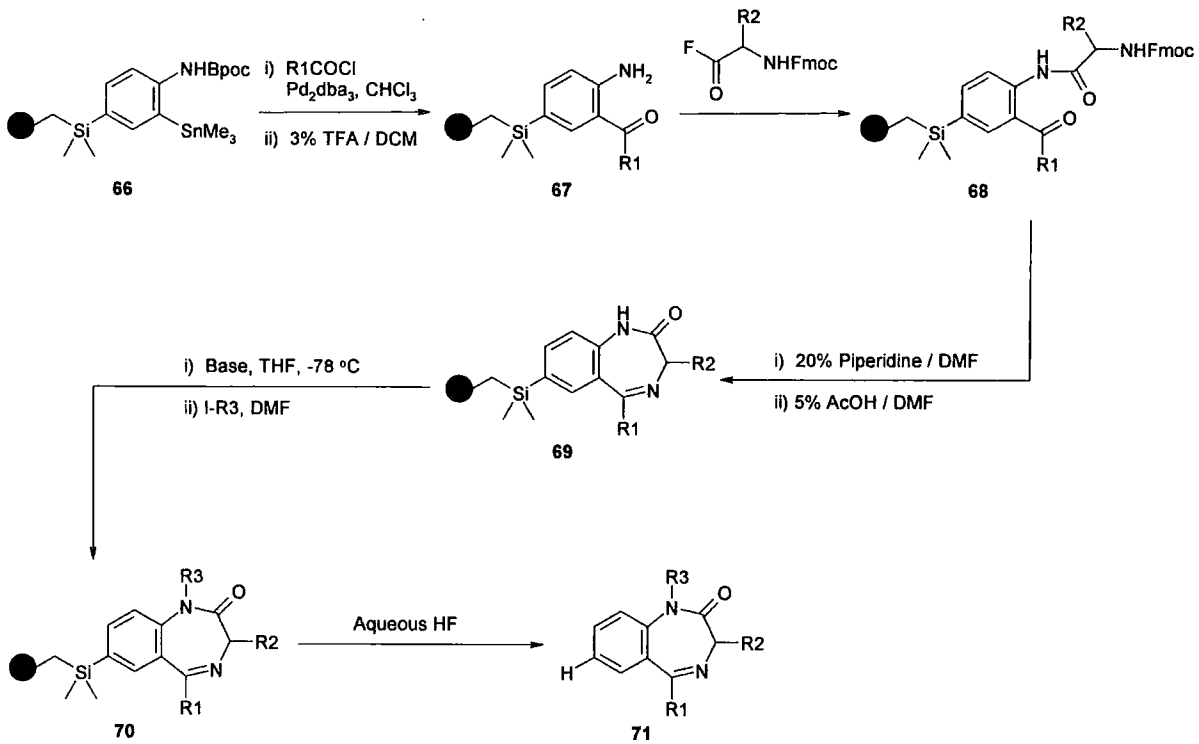
This concludes a review of traditional linker units ranging from simple acid- and base-labile linkers to more advanced photocleavable, cyclo-cleavable and safety catch linkers.

1.1.2.2 Traceless Linker Units

A common feature of all the linker units described above is that some polar functionality resulting either directly from the linker unit or from the cleavage reagents used is left at the cleavage site in the target molecule.[7, 26-31] These groups can alter the biological activity of molecules and they can be problematic to remove. Consequently, this has led to the development of traceless linker units which leave a hydrogen residue at the cleavage site of the molecule. No trace of the linker unit to which the substrate was attached is left in the cleaved product. Ellman was a pioneer in this field and so this review begins with his seminal silicon based traceless linker unit.

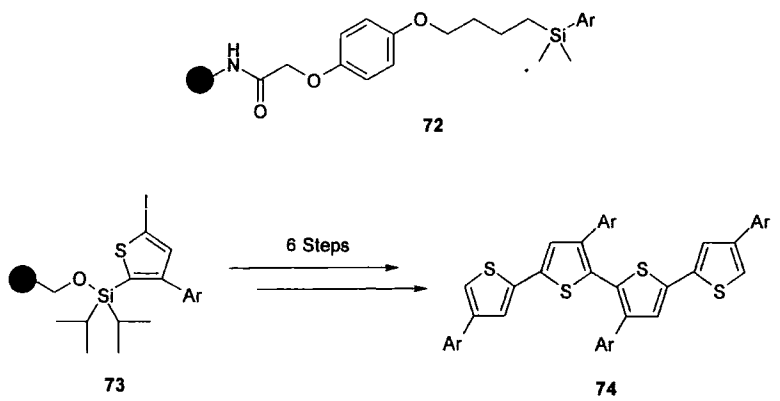
Silicon Traceless Linker Units

In 1995 Ellman introduced a silicon based traceless linker **66** which uses the well established protodesilylation of Si-Ar bonds to achieve traceless cleavage.[42, 43] It was exploited in the solid phase synthesis of benzodiazepines, Scheme 1.25. Initially resin-bound stannane **66** was coupled with an acid chloride using a Stille reaction to yield ketone **67**. The free amine was the coupled with an Fmoc-protected amino acid to give **68**. Fmoc-deprotection using piperidine promoted cyclisation to give resin-bound benzodiazepine **69** which was further alkylated giving **70**. Cleavage was then achieved using aqueous HF to yield benzodiazepine **71** possessing a hydrogen at the cleavage site.



Scheme 1.25

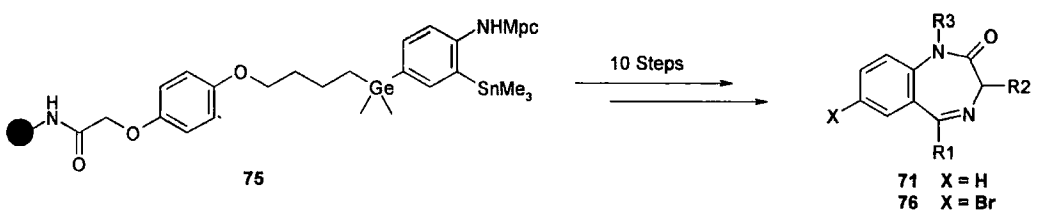
The drawback with Ellman's original linker **72** is that it requires a 5 step synthesis to introduce it from aminomethyl polystyrene.[42] Therefore research has focussed on alternatives and in 1996 Showalter introduced a modified version **73** which has become the most synthetically useful.[44] For example, Bauerle *et al.* used the Showalter linker in the synthesis of oligo-3-arylthiophenes **74**, Scheme 1.26.[45] Since Showalter's linker, a number of other silicon-based linkers have been developed and utilised in the solid phase organic synthesis of aryl compounds, heteroaryl compounds and natural products. They work along similar lines to those already described and continue to be useful tools to solid phase chemists.



Scheme 1.26

Germanium Traceless Linker Units

Concurrent with his synthesis of benzodiazepines using a silicon-derived traceless linker unit as described above, Ellman also introduced a traceless linker based upon germanium **75**.[43] The key advantage over its silicon counterpart is that the germanium linker is tolerant of many more functional groups. In contrast, the obvious disadvantage is the high cost of germanium when compared to silicon and again a 6-step synthesis is required. Ellman employed the germanium linker to synthesise benzodiazepines using identical chemistry to that described for the silicon linker. Conventional cleavage using TFA left a hydrogen at the cleavage position **71** whereas cleavage of the carbon – germanium bond using bromine resulted in the bromo derivative **76**, Scheme 1.27.

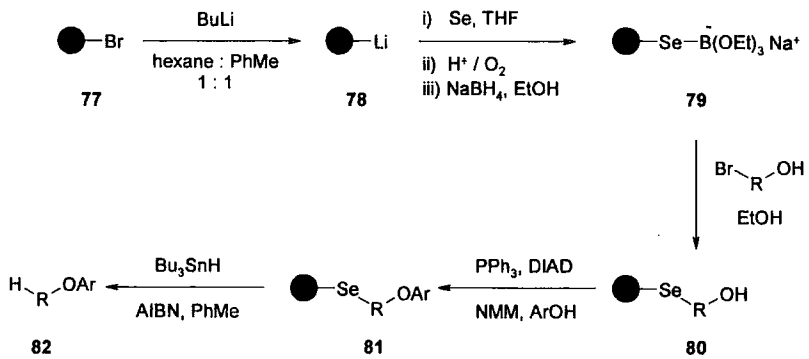


Scheme 1.27

Selenium Traceless Linker Units

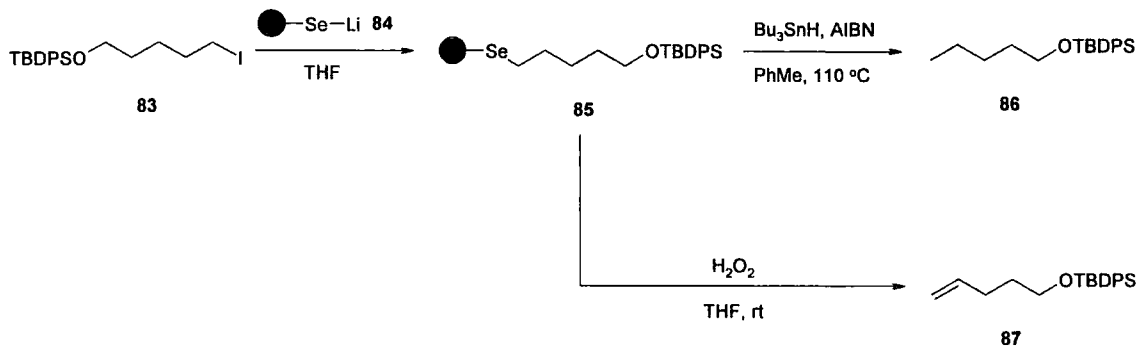
Traceless linker units based upon selenium are a recent development in solid phase organic synthesis and they have been used extensively since their

introduction. The first selenium traceless linker unit **79** was developed by Ruhland *et al.* in 1996.[46] Bromopolystyrene **77** was metallated with butyllithium and the resulting lithiated polystyrene **78** was treated with selenium powder. Subsequent air oxidation gave diselenides which were reduced with sodium borohydride to give selenium linker **79** as the sodium seleno(triethyl)borate complex, Scheme 1.28. Haloalcohols were loaded on to the linker unit **80** and they were converted into resin-bound ethers **81** using Mitsunobu chemistry. The phenolic ethers were then cleaved using radical chemistry to leave a proton at the cleavage site in **82**. This represents an interesting class of linker unit as it is the first time that radical reactions have been used in the cleavage step.



Scheme 1.28

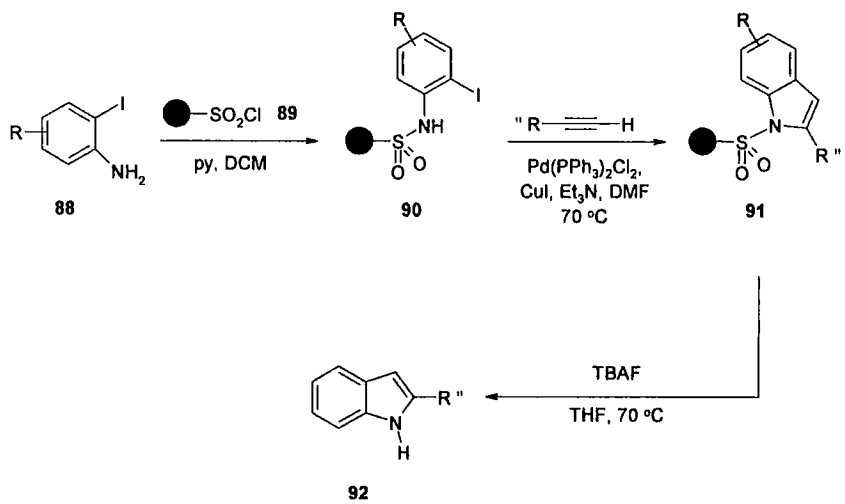
A similar lithium-selenide-based traceless linker **84** was also reported by Nicolaou in 1996.[47] Protected iodoalcohol **83** was loaded giving **85**. Nicolaou demonstrated the analogous radical cleavage to that described above to leave a proton at the cleavage site **86**. However, an additional cleavage protocol was also reported in which oxidation of **86** and spontaneous cleavage gave alkene **87**, Scheme 1.29. Selenium linkers represent an attractive class of traceless linker unit and they are continuing to be developed and exploited in the literature.



Scheme 1.29

Sulfur Traceless Linker Units

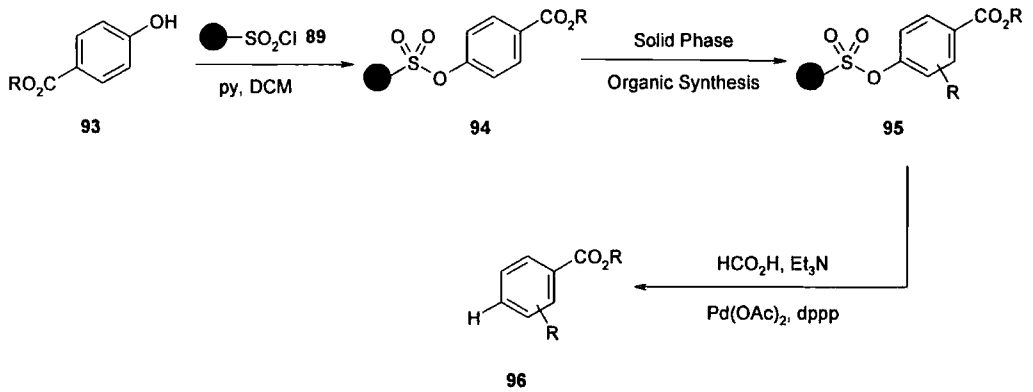
One example of a traceless sulfonyl linker unit has been reported by Zhang *et al.* and used in the synthesis of indoles *via* a palladium-mediated cyclisation, Scheme 1.30.[48] 2-Iodoanilines **88** were loaded on to sulfonyl chloride polystyrene resin **89**. The resulting resin-bound iodoanilines **90** were then cyclised using palladium-mediated heteroannulation with terminal alkynes to give the corresponding indoles **91**. Traceless cleavage of indoles **92** was achieved using TBAF to leave a hydrogen at the cleavage site.



Scheme 1.30

As an alternative, Wustrow has developed an arylsulfonate linker unit **94** prepared by loading phenols **93** on to cross-linked benzenesulfonyl chloride

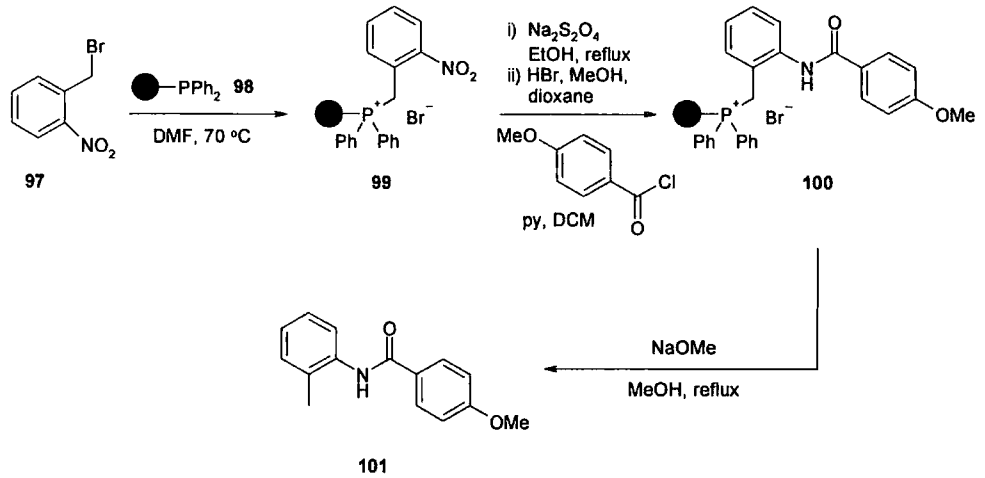
polystyrene resin **89**.[49] Following the desired synthetic transformations **95**, a palladium-catalysed transfer hydrogenation reaction results in cleavage to leave a hydrogen residue at the cleavage site in **96**, Scheme 1.31. One drawback of this linker unit is that the aromatic group must possess electron-withdrawing groups for traceless cleavage to be possible. However, most of the early sulfur-based linker units come under the classification of diversity linker units and so will be discussed further in Section 1.1.2.3.



Scheme 1.31

Phosphorus Traceless Linker Units

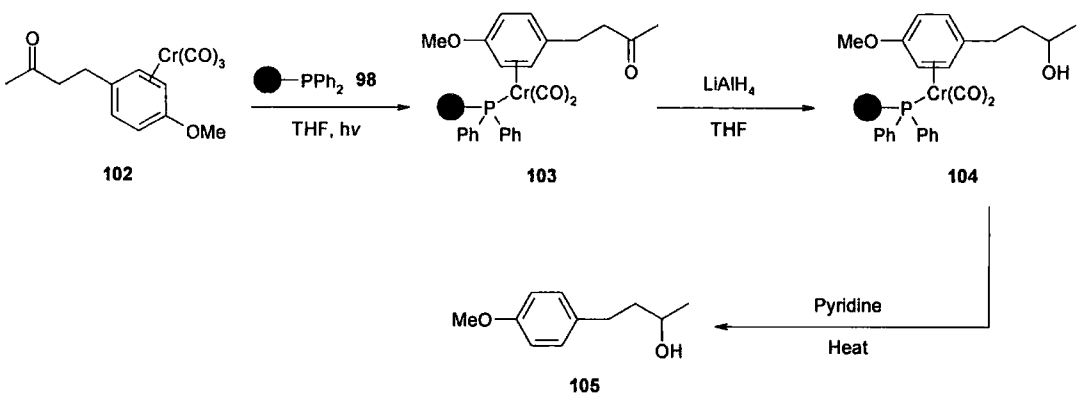
Only a single example of a phosphorus-based traceless linker unit **99** has been reported by Hughes in 1996.[50] The commercially available polystyrene bound analogue of triphenyl phosphine **98** was functionalised with 2-nitrobenzyl bromide **97** to give solid-supported phosphonium salt **99**. This was then reduced to the aniline and further functionalised to give **100** before releasing the toluene derivative **101** on treatment with sodium methoxide in methanol, Scheme 1.32. Diversity cleavage has also been demonstrated using Hughes' phosphorus linker and will be described in Section 1.1.2.3.



Scheme 1.32

Chromium Traceless Linker Units

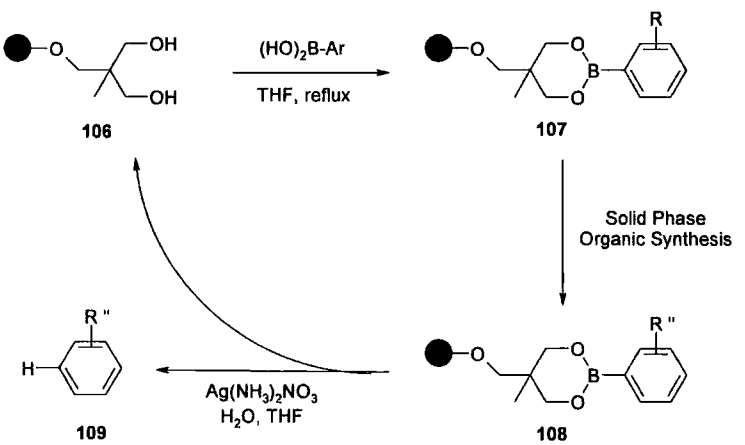
An unusual traceless linker based on chromium **103** was introduced by Gibson *et al.* in 1999.[51] A chromium carbonyl complex **102** was loaded on to polystyrene phosphine resin **98** to give the linker unit **103**. Reduction of the ketone was carried out using lithium aluminium hydride to give resin-bound alcohol **104** and then traceless cleavage was achieved by heating in pyridine to give alcohol **105**, Scheme 1.33. This linker unit has also been employed by Rigby and continues to find use in solid phase organic synthesis.[52]



Scheme 1.33

Boron Traceless Linker Units

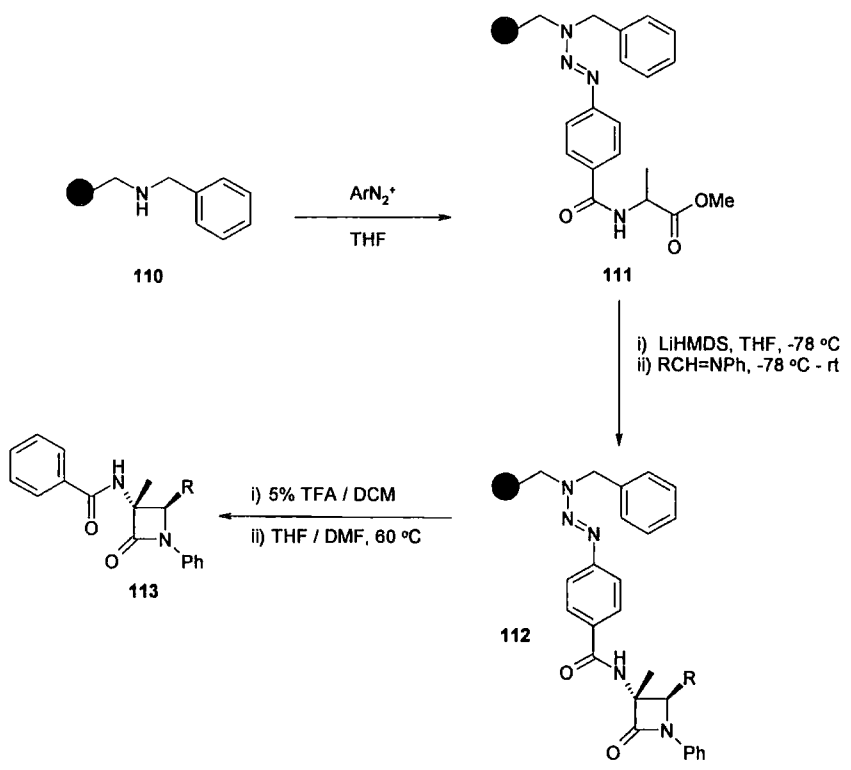
The boronate traceless linker **107** was introduced by Deluze *et al.* in 2000.[53] A macroporous support **106** was prepared allowing for the loading of boronic acids. This allowed for solid phase organic synthesis to be carried out on the aromatic group of the boronic acid **108** and then mild traceless cleavage of the aromatic compound **109** was achieved using silver diamine nitrate in water and THF, Scheme 1.34. The advantage of this cleavage technique was that in addition to leaving a hydrogen at the cleavage site of the aromatic compound, it also regenerated the linker unit **106** allowing for economic recycling.[53]



Scheme 1.34

Nitrogen Traceless Linker Units

The use of nitrogen-based traceless linker units has been concentrated on the T1 triazene linker unit introduced by Bräse and Enders in 1998.[54] Benzylamine linker **110** was synthesised from Merrifield resin and then diazonium salts were coupled to give triazene linker **111**. Enders demonstrated the use of this linker in the synthesis of β-lactams from **111**.[55] Ester enolate-imine condensation resulted in resin-bound β-lactams **112** and then traceless cleavage was achieved using 5% TFA / DCM followed by heating in THF / DMF to remove the residual diazonium functionality to give β-lactams **113**, Scheme 1.35. The triazene T1 linker unit continues to be much exploited in solid phase organic synthesis.



Scheme 1.35

In summary, a wide range of synthetically useful traceless linkers have been developed. They are based upon a variety of different elements and synthetic strategies but the common feature is that they all leave a hydrogen residue at the cleavage site of the molecule.

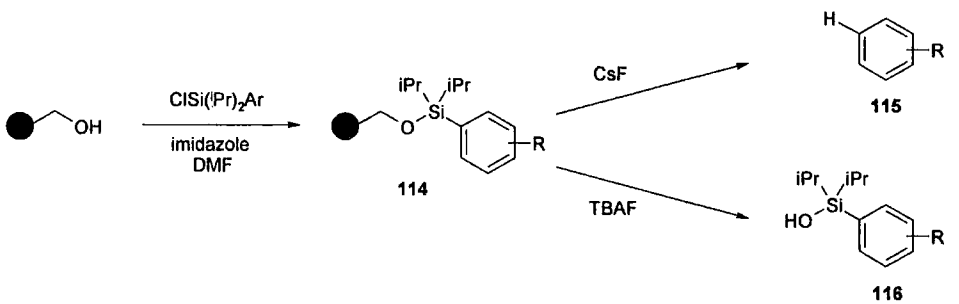
1.1.2.3 General Diversity Linker Units

While a hydrogen residue will not alter the biological activity of target molecules like the polar functional groups resulting from traditional linker units, synthetically its use is limited to demetallation, radical, and C-H activation reactions on suitably activated hydrogens. Therefore, linker technology has evolved from traceless linkers to more sophisticated diversity linker units which utilise the cleavage step in solid phase organic synthesis for the incorporation of further diversity into target molecules. They do not result in unwanted polar functional

groups or simple hydrogen atoms but, in contrast, allow the solid phase chemist to control what functionality is left at the cleavage site of a target molecule. This section describes general diversity linker units which use conventional reactions to achieve cleavage. Section 1.1.2.4 described diversity linker units which specifically use transition-metal-catalysed cross-coupling reactions during the cleavage step.

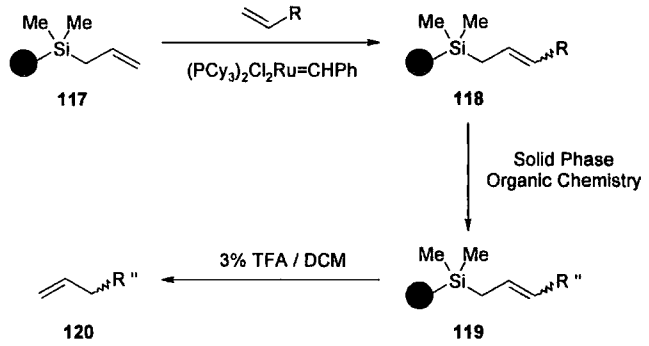
Silicon Diversity Linker Units

As in the case of traceless linker units, early diversity linker units were based upon silicon. Traceless cleavage using Showalter's silicon-based linker unit **114** has already been described but it can also be employed as a diversity linker unit. For example, traceless cleavage of the aromatic group to leave a hydrogen residue **115** can be achieved on treatment with caesium fluoride. In contrast, new functionality can be introduced during the cleavage step and if treated with TBAF the aromatic group is cleaved as the dialkylarylsilanol **116**, Scheme 1.36.[56]



Scheme 1.36

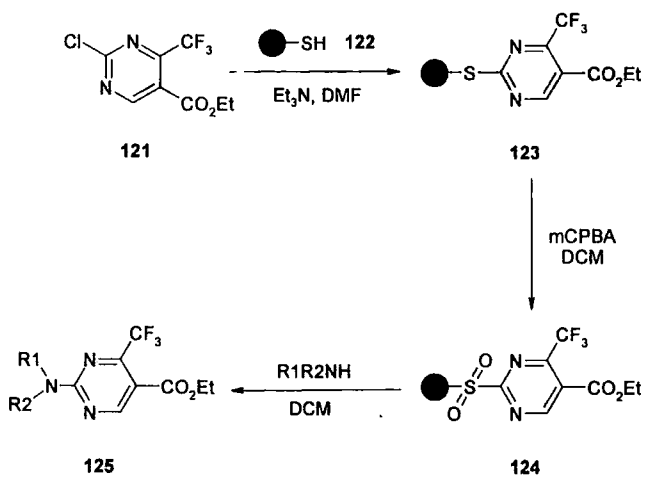
Alternatively, silicon-based linker **117** has also been developed which leaves an allyl group upon cleavage. Introduced by Blechert *et al.* in 1997, initially alkenes are loaded using a cross-metathesis reaction to give **118**.[57] These can then be derivatised further if required to give **119** and treatment with 3% TFA / DCM cleaves the target molecule **120** with a terminal allyl group at the cleavage site, Scheme 1.37.



Scheme 1.37

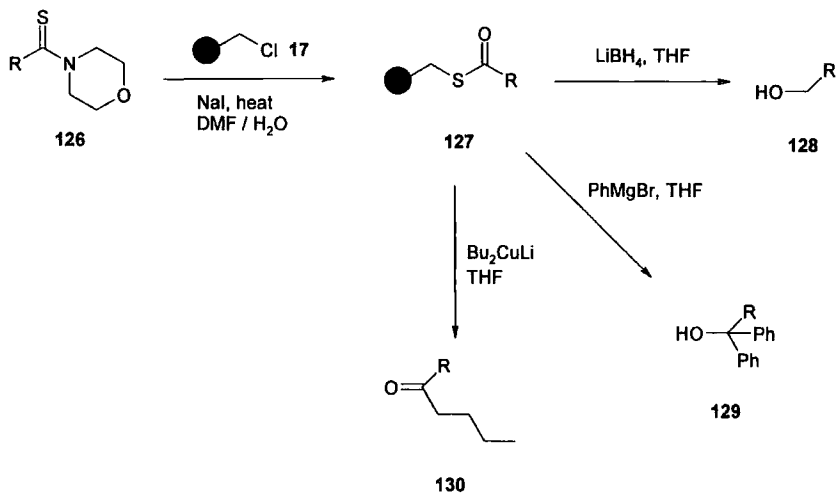
Sulfur Diversity Linker Units

A number of different sulfur-based diversity linker units have been developed in the last 10 years. The first was introduced by Suto and Gayo and has already been described briefly as a safety catch linker.[41] An example of its use as a diversity linker is in the synthesis of functionalised pyrimidines **125**. Initially pyrimidines **121** were loaded on to TentaGel thiol resin **122** to yield resin-bound thioether **123**. Oxidation to the corresponding sulfone **124** was necessary to activate the safety catch linker for cleavage and this was carried out using mCPBA. Cleavage was carried out by nucleophilic aromatic substitution using primary and secondary amines to give functionalised pyrimidines **125** with amines at the cleavage site of the molecule, Scheme 1.38.[41]



Scheme 1.38

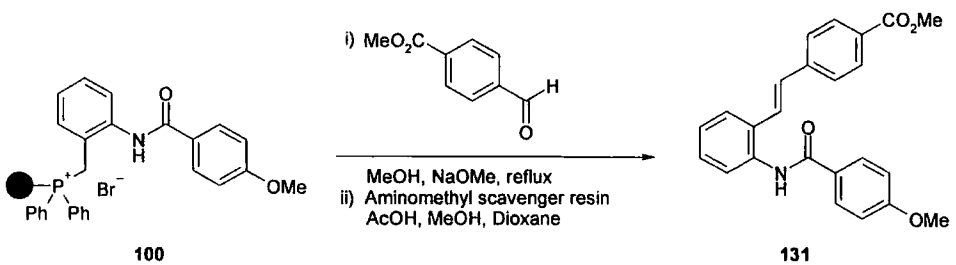
Bradley introduced an alternative diversity linker unit based upon thioesters.[58] Merrifield resin **17** was reacted with thioamides **126** to give resin-bound thioesters **127**. Diversity cleavage was then achieved to leave a variety of functional groups at the cleavage site of the molecule. For example, cleavage using lithium borohydride gave primary alcohols **128** whereas reaction with phenyl magnesium bromide resulted in tertiary alcohols **129**. Substrates were also cleaved as ketones **130** if a softer organometallic reagent such as an organocuprate was used, Scheme 1.39.



Scheme 1.39

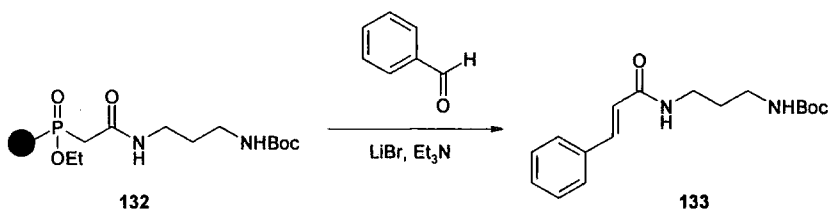
Phosphorus Diversity Linker Units

The phosphorus linker unit introduced by Hughes and discussed in Section 1.1.2.2 as a traceless linker unit has also been utilised as a diversity linker unit.[50] For example, resin-bound phosphonium salt **100**, generated as previously described, can be cleaved using Wittig chemistry to yield 3 : 1 mixtures of the corresponding *E*/*Z* alkenes **131**, Scheme 1.40. The aminomethyl resin in the second step was used to scavenge unreacted aldehyde.



Scheme 1.40

A further example of a phosphorus-based diversity linker unit was reported by Johnson and Zhang.[59] Cleavage of substrates from linker unit **132** is achieved by reacting with aldehydes in a solid-supported version of the Horner-Wadsworth-Emmons reaction. This introduces an alkene functionality at the cleavage site of the molecule **133**, Scheme 1.41.

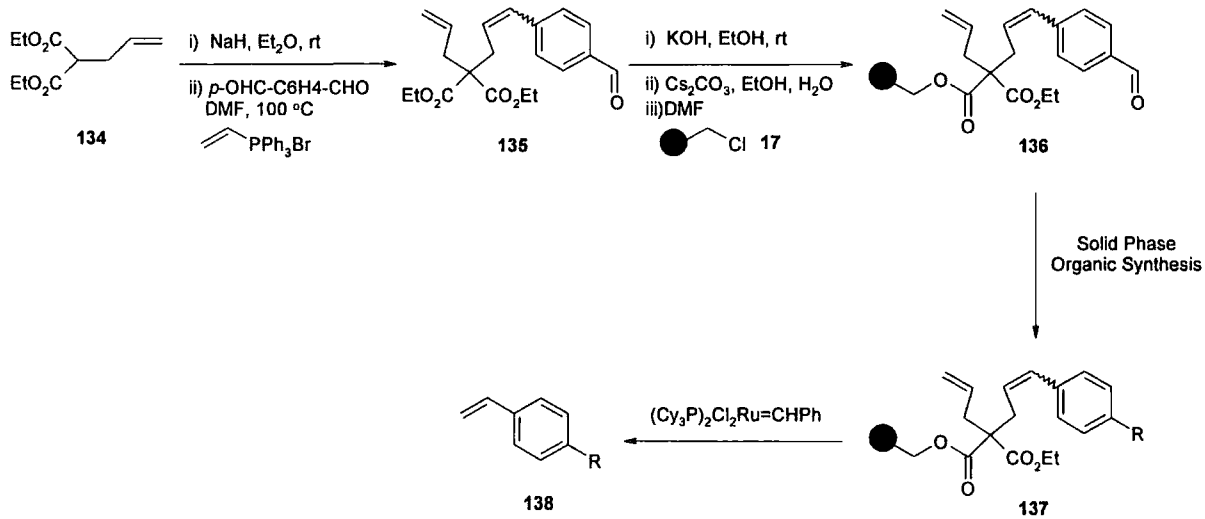


Scheme 1.41

Ring Closing Metathesis Diversity Linker Unit

Peters and Blechert introduced a diversity linker unit in 1997 which utilises ring closing metathesis to leave an alkene at the cleavage site of the molecule.[60] Terephthalaldehyde was mono-olefinated in a tandem Michael-Wittig reaction with allylmalonate **134** and triphenylvinylphosphonium bromide to give bisalkylated malonate **135**. Selective saponification yielded the monoacid derivative of **135** which was loaded on to Merrifield resin **17** to give linker unit **136**. The aromatic group was modified using standard solid phase organic synthesis **137** and cleavage was achieved using a cross-metathesis reaction employing Grubb's catalyst to leave an alkene at the cleavage site in **138**, Scheme 1.42. This linker unit continues to find use in solid phase synthesis and

has also been utilised by Knerr and Schmidt in the synthesis of oligonucleotides.[61] This concludes a summary of diversity linker units which use conventional reactions to give further diversity in target molecules upon cleavage.



Scheme 1.42

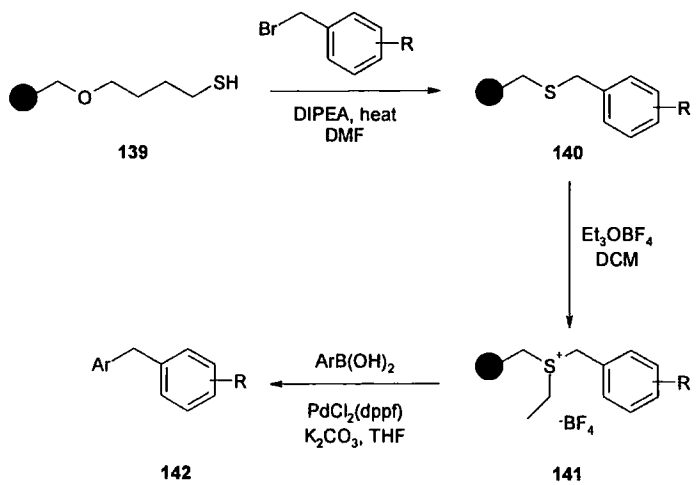
1.1.2.4 Transition Metal Cleavable Diversity Linkers

The linker units described in the previous section use traditional reactions to achieve diversity cleavage. However, in recent years a growing number of diversity linker units have been developed which use transition-metal-catalysed cross-coupling reactions to achieve diversity cleavage. This section therefore gives representative examples of this type of linker unit ranging from resin-bound electrophiles (sulfur, phosphorus, boron, nitrogen and perfluoroalkanesulfonyl linker units) to resin-bound nucleophiles (tin based linkers).

Sulfur Transition Metal Cleavable Diversity Linker Units

An example of a sulfur-based diversity linker unit which uses Suzuki reactions to leave aryl groups at the cleavage site was introduced by Wagner *et al.* in 2000.[62] Analogues of benzyl bromide were loaded on to thiol resin **139** to give resin-bound thioethers **140**. Treatment of these thioethers with triethyloxonium

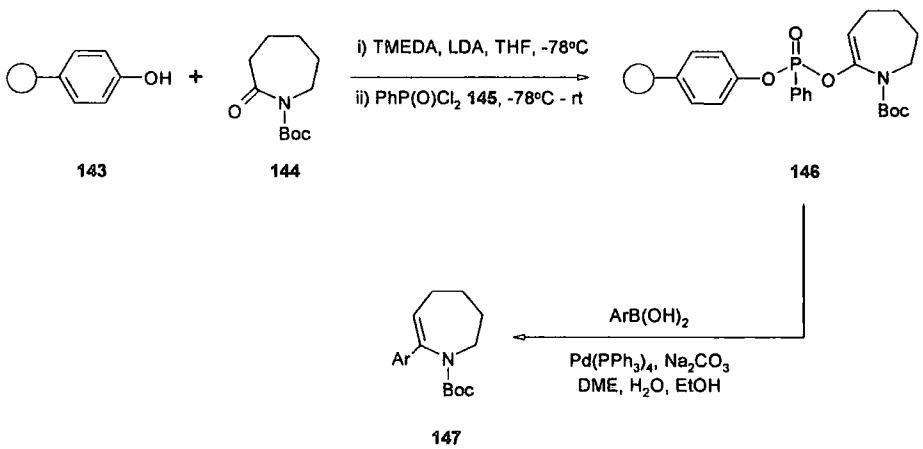
tetrafluoroborate resulted in solid-supported benzylsulfonium salts **141** and then diversity cleavage was achieved using a palladium-catalysed Suzuki reaction with boronic acids. This cleaved target materials as biphenylmethyl derivatives **142**, Scheme 1.43. One drawback of this cleavage procedure was contamination resulting from homo-coupled boronic acid. However despite this, the Wagner linker and other examples discussed indicate that sulfur-based diversity linker units are powerful tools set to play a continuing role in solid phase organic synthesis.



Scheme 1.43

Phosphorus Transition Metal Cleavable Diversity Linker Units

A phosphorus based linker unit has been developed by Steel *et al.* which utilises transition-metal-catalysed cross-coupling reactions to achieve diversity cleavage.[63] The linker unit is a resin-bound phosphonate **146** which is prepared in a one-pot procedure from phenol on polystyrene **143**, Boc-protected ε-caprolactam **144** and phenylphosphonic dichloride **145**. Diversity cleavage has been demonstrated using palladium-catalysed Suzuki reactions to leave aryl groups at the cleavage site of target molecules **147**, Scheme 1.44.

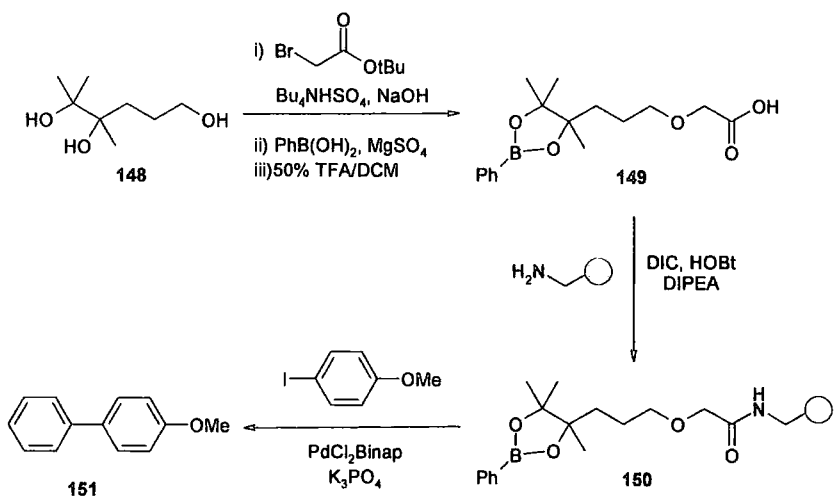


143 144 146 147

Scheme 1.44

Boron Transition Metal Cleavable Diversity Linker Units

Burgess introduced a boron-based diversity linker 150 in 1999.[64] Boronate 149 was prepared in 3 steps from triol 148 and loaded on to Rink amide resin using standard peptide coupling techniques, Scheme 1.45. The aromatic group was then cleaved using a Suzuki reaction with 4-iodomethoxybenzene to yield biphenyl 151.

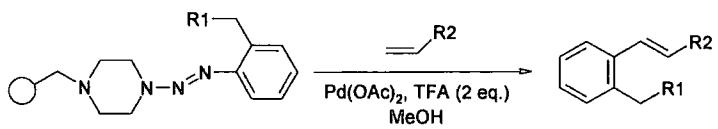


148 149 150 151

Scheme 1.45

Nitrogen Transition Metal Cleavable Diversity Linker Units

Bräse's triazene linker unit has found most use as a traceless linker which leaves a hydrogen residue following cleavage.[54, 55] However, more recently Bräse has also shown that diversity cleavage is possible under cross-coupling conditions to leave a range of groups at the cleavage site of the target molecule. For example, an aryl group bound to a resin through the triazene linker **152** can be cleaved using a Heck reaction to leave an alkene at the cleavage site **153**, Scheme 1.46.[65]

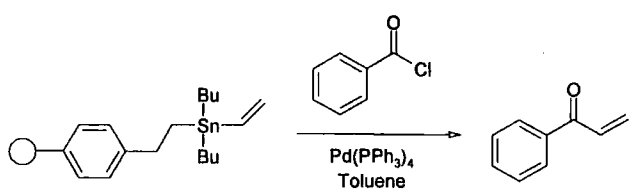


152 **153**

Scheme 1.46

Tin Transition Metal Cleavable Diversity Linker Units

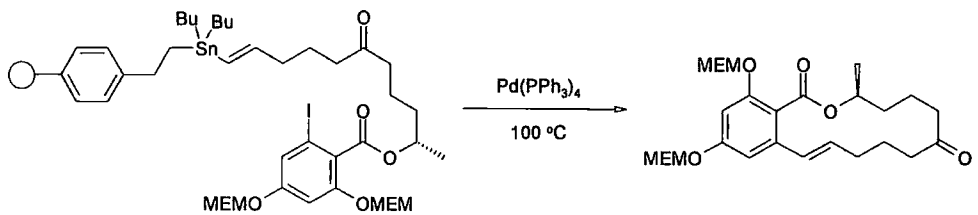
Polymer-supported organotin reagents were introduced by Kuhn in 1994.[66] Linker unit **154** was prepared by a Grignard reaction on to a solid-supported tin chloride. Cleavage could then be achieved using a Stille cross-coupling reaction to leave, for example, a benzoyl group at the cleavage site of the molecule **155**. The main advantage of using a polymer bound organotin reagent is that following the Stille cleavage reaction, all tin by-products remain attached to the polymer allowing for their efficient removal.



154 **155**

Scheme 1.47

Nicolaou utilised this organotin linker unit in the synthesis of a precursor of the natural product (*S*)-zearalenone 157, Scheme 1.48.[67] In this case, the organotin linker unit 156 is bifunctional. Firstly it is behaving as a transition metal cleavable diversity linker unit but since the Stille cleavage reaction is intramolecular, the linker unit is also functioning as a cyclo-cleavable linker unit.

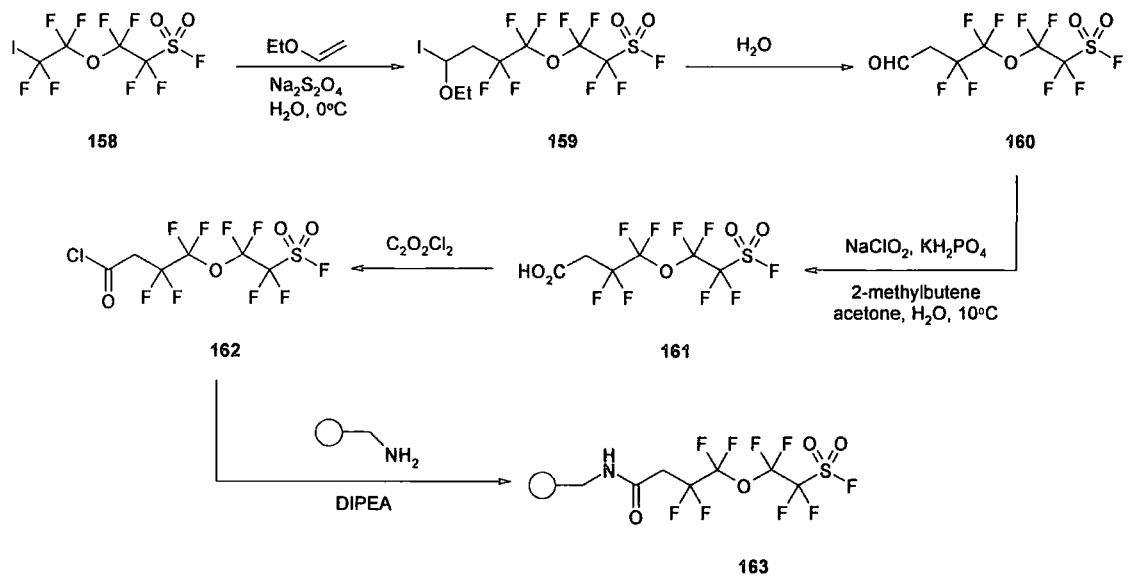


156 157

Scheme 1.48

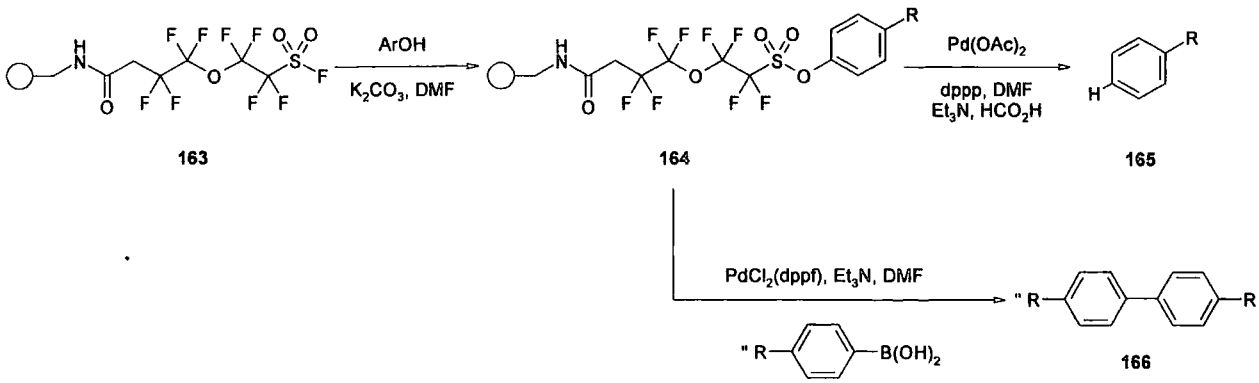
Perfluoroalkanesulfonyl Diversity Linker Unit

Concurrent with the efforts to develop a perfluoroalkanesulfonyl diversity unit described in Chapters 2 – 4 of this thesis, a similar linker unit was reported by Pan and Holmes in 2001.[68, 69] They derived perfluoroalkanesulfonyl linker 163 in 5 steps from iodosulfonyl fluoride 158, Scheme 1.49. Initially, iodosulfonyl fluoride 158 underwent a radical reaction with ethyl vinyl ether to yield iodide 159 which then gave aldehyde 160 on treatment with water. Aldehyde 160 was oxidised to carboxylic acid 161, converted to the corresponding acid chloride 162 and then loaded on to amino TentaGel to give a perfluoroalkanesulfonyl linker unit 163.



Scheme 1.49

Phenols were loaded using potassium carbonate to give solid-supported aryl triflates 164 and traceless cleavage was demonstrated using palladium catalysed transfer hydrogenation to leave a hydrogen at the cleavage site 165.[68] In further applications, diversity cleavage using Suzuki reactions cleaved target molecules as biphenyls 166, Scheme 1.50.[69] This shows that diversity cleavage is possible from solid-supported analogues of aryl triflates. However, the main disadvantages with Holmes' linker unit are the high cost of iodosulfonyl fluoride 158 and the 5 step synthesis of the linker unit. Both of these factors mean that the linker unit has not been exploited in solid phase organic synthesis following the original paper.

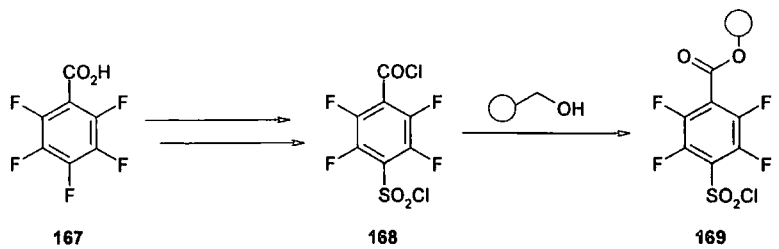


163 164 165 166

Scheme 1.50

Fluoroarylsulfonate Diversity Linker Unit

The synthetic and economic problems associated with the perfluoroalkanesulfonyl linker unit reported by Holmes have been overcome with the development of a fluoroarylsulfonate linker 169. This linker was reported independently by Cammidge[70] and Ganesan.[71] Both groups reported a fluoroarylsulfonate diversity linker unit 169 based upon a perfluorobenzene unit. Sulfonyl chloride 168 was prepared from pentafluorobenzoic acid 167 and loaded on to hydroxymethyl TentaGel® to give resin-bound sulfonyl chloride 169, Scheme 1.51.

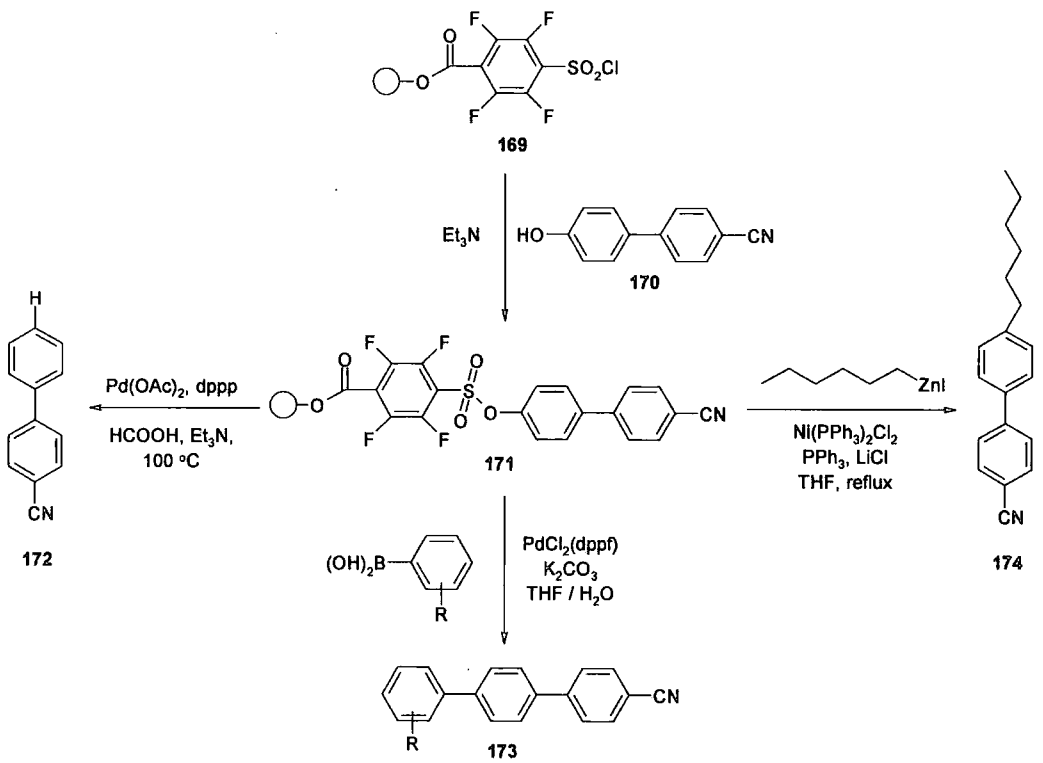


167 168 169

Scheme 1.51

Traceless and diversity cleavage was demonstrated by both groups using several different strategies. For example, Cammidge loaded 4-hydroxybiphenyl-4'-carbonitrile 170 on to linker unit 171 using triethylamine. Traceless cleavage was demonstrated using formic acid to leave a hydrogen residue at the cleavage site 172. Alternatively, diversity cleavage was demonstrated using Suzuki and

Negishi reactions to leave aryl groups 173 and alkyl groups 174 at the cleavage site of the molecule respectively, Scheme 1.52. This is a powerful diversity linker unit which should be much exploited in the future of solid phase organic synthesis.



Scheme 1.52

1.1.2.5 Conclusions

- Traditional linker units used simple acid, base and photocleavage conditions to free target molecules from solid supports. These evolved into more sophisticated cyclo-cleavable and safety catch linker units.

- The main disadvantage of traditional linker units is the polar functionality left in the target molecule following cleavage. This can have a pronounced effect on biological activity and, if unwanted, is difficult to remove.

- In attempts to overcome this problem, a wide range of traceless linker units have been developed which leave a hydrogen residue at the cleavage site of the target molecule.

- Building on traceless linker units, recent linker units that have been developed are diversity linkers. These are powerful tools for the solid phase organic chemist as they utilise the cleavage step to incorporate further diversity into target molecules.

1.1.3 Analytical Techniques in Solid Phase Organic Synthesis

One of the major challenges in solid phase organic chemistry is determining the outcome of a synthesis. This could be determining whether or not a substrate has been loaded on to a solid support or if a synthetic transformation carried out on a resin-bound substrate has been successful. There are a number of different techniques available for analysis of resin-bound substrates ranging from simple colorimetric tests to more sophisticated magic angle NMR and IR spectroscopy.

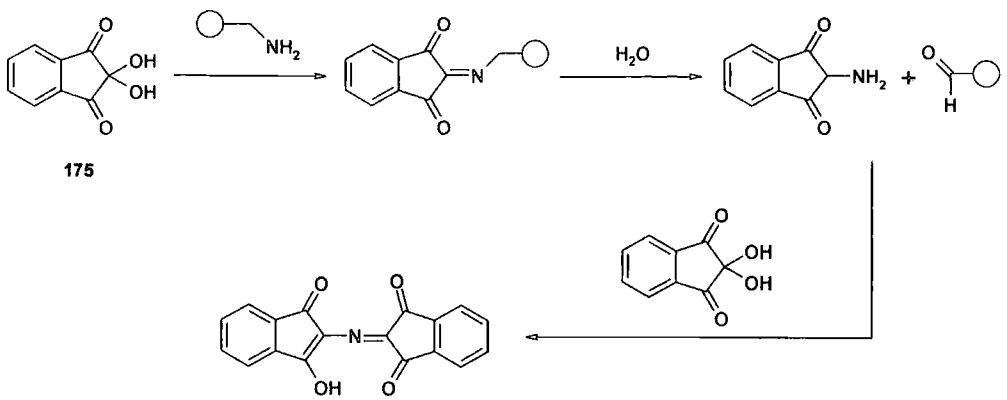
1.1.3.1 Solution Phase Analysis

Often the best form of analysis of resin-bound substrates attached to cleavable linker units is to cleave the substrate from a small portion of resin (20 – 50 mg). Conventional solution phase analytical techniques can then be used to identify the substrate. However, if reactions are being done on a small scale and there isn't enough resin to sacrifice in a cleavage test or if reactions are being carried out on a non-cleavable support then alternative techniques are required.

1.1.3.2 Colorimetric Tests

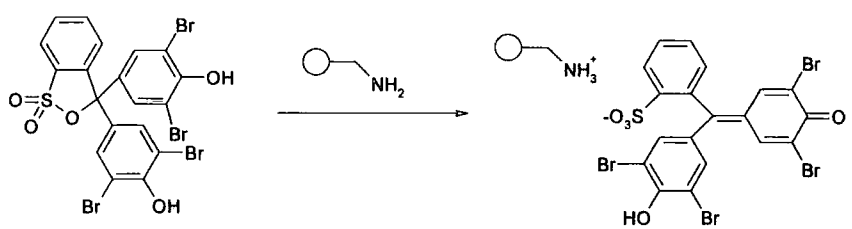
One of the first 'on-bead' analytical tests used in solid phase peptide synthesis was the Kaiser test.[7, 72] This test is used to detect even small amounts of primary amines and so is ideal for monitoring acylation reactions. Treatment of an amino resin with a small portion of ninhydrin 175 and subsequent heating to 120 °C for

about 5 minutes gives a blue colour if amines are present. This intense blue colour results from the formation of Ruhemann's complex 176, Scheme 1.53.



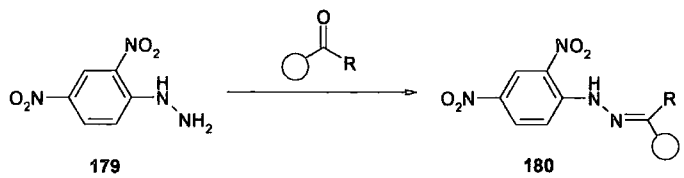
Scheme 1.53

Presently, bromophenol blue (3',3",5',5"-tetrabromophenol sulfonylphthalein) 177 has become the indicator of choice for confirming the presence or absence of amines.[72, 73] Deprotonation of the reagent by free primary or secondary amines present on the resin leads to an intense blue colour resulting from the conjugated species 178, Scheme 1.54. Bromophenol blue is non-destructive, unlike the Kaiser test, and excess reagent can be washed away from the resin allowing on-line monitoring of reactions. Aside from these two tests, other tests for amines include choranil, trinitrobenzenesulfonic acid and the fluorescamine test which all work along similar lines.



Scheme 1.54

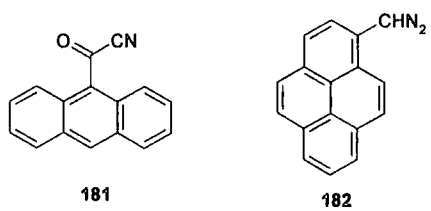
In order to detect the presence of aldehydes and ketones, the classical dinitrophenylhydrazine (DNP) test used in solution phase analysis has been adapted for solid phase synthesis.[72] The formation of imine 180 from DNP 179 in the presence of aldehydes and ketones results in strong orange coloured beads, Scheme 1.55.



179 180

Scheme 1.55

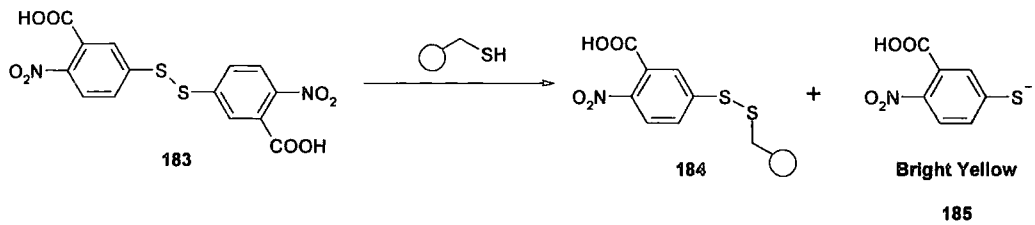
Alcohols can be monitored using 9-anthroyl nitrile 181 or 1-pyrenyldiazomethane 182. These are sensitive tests which require only a small sample of resin and they find particular use in confirming whether or not a substrate has been loaded on to a hydroxy functionalised resin, Scheme 1.56.[7, 72]



181 182

Scheme 1.56

Thiols can be detected using Ellman's reagent 183. For example, if a thiol functionalised resin is being loaded then any unreacted sites will rapidly form a disulfide bridge with Ellman's reagent 184 and releases a thiolate ion 185 which gives the resin an intense yellow colour, Scheme 1.57.[72, 74]



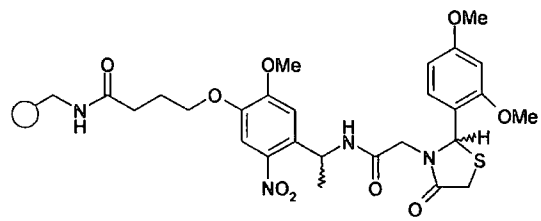
Scheme 1.57

1.1.3.3 Magic Angle NMR Spectroscopy

The colouring techniques described above are ideal for analysing certain solid phase reactions. However, their use is limited to specific reactions and alternative methods of analysis are required when it is not possible to rely on a colorimetric test. The most established method of analysis for solution phase reactions is NMR spectroscopy. However, analysis of resin-bound substrates using NMR spectroscopy presents a new challenge to organic chemists.[7, 75] Resin-bound substrates tend to give broad poorly resolved signals due to the lack of mobility and signals are often masked by unwanted background signals resulting from the polymer supports. Early NMR spectroscopy of solid phase samples was done in the gel phase by swelling samples of resin in solvent and analysing ^{19}F and ^{13}C nuclei. However, gel phase NMR is unsuitable for ^{1}H NMR spectroscopy due to line broadening and so an alternative technique was required. Attempts to overcome the problem of obtaining ^{1}H NMR spectra led to the application of magic angle spinning NMR spectroscopy (MAS-NMR), originally developed for solid state NMR spectroscopy, to allow analysis of solid phase reactions.[75-77]

MAS-NMR spectroscopy has revolutionised the quality of gel phase ^{1}H NMR spectra. The line broadening seen in gel phase ^{1}H NMR spectra is due to residual dipolar coupling and variations in bulk magnetic susceptibility of the sample. However, it has been shown that this dipolar coupling is angularly dependant and can be significantly reduced by the use of magic angle spinning. Spinning the sample at the magic angle of 54.7° reduces the dipolar coupling to

zero which in turn greatly reduces line broadening. In addition, rapid sample spinning averages fluctuations in magnetic susceptibility to further reduce line broadening and both of these effects lead to well resolved ^{1}H NMR spectra of resin-bound substrates. For example, Fitch used MAS-NMR spectroscopy to record the ^{1}H NMR spectra of 4-thiazolidinone **186**, Scheme 1.58.[77] As the technique has become more sophisticated, the recording of C-H correlated and other 2-dimensional NMR spectra has also been achieved.[78]



186

Scheme 1.58

1.1.3.4 ^{19}F NMR Spectroscopy

The recording of ^{19}F NMR spectra of fluorine-containing solid-supported materials is in comparison much less problematic than obtaining ^{1}H NMR spectra.[7, 8, 75, 79] As solid supports do not routinely contain any fluorine atoms there are no background signals to dominate the spectra and so gel-phase analysis is possible, although ^{19}F MAS-NMR has also been developed. The use of ^{19}F NMR to monitor solid phase reactions has been recently reported by Shapiro[80] and Svensson[81] who both obtained gel phase ^{19}F NMR spectra by swelling 50 – 200 mg of resin in a suitable solvent to give spectra with line widths similar to solution phase ^{19}F NMR spectra. Shapiro also compared gel phase to ^{19}F MAS-NMR spectroscopy and showed that both gave identical results. The main advantage of the use of ^{19}F MAS-NMR spectroscopy in this case was that it required the use of significantly less material which is useful if reactions are being conducted on a small scale (~10 mg resin).

1.1.3.5 Infrared Spectroscopy

The tool box of analytical techniques available for solid phase organic synthesis is further supplemented by the use of infra-red spectroscopy.[7, 8, 75] By observing the appearance or disappearance of critical diagnostic absorptions, certain reactions can be monitored. Alternatively, other reactions can be monitored by observing shifts in absorptions. For example, if a resin-bound carboxylic acid is converted into an acid chloride, it is possible to monitor this reaction by observing the shift in the carbonyl signal.

There are a number of techniques available by which IR spectra of resin-bound substrates can be obtained. Traditionally, before the advent of combinatorial chemistry, Frechet and Schuerch recorded IR spectra of resin beads ground into KBr discs to analyse solid phase oxidation products bound to chloromethylpolystyrene. However, in order to make KBr discs, significant quantities of resin are required (~10 mg) and this is not applicable to library synthesis. More recently, the preferred technique is FT-IR microspectroscopy in which a single resin bead is analysed through an IR microscope. Alternatively, IR spectroscopy by attenuated total reflection (ATR) through the use of a golden gate accessory can also be used to obtain IR spectra of resin-bound substrates. This is the technique employed throughout the current research and it has been found to give well resolved IR spectra of resin-bound intermediates suitable for reaction monitoring.

1.1.3.6 Conclusions

- Analysis of solid phase using simple colorimetric tests allow fast in-line monitoring of a wide range of reactions.

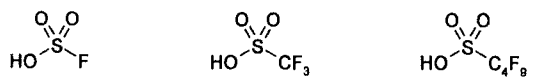
- NMR and IR spectroscopy have both been adapted for solid phase chemistry to allow on-bead analysis of resin-bound substrates.

1.2 Perfluoroalkanesulfonate Esters

The aim of this research is to combine the synthetic advantages of solid phase organic synthesis with the wide variety of chemistry that is possible using aryl perfluorosulfonate esters and develop a perfluoroalkanesulfonyl linker unit. Therefore, this section discusses the chemistry of perfluorosulfonate esters which are widely used compounds in organic synthesis. Perfluorosulfonate esters have been the subject of a number of reviews and this section covers general aspects of their synthesis and reactivity.[82-84]

1.2.1 Alkyl Perfluoroalkanesulfonate Esters

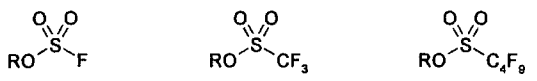
Perfluoroalkanesulfonic acids range from simple fluorosulfonic acid 187 to longer perfluoroalkane chains including trifluoromethanesulfonic acid 188 and nonafluorobutanesulfonic acid 189, Scheme 1.59. These compounds function as strong acids in organic synthesis.



187 188 189

Scheme 1.59

However, perfluoroalkanesulfonic acids find their widest applications in organic synthesis as the corresponding esters: fluorosulfonates 190, trifluoromethane sulfonates (triflates) 191 and nonafluorobutane sulfonates (nonaflates) 192, Scheme 1.60. These perfluoroalkanesulfonates find use as leaving groups and esters 190 – 192 are among the most powerful alkylating agents known. They are able to alkylate a wide range of nucleophiles. This review will begin with general methods for their synthesis.



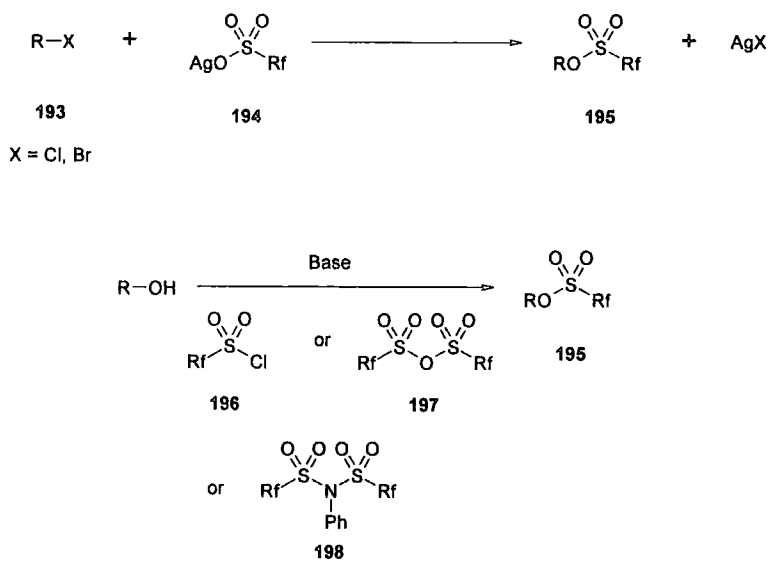
190 **191** **192**

R = Alkyl

Scheme 1.60

1.2.1.1 Synthesis of Alkyl Perfluoroalkanesulfonate Esters

Alkyl perfluoroalkanesulfonate esters **195** are typically prepared in one of two ways. One method of synthesis is the reaction of an alkyl halide **193** with the silver salt of a perfluoroalkanesulfonic acid **194**, Scheme 1.61. Alternatively, and much more commonly, alkyl perfluoroalkanesulfonate esters can be prepared by reacting an alcohol with the corresponding perfluoroalkanesulfonyl chloride **196**, perfluoroalkanesulfonic anhydride **197** or *N*-phenyl-bis-(perfluoroalkylsulfonimide) **198** in the presence of a suitable base.



193 **194** **195**

X = Cl, Br

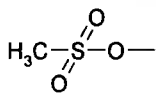
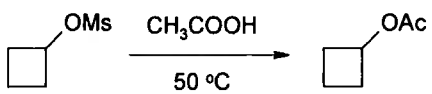
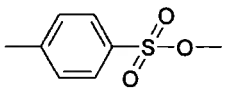
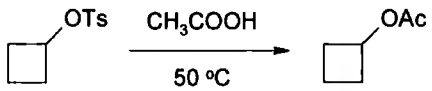
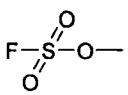
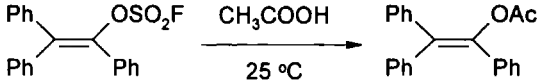
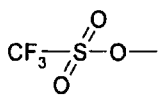
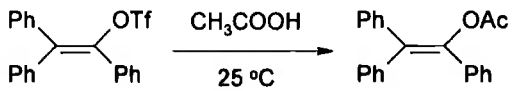
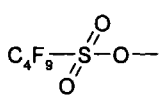
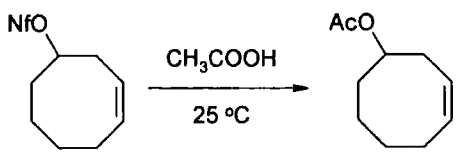
196 **197** **195**

198

Scheme 1.61

1.2.1.2 Leaving Group Ability

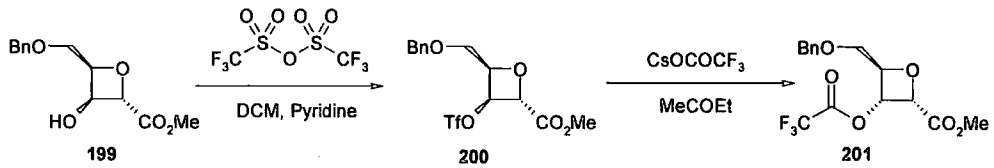
Perfluoroalkanesulfonates find widespread use as leaving groups in organic synthesis. Triflates and nonaflates are among the best leaving groups known and studies have shown that they are some 10^4 – 10^5 times more reactive than their mesylate and tosylate counterparts.[82, 85-87] Relative rates of solvolysis of a range of sulfonate leaving groups are shown in Scheme 1.62. However, at present a direct comparison of leaving group ability is not possible as studies employing the same substrate and solvent system have remain to be attempted.

Leaving Group	Common Name	Reaction	k_{rel}
	Mesylate		1.00
	Tosylate		0.70
	Fluorosulfate		2.9 x 10^4
	Triflate		5.6 x 10^4
	Nonaflate		1.2 x 10^5

Scheme 1.62

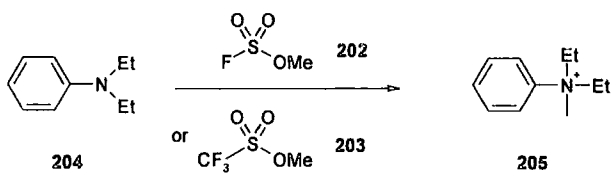
This excellent leaving group ability makes perfluoroalkanesulfonate esters labile towards a wide range of common nucleophiles such as alkoxides, amines and

halides. For example, perfluoroalkanesulfonates may be displaced in S_N2 reactions and in that context they offer a convenient means of inverting the stereochemistry of chiral alcohols. For example, Fleet *et al.* made the triflate 200 of chiral alcohol 199. Reaction of alcohol 199 with caesium trifluoroacetate resulted in trifluoroacetate 201 with opposite stereochemistry which could be hydrolysed to the alcohol in subsequent steps, Scheme 1.63.[88] This lability towards nucleophiles does give rise to one disadvantage of using perfluoroalkanesulfonates which is that they can be prone to solvolysis.



Scheme 1.63

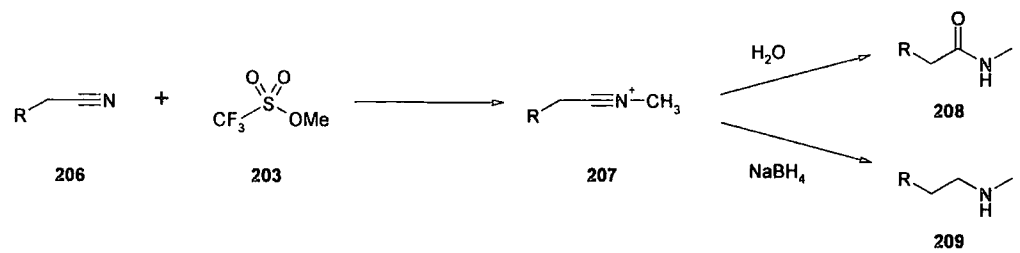
A further demonstration of the leaving group ability of perfluoroalkanesulfonates is seen in their use as alkylating agents. For example, methyl fluorosulfate 202 and methyl triflate 203 are used as methylating agents in organic synthesis and have been used to methylate an enormous range of nucleophilic substrates as well as aromatic compounds. Alder was able to quaternise amines such as *N,N*-diethylaniline 204 with methyl triflate to give 205, Scheme 1.64.[89]



Scheme 1.64

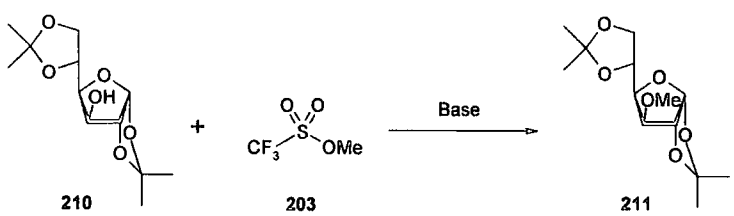
These alkyl perfluoroalkanesulfonate esters also show lability towards weaker nucleophiles. Borch reported the reaction of nitriles 206 with methyl triflate.[90] Initially, nitrilium ions 207 were formed which were either hydrolysed to form

secondary *N*-methyl amides **208** or reduced using sodium borohydride to give secondary amines **209**, Scheme 1.65.



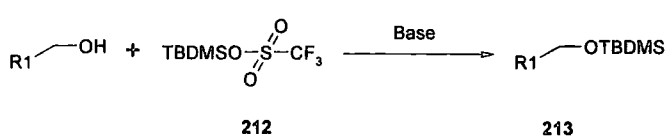
Scheme 1.65

Alternatively, if oxygen is the nucleophile in consideration, then methyl triflate represents a mild and convenient route for the conversion of alcohols to the corresponding methyl ethers. For example, methyl triflate is mild enough to use in carbohydrate chemistry and Berry and Hall reported the methylation of glucofuranose **210** to give the methyl derivative **211**, Scheme 1.66.[91]



Scheme 1.66

A further example of the use of triflates in the alkylation of oxygen nucleophiles is *tert*-butyldimethylsilyl triflate **212**. *tert*-Butyldimethylsilyl triflate offers a mild route for protecting alcohols as the corresponding silyl derivatives **213**, Scheme 1.67.



Scheme 1.67

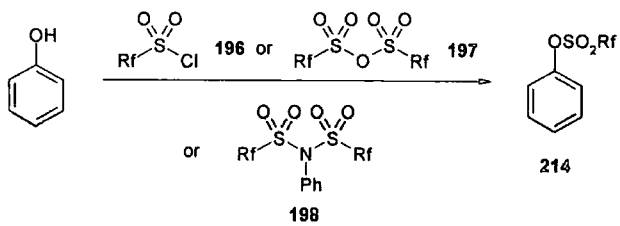
This concludes a summary of the most common applications of alkyl perfluoroalkanesulfonate esters. As the work in this thesis is concerned with aryl and vinyl perfluoroalkanesulfonate esters, attention will turn to a discussion of their synthesis and reactivity.

1.2.2 Aryl and Vinyl Perfluoroalkanesulfonate Esters

The chemistry of aryl and vinyl perfluoroalkanesulfonate esters show different reactivity to their alkyl counterparts. While alkyl perfluoroalkanesulfonate esters are labile towards nucleophiles and prone to solvolysis, in comparison aryl and vinyl perfluoroalkanesulfonate esters are less reactive towards nucleophiles and solvolytic conditions. The applications of aryl and vinyl perfluoroalkanesulfonate esters have expanded considerably in the last 20 years following the discovery that they are reactive under transition-metal-catalysed cross-coupling conditions.

1.2.2.1 Synthesis of Aryl and Vinyl Perfluoroalkanesulfonate Esters

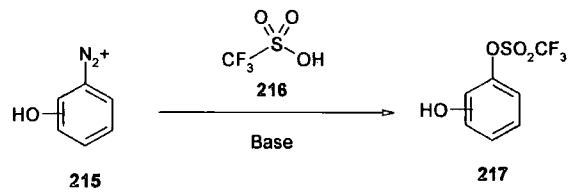
There are a number of methods available for the synthesis of aryl perfluoroalkanesulfonate esters 214.[82, 83] Most commonly, they are prepared by reacting phenols with triflating agents in a similar fashion to that described for alkyl perfluoroalkanesulfonates, Scheme 1.68.



Scheme 1.68

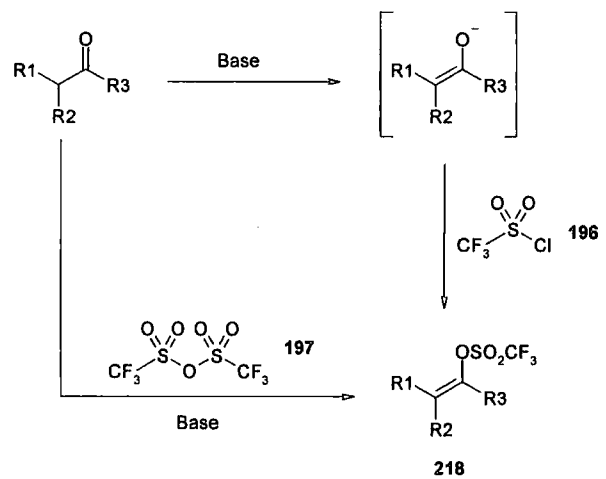
Alternatively, Yoneda *et el.* prepared aryl triflates by the thermal or photochemical decomposition of arenediazonium salts 215 in a solution of triflic acid 216, Scheme 1.69.[92] Using this method it was possible to obtain hydroxyphenyl triflates 217 which are difficult to obtain by other methods. For

example, treating bis phenols with triflic anhydride results in complex mixtures of bis mono and bis triflates.



Scheme 1.69

In comparison, vinyl triflates 218 are prepared from the corresponding carbonyl compounds by trapping the enolate either in a one-step or two-step process, Scheme 1.70.[82, 83, 93]

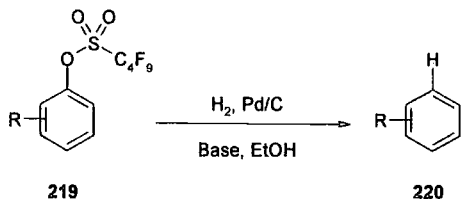


Scheme 1.70

1.2.2.2 Traditional Reactions of Aryl and Vinyl Perfluorosulfonates

Aryl perfluorosulfonates are known to be stable to aromatic electrophilic substitution reactions including nitration, halogenation and sulfonation reactions. Conversely, aryl and vinyl triflates do undergo simple hydrogenolysis reactions as well as nucleophilic substitution. Hydrogenolysis of aryl triflates was demonstrated by Alvarez *et al.* who converted aryl nonaflates 219 into the corresponding hydrocarbons 220 using a hydrogenolysis reaction with a

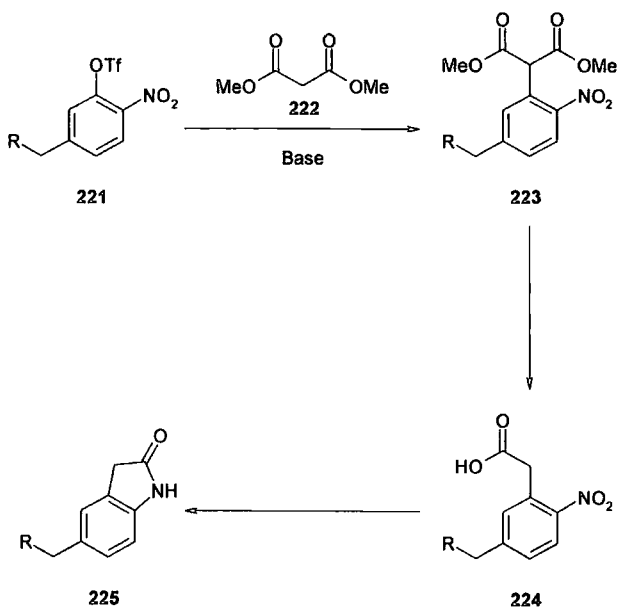
palladium-on-carbon catalyst, Scheme 1.71.[94] This indicates that simple hydrogenation reactions could be used to achieve traceless cleavage of resin-bound substrates from a perfluoroalkanesulfonyl linker unit to leave a hydrogen residue at the cleavage site.



219 220

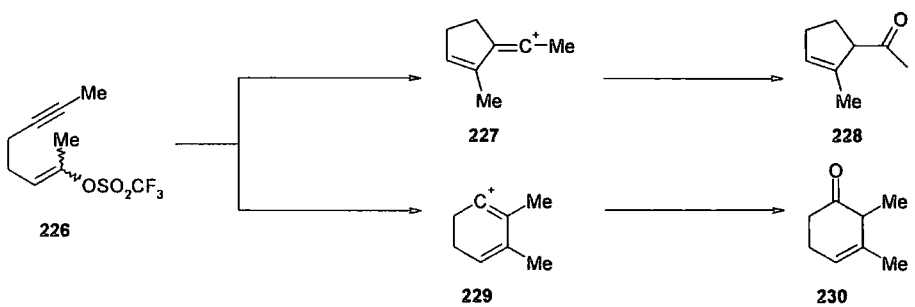
Scheme 1.71

Aryl triflates are known to undergo nucleophilic aromatic substitution on appropriately substituted aromatic rings. For example, Atkinson demonstrated that 2-nitroaryl triflates 221 underwent nucleophilic aromatic substitution by the anion of dimethyl malonate 222 to give dimethyl nitroaryl malonates 223, Scheme 1.72.[95] These could be converted into nitroarylacetic acids 224 and subsequently oxindoles 225. Therefore, nucleophilic aromatic substitution represents a second possible diversity cleavage strategy which could be employed to cleave resin-bound substrates from a perfluoroalkanesulfonyl linker unit.



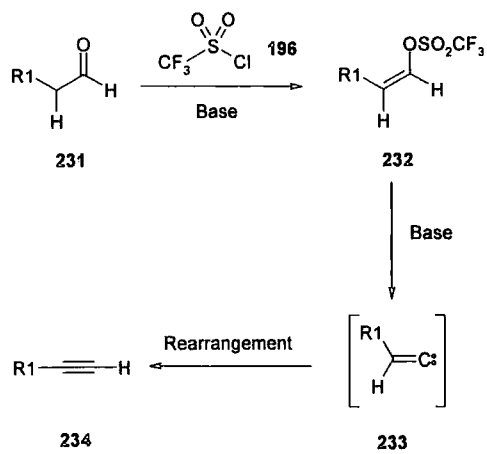
Scheme 1.72

The analogous hydrogenation and substitution reactions described for aryl triflates are also applicable to vinyl triflates. However, reflecting on the good leaving group properties of perfluorosulfonate esters, vinyl perfluorosulfonates find their widest applications in the solvolytic generation of vinyl cations and *via* α–elimination to give unsaturated carbenes. These intermediates are otherwise difficult to obtain in organic synthesis. For example, Chandy and Hanack reported that enynyl triflate 226 reacted in various solvents and with participation of the triple bond to yield mainly cation 227 and small amounts of cation 229 as a by-product. These gave rise to ketones 228 and 230 respectively upon work-up, Scheme 1.73.[96]



Scheme 1.73

An example of vinyl triflates reacting through a carbene intermediate was reported by Stang *et al.* in 1974.[97, 98] The reaction is synthetically very useful as overall it represents the conversion of an aldehyde into the corresponding alkyne. Initially the enolate of aldehyde 231 was trapped as the triflate 232, Scheme 1.74. Upon heating, triflic acid was eliminated to give carbene 233 which possessed a β-hydrogen. Carbene 232 underwent quantitative rearrangement to give an alkyne 234. Aside from these traditional reactions, aryl and vinyl triflates have also become very popular reagents in transition-metal-catalysed cross-coupling reactions.



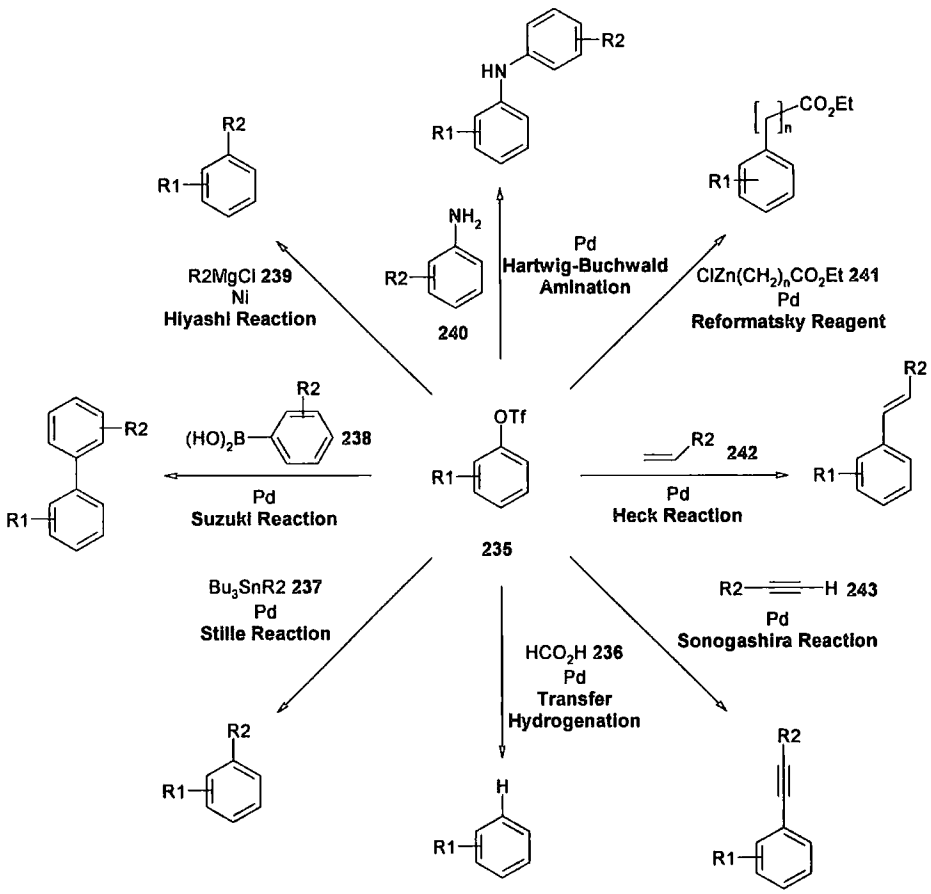
231 232 233 234

Scheme 1.74

1.2.2.3 Transition-Metal-Catalysed Cross-Coupling Reactions

The use of aryl and vinyl perfluorosulfonates in organic synthesis has greatly expanded following the discovery that they undergo transition-metal-catalysed cross-coupling reactions with a wide range of organometallics. As aryl perfluorosulfonates have been employed in the current research, they will be used to give representative examples. However, the reactions are equally applicable to vinyl triflates. For example, aryl triflates 235 can react with formic acid 236 (transfer hydrogenation), organostannanes 237 (Stille Reaction), organoboronates 238 (Suzuki Reaction), Grignard reagents 239 (Hiyashi Reaction), amines 240 (Hartwig-Buchwald Amination), organozinc compounds

241 (Reformatsky Reaction), alkenes 242 (Heck Reaction) or alkynes 243 (Sonogashira Reaction).[1] This wide range of reactions is illustrated in Scheme 1.76 but a detailed description of each is beyond the range of this introduction. Therefore, the typical mechanism of transition-metal-catalysed cross-coupling reactions with aryl triflates will be illustrated using the Stille and Suzuki reactions as examples.

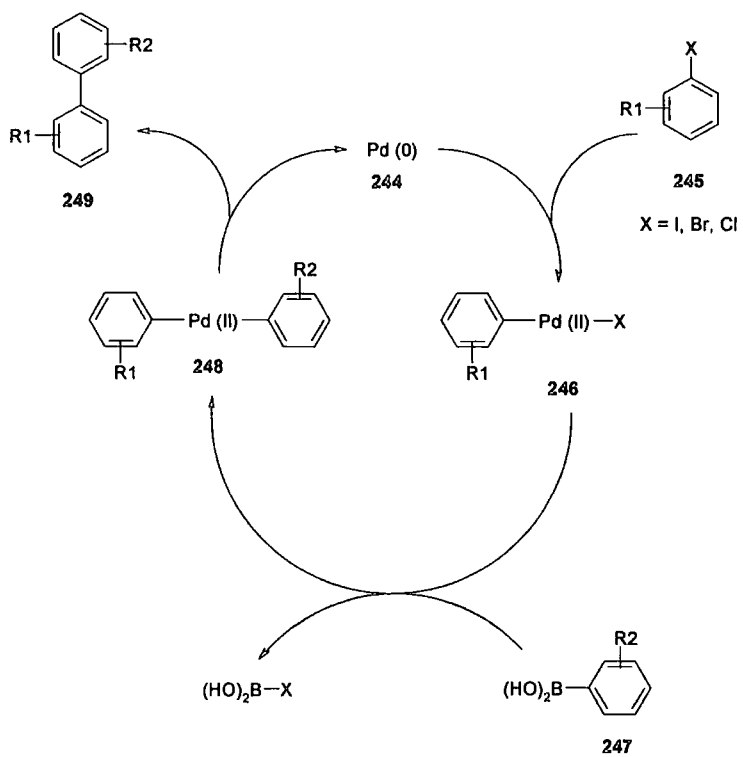


Scheme 1.75

Suzuki Reactions with Aryl Perfluorosulfonate Esters

The palladium-catalysed cross-coupling reaction of aryl boronic acids 247 with aryl halides 245 in the presence of a base to yield biaryls 249 was introduced by Suzuki in 1981.[99] The mild reaction conditions, compatibility with a range of functional groups and ready availability of boronic acids, have made it one of the

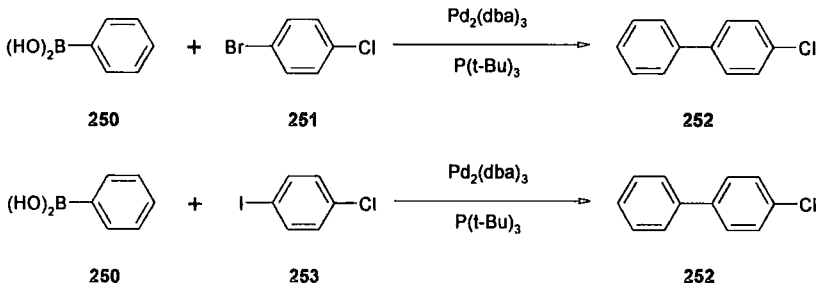
most powerful carbon-carbon bond forming reactions in organic synthesis. Furthermore, the low toxicity and water solubility of boron based by-products means the Suzuki reaction has major advantages over other cross-coupling reactions, such as the organostannane-based Stille reaction. Suzuki reactions proceed *via* the general catalytic cycle shown in Scheme 1.76 The first step is the oxidative addition of the aryl halide 245 to palladium (0) 244 to give an aryl-palladium(II)-halide 246. Transmetallation with the aryl boronic acid 247 then occurs so that both aryl groups are bonded to the palladium centre 248. The final step is reductive elimination which yields biphenyl 249 and regenerates the palladium(0) catalyst.



Scheme 1.76

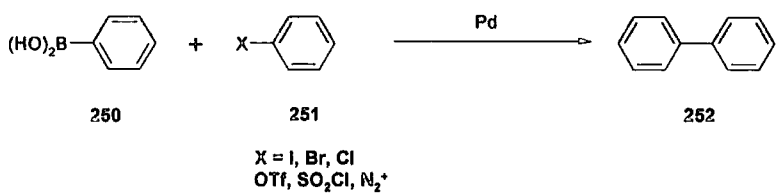
Initially, substrates were aryl halides and the order of reactivity was discovered to be Ar-I > Ar-Br > Ar-Cl. This has been confirmed by selectivity experiments carried out by Fu.[3] For example, it was shown that if phenyl boronic acid 250

was reacted with 1-bromo-4-chlorobenzene 251 then the C-Br bond reacted preferentially to give exclusively chlorinated biphenyl 252. Likewise, in the reaction between 1-chloro-4-iodobenzene 253, the C-I bond reacted to yield biphenyl 252, Scheme 1.77.



Scheme 1.77

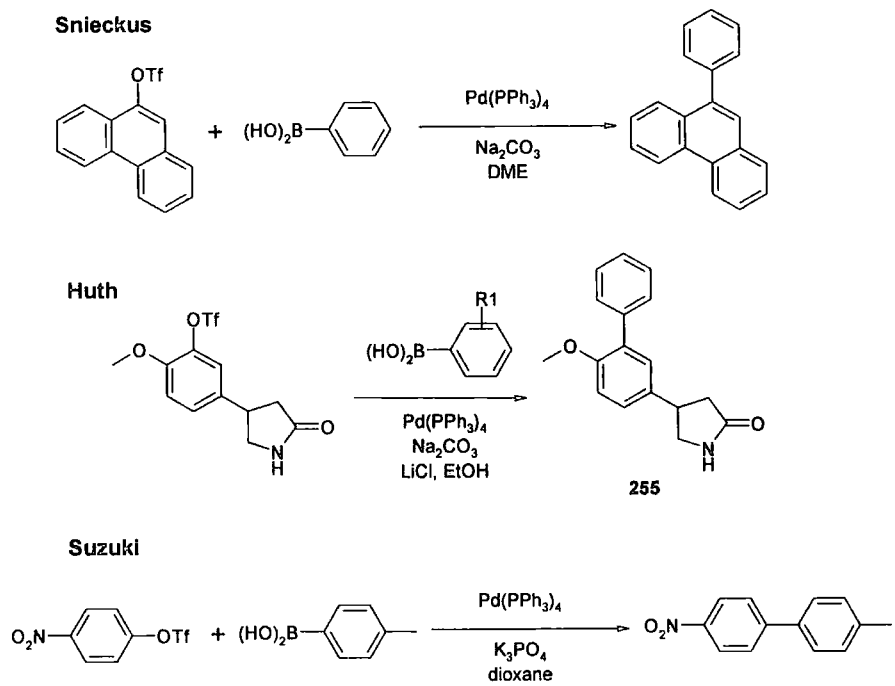
Since the original Suzuki reactions using aryl halides, a wide range of reaction conditions have been developed using different substrates and palladium catalysts. Catalysts such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$(binap) and $PdCl_2$(dppf) are now routinely employed and alternative substrates include aryl triflates,[1-6] arenediazonium salts[1] and aryl sulfonyl chlorides,[100] Scheme 1.78. The reactivity of arenediazonium salts and aryl sulfonyl chlorides is greater than aryl bromides while aryl triflates are known to be slightly less reactive than aryl bromides: Ar-I > Ar-N_2^+ ~ Ar-SO_2Cl > Ar-Br ≥ Ar-OTf > Ar-Cl.



Scheme 1.78

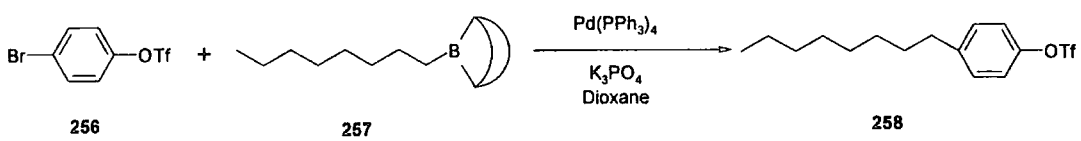
The use of aryl triflates instead of aryl halides as substrates for Suzuki cross-coupling reactions with aryl boronic acids was reported in the early 1990s independently by Snieckus,[4] Huth[5] and Suzuki,[6] Scheme 1.79. Snieckus and

Suzuki both reported a range of simple biphenyls while Huth synthesised a range of substituted pyrrolidinones 255.



Scheme 1.79

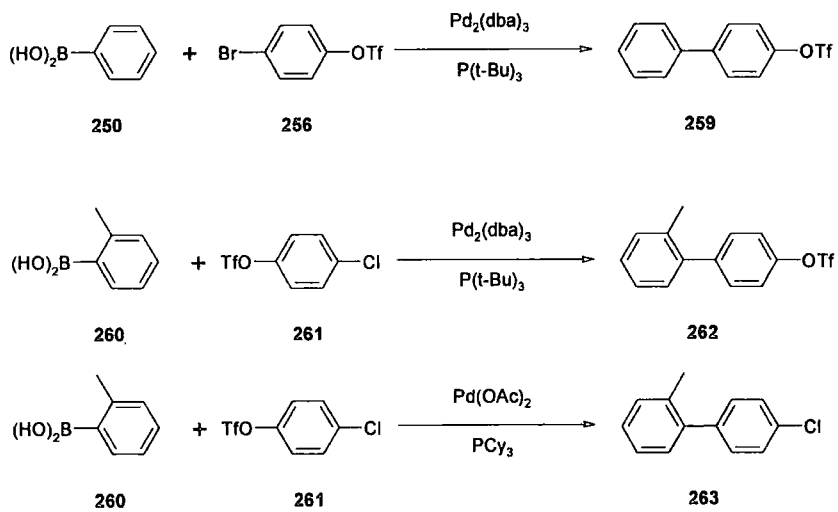
The reactivity of aryl triflates is slightly lower than aryl bromides: Ar-I > Ar-Br ≥ Ar-OTf > Ar-Cl and this was confirmed by Suzuki in the original paper. It was shown that 4-bromophenyltriflate 256 reacted with 9-alkyl-9-BBN derivative 257 exclusively through the C-Br bond to yield the triflated product 258, Scheme 1.80.[6]



Scheme 1.80

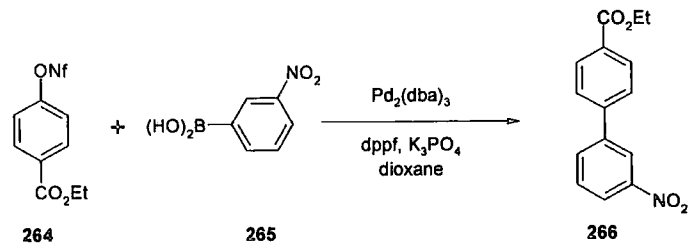
Similar results have also been demonstrated by Fu.[3] In the reaction of 4-bromophenyltriflate 256 with phenyl boronic acid 250 it was shown that the triflate

was unreactive using $Pd_2(dba)_3$ / P(*t*-Bu)$_3$ and the bromide reacted exclusively to yield biphenyl 259, Scheme 1.81. Furthermore, Fu was also able to demonstrate some interesting selective reactions using 4-chlorophenyltriflate 261. Typically, aryl triflates are more reactive than aryl chlorides. However, due to the low reactivity of aryl triflates to the $Pd_2(dba)_3$ / P(*t*-Bu)$_3$ system, Fu showed it was possible to react *o*-tolyl boronic acid 260 exclusively with the aryl chloride to give biphenyl 262. However, if the $Pd(OAc)_2$ / PCy_3 catalyst / ligand system was used instead, then the triflate reacted exclusively to give chlorinated biphenyl 263. This selective reactivity is a powerful tool in organic synthesis and these reactions also demonstrate the importance of choosing appropriate cross-coupling conditions for substrates being used.



Scheme 1.81

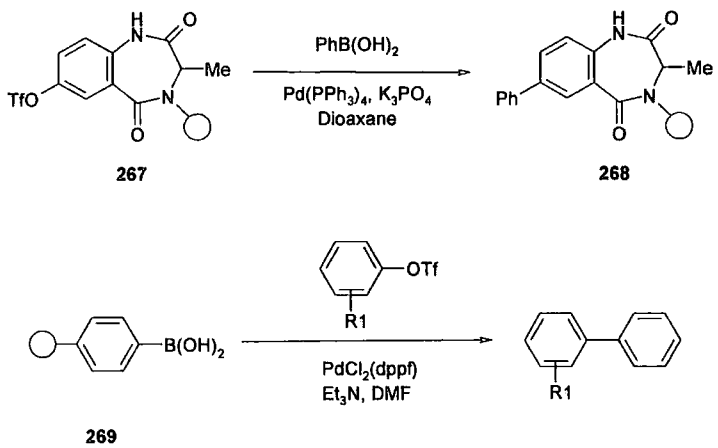
Higher aryl perfluorosulfonate esters are also known to be reactive in Suzuki cross-coupling reactions and they have been shown to have reactivity similar to aryl triflates.[101] An example of their use is the cross-coupling of aryl nonaflate 264 with nitrophenyl boronic acid 265 demonstrated by Rottländer and Knochel to yield biphenyl 266, Scheme 1.82.[102]



264 265 266

Scheme 1.82

More recently, Suzuki reactions have also been adapted for solid-supported aryl triflates.[2] For example, Goff and Zuckermann were able to functionalise resin-bound triflate 267 using a Suzuki reaction to give functionalised benzodiazepine 268.[103] Equally, the order of events can be reversed so that the boronic acid is bound to the solid support 269 and the triflate is in solution, Scheme 1.83.[2]

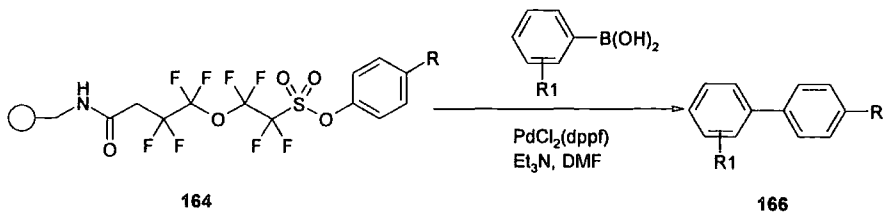


267 268

269

Scheme 1.83

Furthermore, if the triflate group is the means of attachment of aryl groups to a solid support, then Suzuki reactions can be used to cleave resin-bound substrates. This concept is the central theme of the current project and has been discussed with respect to Holmes' perfluoroalkanesulfonyl diversity linker unit.[68, 69] Solid-supported analogues of aryl triflates 164 were cleaved using a standard Suzuki reaction to give biphenyls 166, Scheme 1.84.



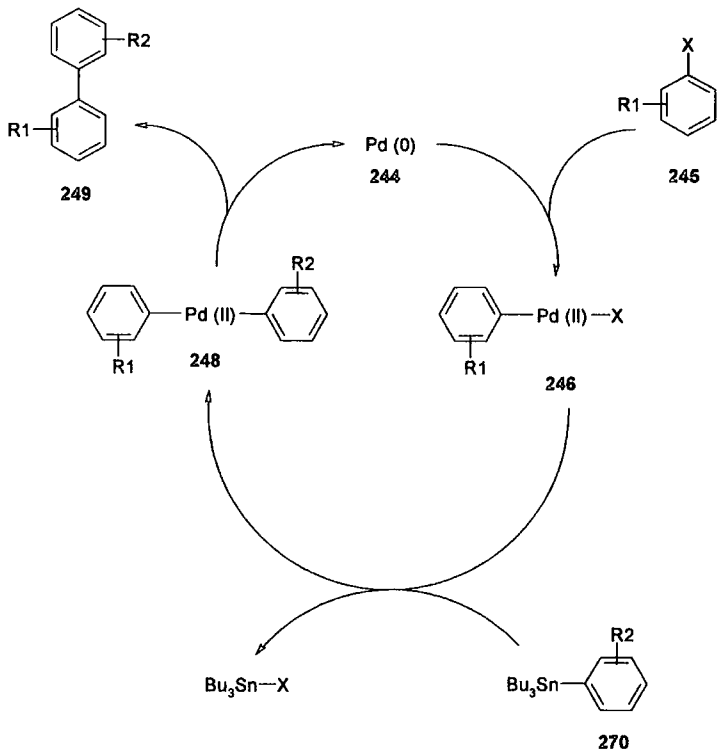
164 166

Scheme 1. 84

Stille Reactions with Aryl Triflates

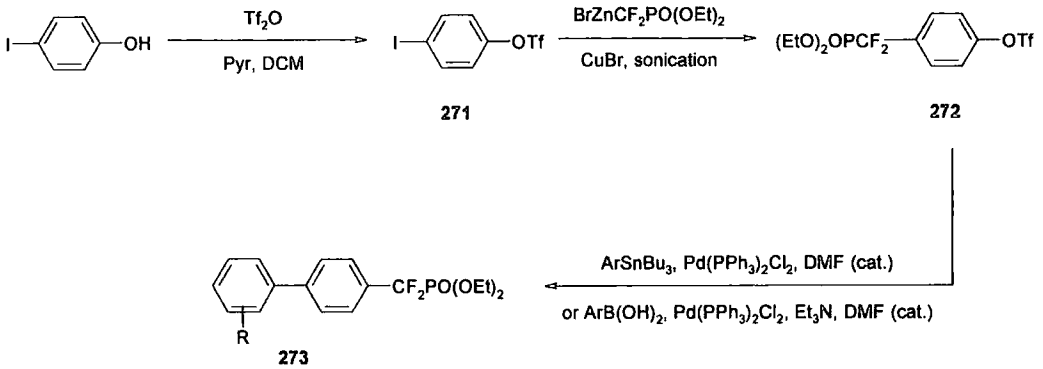
The cross-coupling reaction of aryl halides 245 with organostannanes 270, Scheme 1.85, was reported by Stille in 1978.[104] Since its introduction, the Stille reaction has been much exploited in organic synthesis due to its tolerance of a wide range of functional groups and its stability to moisture. However, the major limitation of the Stille reaction is the toxicity of organostannane by-products and the traditional problems associated with removing them from reaction mixtures. Nevertheless, the increasing availability of organostannanes means that the reaction has received much attention in the literature.[1, 2, 105, 106]

Stille reactions proceed via a similar catalytic cycle to that described for the Suzuki reaction. Initially, oxidative addition of the aryl halide 245 to palladium (0) 244 gives aryl-palladium (II)-halide 246. The second step is transmetalation with the organostannane 270 to give the diarylated palladium (II) species 248. Finally, reductive elimination gives biphenyl 249 and regenerates palladium (0) to complete the catalytic cycle, Scheme 1.85.



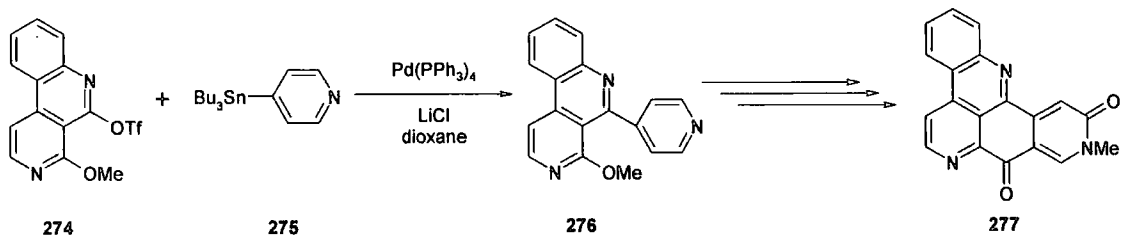
Scheme 1.85

Stille reactions were traditionally carried out using aryl halides in the presence of a palladium catalyst and a phosphine ligand to promote reaction.[101] However, like Suzuki reactions, Stille reactions are no longer confined to aryl halides as substrates. The use of aryl triflates as substrates in Stille cross-coupling reactions was first reported in the 1990s by a number of groups and the order of reactivity is the same as that previously described: Ar-I > Ar-Br ≥ Ar-OTf > Ar-Cl.[1,2] Stille reactions with aryl triflates have been demonstrated by Percy who used them in the synthesis of aryl difluorophosphate building blocks.[107] Initially the triflate of 4-iodophenol 271 was prepared and this underwent a Shibuya coupling to yield aryl difluorophosphate 272. Aryl triflates are unreactive to Shibuya conditions but further diversity could be introduced to the aryl group using Stille or Suzuki reactions to give biaryl scaffolds 273, Scheme 1.86.[107]



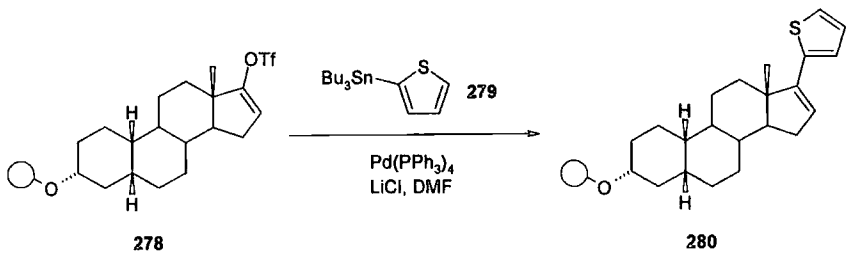
Scheme 1.86

A further example of the use of the Stille reaction of aryl triflates has been demonstrated in total synthesis. Snieckus reported the use of triflate 274 in the synthesis of the marine alkaloid amphimedine 277.[108] The Stille reaction with pyridylstannane 275 was carried out using $Pd(PPh_3)_4$ and lithium chloride to yield intermediate 276 which was then progressed to the natural product, Scheme 1.87.



Scheme 1.87

In recent years, Stille reactions have also been adapted for solid phase chemistry.[2] Stille reactions are particularly appropriate for solid phase synthesis as traditional purification problems when organostannanes are used in solution phase reactions can be overcome in solid phase synthesis. As target molecules are bound to solid supports, tin by-products can easily be removed by filtering the solid support and washing it with copious amounts of solvent. For example, Koot reported substituted steroid 280 which was obtained from the Stille cross-coupling reaction between resin-bound triflate 278 and 2-(tributylstannyl) thiophene 279, Scheme 1.88.[109]



Scheme 1.88

Alternatively, if solid-supported organostannanes are used then by-products remain bound to the support following reactions. These polymer supported organostannanes reagents have already been discussed in the context of transition metal cleavable diversity linker units in Section 1.1.2.4. This concludes a review of transition metal catalysed cross-coupling reactions using aryl triflates. The large number of possible reactions indicates that diversity cleavage from a resin-bound analogue of an aryl triflate will be possible to leave a diverse range of functionalities at the cleavage site of the target molecule.

1.2.3 Conclusions

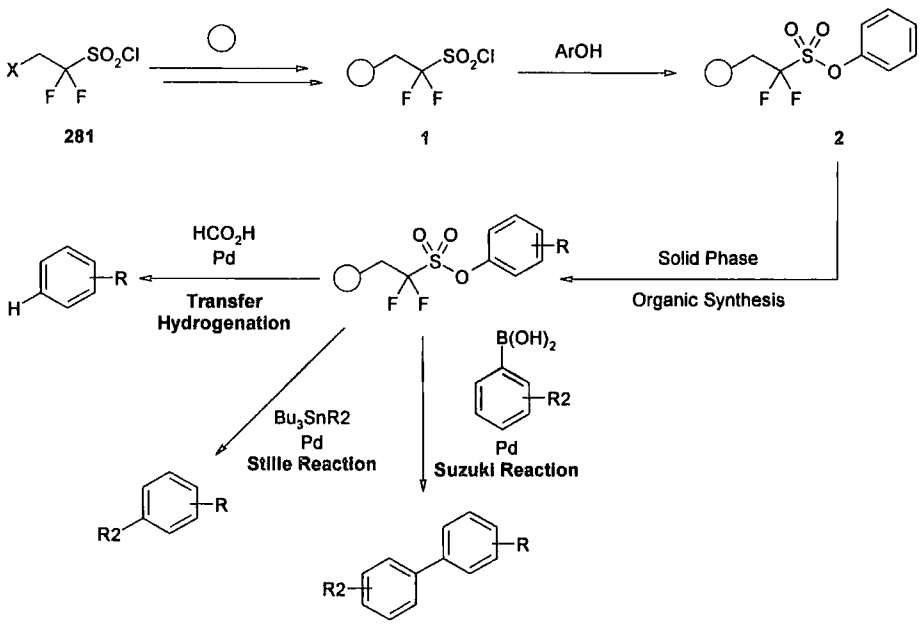
- Alkyl perfluoroalkanesulfonates are among the best leaving groups in organic synthesis. They are displaced by a wide range of nucleophiles and also find widespread use as alkylating agents in organic synthesis.

- Conversely, aryl and vinyl perfluoroalkanesulfonates are more stable than their alkyl counterparts. Traditional reactions of aryl and vinyl perfluorosulfonates include nucleophilic substitution and hydrogenation. Vinyl perfluorosulfonates are also used to generate cations and carbenes.

- Aryl and vinyl perfluoroalkanesulfonates are both substrates for a wide range of transition-metal-catalysed cross-coupling reactions in which they have reactivity similar to aryl bromides.

1.3 Background to the Current Research

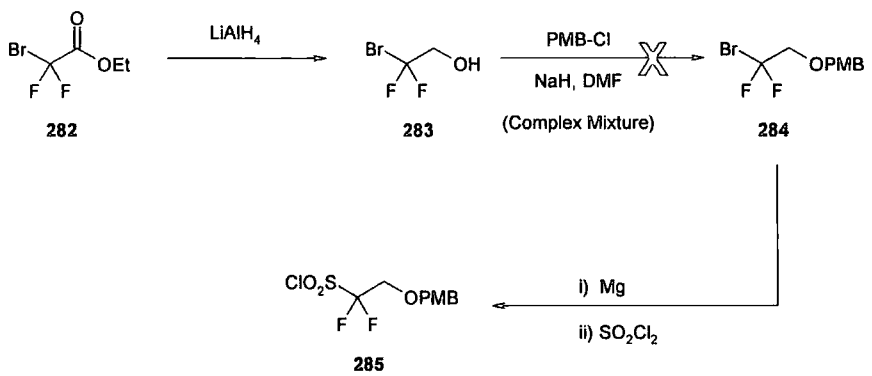
The aim of the current project was to develop a novel perfluoroalkanesulfonyl diversity linker unit 1 based upon the triflate group for use in solid phase organic synthesis. To this end, the strategy was to synthesise a bifunctional molecule 281 which contained a perfluoroalkanesulfonyl chloride or perfluoroalkanesulfonic acid in addition to some functionality which could be used as a point of attachment to a solid support. Loading on to a resin would then provide a solid-supported triflating agent to which phenols could be loaded to give resin-bound analogues of aryl triflates 2. These solid-supported perfluorosulfonate esters were expected to be stable to a wide range of synthetic conditions like their solution phase counterparts. Following solid phase synthesis, traceless and diversity cleavage was envisaged using transition-metal-catalysed cross-coupling reactions to leave a range of functionalities at the cleavage site of the target molecule, Scheme 1.89.



Scheme 1.89

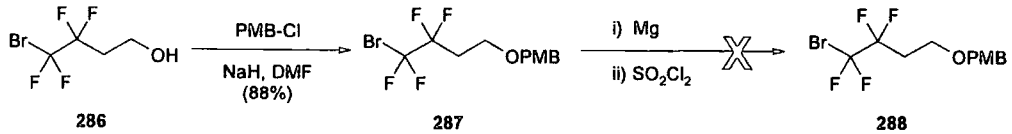
1.3.1 Previous Work in the Group

Previous work towards a perfluoroalkanesulfonyl linker unit was carried out by de Sousa using a number of different strategies. Initially, commercially available bromoester 282 was investigated as a possible starting material.[110] Reduction of the ester yielded alcohol 283 which could be attached to a solid support through the hydroxyl functionality. It was then intended to protect alcohol 284 and make the corresponding Grignard reagent which could be added to sulfuryl chloride to give sulfonyl chloride 285. However, during the protection step, protected alcohol 284 was formed with an inseparable by-product ascribed to elimination of HF, Scheme 1.90. Therefore this route was abandoned at this stage. However, this result indicated that a methylene spacer unit could be problematic as it appeared insufficient to give the molecule stability and so de Sousa decided to change to an ethylene spacer.



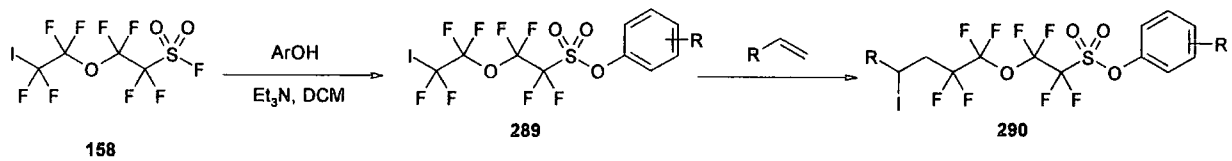
Scheme 1.90

With the aim of extending the linker unit to an ethylene spacer unit, commercially available bromoalcohol 286 was selected as a starting material.[110] Protection of the alcohol with *para*-methoxybenzyl chloride gave 287 but subsequent conversion into sulfonyl chloride 288 using Grignard chemistry proved problematic and unrepeatable, Scheme 1.91. Consequently this route was also abandoned and an alternative strategy was required.



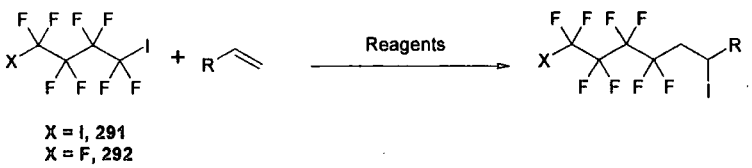
Scheme 1.91

Commercially available iodosulfonyl fluoride 158 was selected as a possible alternative route towards a perfluoroalkanesulfonyl linker unit. This represented an attractive starting material as the sulfonyl fluoride was in place allowing for de Sousa to generate perfluoroalkanesulfonate esters 289, Scheme 1.92.[110] With 289 in hand, the strategy was then to use the perfluoroalkyl iodide to add 289 to an alkene bearing some functionality suitable for loading a linker unit onto a solid support to give 290.



Scheme 1.92

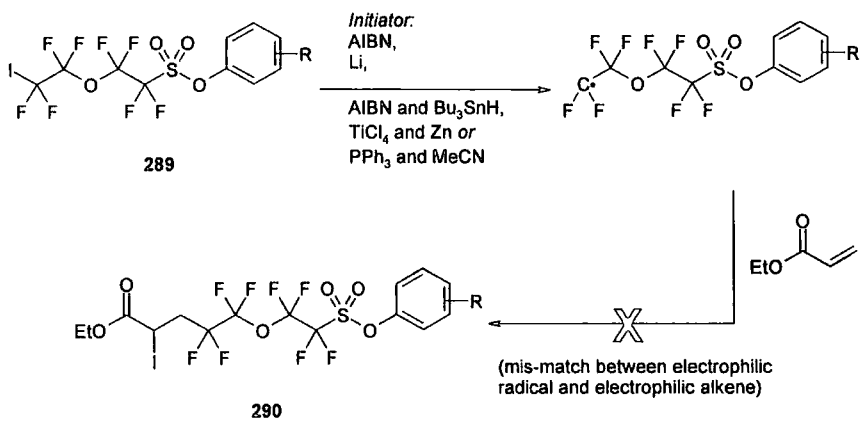
At this stage, de Sousa turned his attention to fluorinated free radical chemistry as a way of adding a perfluoroalkanesulfonyl group to an alkene to give 290 which could subsequently be loaded onto a solid support. Fluorinated free radicals have been reviewed in the literature and a wide variety of chemistry has been demonstrated with them.[111-115] While a review of the chemistry of fluorinated radicals is beyond the scope of this thesis, their reactivity towards alkenes is pertinent. Perfluoroalkyl radicals can be generated from a number of sources but diiodoperfluoroalkanes 291 and iodoperfluoroalkanes 292 have been used extensively throughout this thesis and so are given as a representative example. Their addition to alkenes has been catalysed by a range of additives, Scheme 1.93.



Reagents: AIBN,[111, 112] AIBN and Bu_3SnH,[113] Li,[114] Ti,[111, 112] PPh_3,[115] etc.

Scheme 1.93

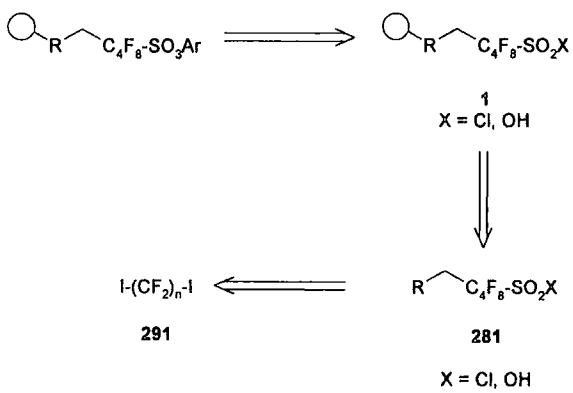
Building on this literature precedent, de Sousa investigated the reaction of iodide 289 with ethyl acrylate using a range of methods, Scheme 1.94. However, all attempts proved unsuccessful and no reaction to give 290 was observed, Scheme 1.94. In hindsight, this can be put down to a mismatch between the electrophilic perfluoroalkyl radical generated from 290 and the electrophilic double bond of ethyl acrylate leading to an unfavourable reaction and consequently no product. Furthermore, concurrent with de Sousa's efforts at this stage, Pan and Holmes published a perfluoroalkanesulfonyl linker unit derived from iodosulfonyl fluoride 158 as described in Section 1.1.2.4.[68, 69] As a result of both of these factors, this route was not progressed any further.



Scheme 1.94

Although Holmes' linker demonstrated the concept of a perfluoroalkanesulfonyl diversity linker was a viable one, the high cost of iodo sulfonyl fluoride 158 (~£20 / g) and the several step synthesis involved limited the practicality of the solution.

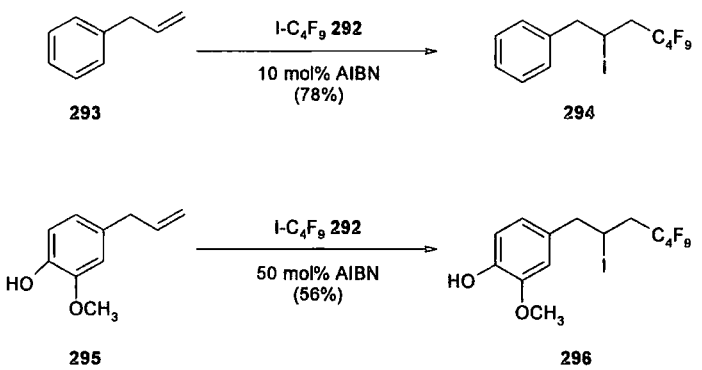
Therefore, a cheap and efficient route to a perfluoroalkanesulfonyl linker unit still had applications in solid phase organic synthesis. With this goal in mind de Sousa turned to investigating diiodoperfluoroalkanes as a possible starting point. They are relatively cheap, commercially available starting materials. Furthermore, a variety of chain lengths (n = 2 - 8) would allow for reactivity tuning as increasing the length of the perfluoroalkane chain increases the reactivity of perfluoroalkanesulfonate esters as previously discussed. Therefore, the next strategy was to derive a perfluoroalkanesulfonyl linker unit 1 from a bifunctional sulfonic acid 281, which in turn could be synthesised from diiodoperfluoroalkanes 291, Scheme 1.95.



Scheme 1.95

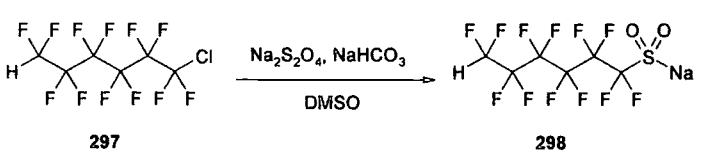
It was necessary to functionalise one end of a diiodoperfluoroalkane with some group which could be used as a point of attachment to a solid support. To this end de Sousa investigated radical reactions with alkenes. Brace has shown that iodoperfluoroalkanes can be added to electron-rich alkenes in the presence of a suitable radical initiator such as AIBN.[116, 117] Therefore, in preliminary unoptimised studies 1-iodononafluorobutane 292 was selected as a model system and de Sousa was able to generate an electrophilic perfluoroalkyl radical using AIBN and add it to nucleophilic alkenes. Reaction with allyl benzene 293 was attempted as a model system and proceeded with 10 mol% AIBN to give iodide 294 in 78% yield. With this result in hand, de Sousa attempted the

analogous reaction using eugenol 295. Eugenol is a commercially available analogue of allyl benzene and the attraction was that the phenol offered a convenient means of attachment to a solid support. The analogous reaction with 1-iodononafluorobutane 292 was attempted but found to be slow. However, if the amount of AIBN employed was increased to 50 mol%, then iodide 296 was generated in 56% yield, Scheme 1.96. This difference in reactivity was attributed to the free phenol complicating the reaction.



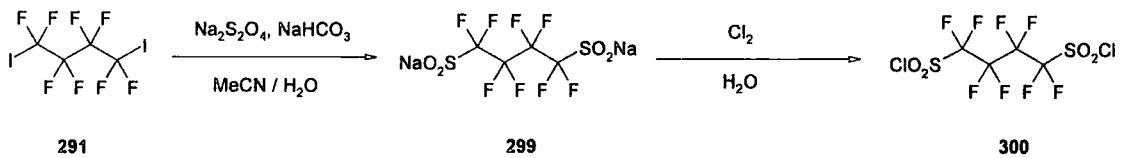
Scheme 1.96

With chemistry established for functionalising iodoperfluoroalkanes with a group that could be used to attach a perfluoroalkanesulfonyl linker unit to a solid support, de Sousa then attempted to generate perfluoroalkanesulfonyl groups. To this end the reactions of iodoperfluoroalkanes with sodium dithionite was investigated as sodium dithionite has been used in the literature for the generation of perfluoroalkanesulfonyl groups. For example, Long and Chen showed that perfluoroalkyl chlorides 297 could be converted into sodium sulfite salts 298 using sodium dithionite, Scheme 1.97.[118]



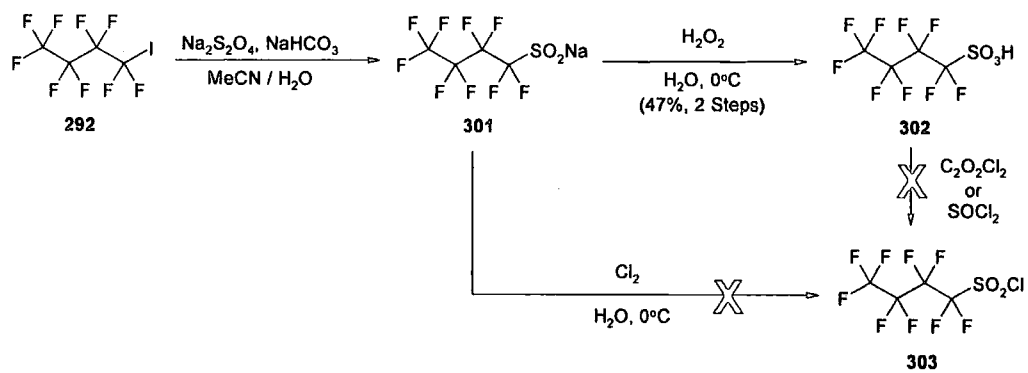
Scheme 1.97

Furthermore, Qiu and Burton were able to convert a range of diiodoperfluoroalkanes including 1, 4-diiodooctafluorobutane 291 into sodium sulfite salts 299 using sodium dithionite, Scheme 1.98. Subsequent chlorination gave easy access to the corresponding sulfonyl chlorides 300.[114]



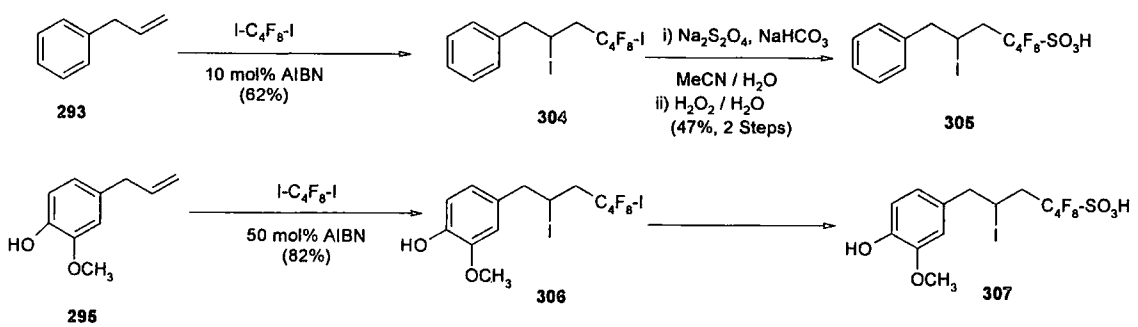
Scheme 1.98

De Sousa showed that this chemistry could be used with 1-iodononafluorobutane 292 as the substrate. Treatment with sodium dithionite following the literature precedent yielded sodium sulfite 301 which could then be oxidised to sulfonic acid 302. However, at this stage de Sousa was unable to convert sodium sulfite 301 into perfluoroalkanesulfonyl chloride 303 due to decomposition during the chlorination, Scheme 1.99. The conversion of sulfonic acid 302 into sulfonyl chloride 303 was also attempted using oxalyl chloride and thionyl chloride. However, neither reagent proved sufficiently reactive to achieve the transformation and in each case starting sulfonic acid was recovered.



Scheme 1.99

With chemistry in place for coupling iodoperfluoroalkanes to alkenes and for oxidising them to perfluoroalkanesulfonic acids, de Sousa also investigated the possibility of introducing both groups into a bifunctional molecule. To this end, 1,4-diiodooctaflurobutane 291 was selected as the starting material. Preliminary results indicated that monoaddition of 1,4-diiodooctafluorobutane to allylbenzene 293 and eugenol 295 occurred to yield mono substituted iodides 304 and 306 respectively. De Sousa was then able to convert iodide 304 derived from allylbenzene into the corresponding sulfonic acid 305, Scheme 1.100. However, eugenol was not taken through to bifunctional sulfonic acid 307 which could be attached to a solid support through the phenol to provide a perfluoroalkanesulfonyl linker unit. Therefore the current project carried on the work of de Sousa from this point.



Scheme 1.100

1.3.2 Aims of the Current Research

Preliminary studies carried out by de Sousa indicated that diiodoperfluoroalkanes showed promise as precursors to a perfluoroalkanesulfonyl linker unit, but a number of issues still required investigation:

1 The efficiency of the radical addition of 1,4-diiodooctafluorobutane to allylbenzene and eugenol to produce significant quantities of pure iodides 304 and 306 respectively needed to be established.

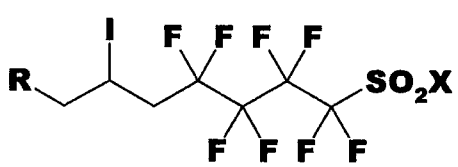
2 Methodology for the oxidation of iodide 306 to the corresponding sulfonic acid and/or sulfonyl chloride 307 and subsequent loading of phenols to provide aryl perfluorosulfonate esters required development.

3 Attachment of iodide 306 to a solid support through the phenol and subsequent solid phase chemistry studies required investigation.

This thesis therefore describes the continuation of de Sousa's early work and Chapter 2 begins with approaches towards a perfluoroalkanesulfonyl linker unit from 1,4-diiodooctafluorobutane.

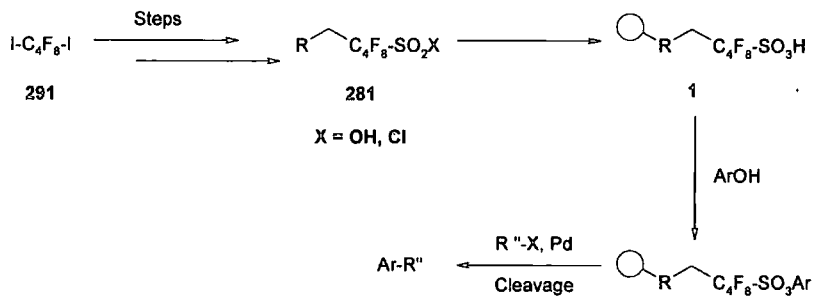
CHAPTER 2

APPROACHES TOWARDS A PERFLUOROSULFONYL LINKER UNIT



2 Preliminary Reactions

As discussed in the previous chapter, the initial approach was to derive a perfluorosulfonyl linker unit 1 from diiodoperfluoroalkanes 291. The strategy was to couple one iodide to an alkene possessing some functionality suitable for attaching the linker unit on to a solid support. This would leave the other iodide free to oxidise to a perfluorosulfonic acid or perfluorosulfonyl chloride, suitable for the loading of phenols, Scheme 2.1.

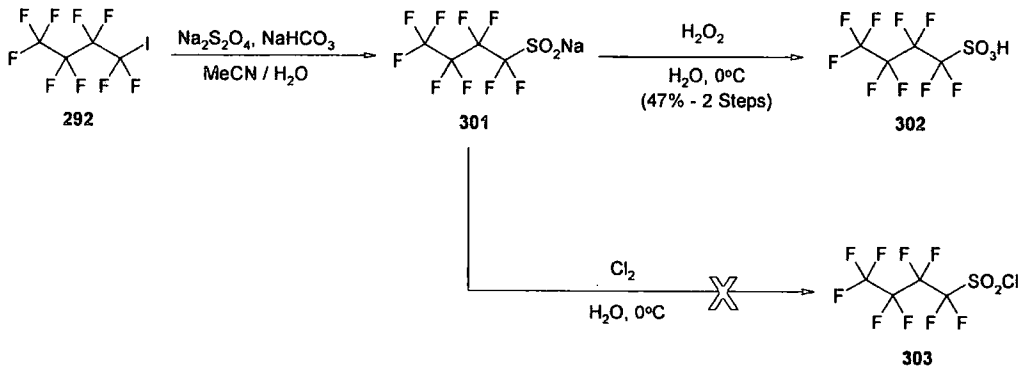


Scheme 2.1

In early work, de Sousa had established chemistry for the coupling of 1-iodononafluorobutane 292 to alkenes as described in Chapter 1. However, the efficiency of this chemistry for the production of significant quantities of material still needed to be established. Furthermore, reliable routes to perfluorosulfonic acids and perfluorosulfonyl chlorides had not been developed and so initial work concentrated in these areas.

The conversion of diiodoperfluoroalkanes into the corresponding sodium sulfite salts has been demonstrated by Qiu and Burton using sodium dithionite as described in Section 1.3.1.[119] Therefore, radical addition of sodium dithionite to 1-iodononafluorobutane 292 was carried out using the same conditions to yield sodium sulfite 301, Scheme 2.2. The reaction was monitored by ^{19}F NMR spectroscopy and quantitative conversion of 1-iodononafluorobutane 292 was seen in 6 h as observed by the replacement of the CF_2-I signal at -59 ppm with a CF_2-SO_2Na signal at –127 ppm. Treatment of sodium sulfite 301 with aqueous

hydrogen peroxide for 16 h gave sulfonic acid 302 in 47% yield. This was confirmed by a broad sulfonic acid signal at 7.92 ppm in the ^{1}H NMR spectrum and a sulfonic acid stretch at 3357 cm^{-1} in the infra red spectrum. However, treatment of sodium sulfite 301 with chlorine did not yield expected sulfonyl chloride 303 but rather resulted in an unidentified product possessing a CF_3 group but only 2 x CF_2 groups. It was not possible to identify this material by mass spectrometry. However, as it was not possible to generate a sulfonyl chloride directly from the sodium sulfite, attention turned to conversion of sulfonic acid 302 into sulfonyl chloride 303.

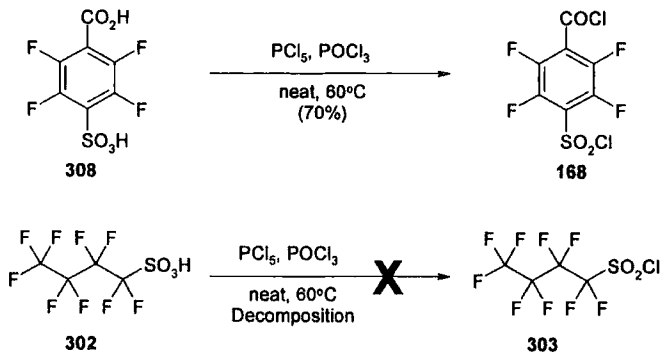


292 301 302 303

Scheme 2.2

It had already been shown by de Sousa that oxalyl chloride and thionyl chloride were not reactive enough to achieve the desired transformation.[110] However, the conversion of sulfonic acids into sulfonyl chlorides using phosphorous pentachloride is well documented in the literature.[120-122] For example, Fielding and Shirley converted 4-sulfo-2,3,5,6-tetrafluorobenzoic acid 308 into the corresponding sulfonyl chloride 168 by treatment with a combination of phosphorous pentachloride and phosphoryl chloride, Scheme 2.3.[122] However, reaction of perfluorosulfonic acid 302 under analogous conditions resulted in decomposition, seen by many peaks in the ^{19}F NMR spectrum. At this stage it was apparent that perfluorosulfonic acid 302 was unstable to conventional chlorination conditions. Therefore, as de Sousa had shown that coupling 1,4-diiodooctafluorobutane 291 to allylbenzene 293 and subsequent oxidation

provided access to a more stable sulfonic acid **305** as described in Section 1.3.1, it was decided to develop this chemistry further. It was speculated that generating sulfonyl chlorides from the more stable sulfonic acid would be more practical and work in this area is described below.



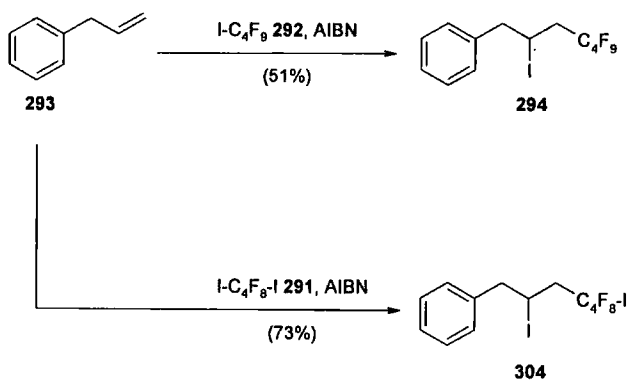
Scheme 2.3

2.1 Bifunctional Sulfonic Acids

2.1.1 Allylbenzene-derived Sulfonic Acids

De Sousa had shown that 1-iodononafluorobutane **292** could be coupled to allylbenzene **293** to give iodide **294**.[110] This chemistry was repeated and allylbenzene was added to a neat mixture of 1-iodononafluorobutane and 10 mol% AIBN, Scheme 2.4, and the reaction was then heated to 70 °C. This order of events was followed for all radical reactions of this type throughout this project. While unusual for radical reactions which would typically involve heating the initiator and iodide first and then adding the alkene slowly over time, it was found that carrying reactions out in this fashion did result in good yields of product. The reaction was monitored by ^{19}F NMR spectroscopy and after 16 h the CF_2-I signal at -59 ppm had been completely replaced by a CH_2-CF_2 signal seen as a multiplet between -111 and -115 ppm. Purification by distillation using a Kugelrohr bulb-to-bulb distillation apparatus yielded known iodide **294** in 51% yield and this was confirmed by a molecular ion in the EI mass spectrum at m/z = 464. With this chemistry established, attention turned to the reaction of 1 equivalent of 1,4-diiodooctafluorobutane **291** with 1 equivalent of allylbenzene

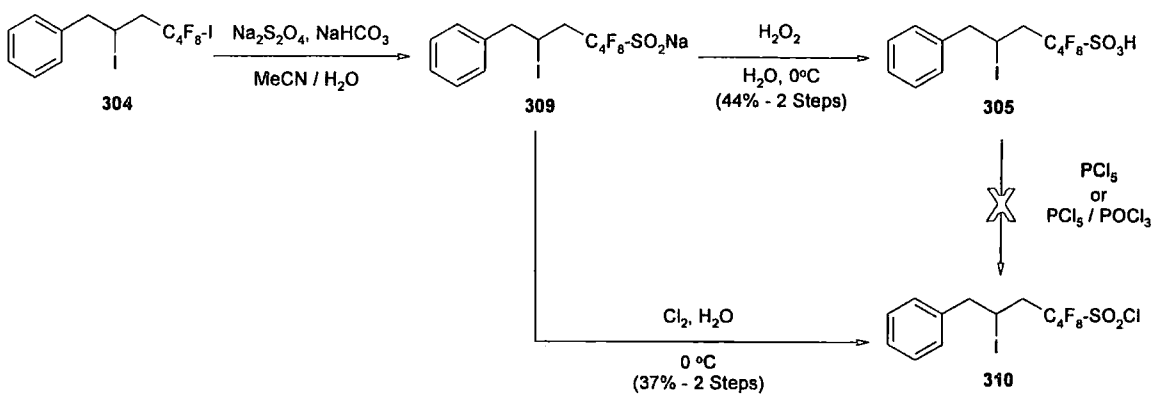
293. Similarly, this reaction was carried out neat at 70 °C using 10 mol% AIBN and gave exclusively mono-substituted iodide **304** in 73% yield following Kugelrohr distillation, Scheme 2.4. This was a promising result as it left the terminal difluoroiodomethyl unit available for oxidation to a sulfonic acid and indicated that addition of a second molecule of allylbenzene to it was unfavourable. ^{19}F NMR spectroscopy showed the appearance of a multiplet between –111 and –115 ppm (CH_2-CF_2) and iodide **304** was confirmed by a molecular ion at m/z = 571.8735 in the EI HRMS which was in agreement with the calculated value of 571.8739 for $C_{13}H_{10}F_8I_2$.



Scheme 2.4

With iodide **304** in hand, efforts were turned to the sulfonation reaction. Treatment of iodide **304** with 2 equivalents of sodium dithionite at room temperature gave quantitative conversion into sodium sulfite **309**, seen by the replacement of the CF_2-I signal at –59 ppm with a CF_2SO_2Na signal at –127 ppm in the ^{19}F NMR spectrum. Inorganic materials were removed by filtration and the crude mixture was dried *in vacuo* and used without further purification. Oxidation to perfluorosulfonic acid **305** was achieved in 44% yield on treatment with hydrogen peroxide at 0 °C and subsequent acidification, Scheme 2.5. The formation of sulfonic acid **305** was confirmed by a broad SO_3H absorption at 3475 cm^{-1} in the IR spectrum and a molecular ion at m/z = 524.9260 ($M\text{-}H^+$) in ES HRMS was in agreement with the calculated value of 524.9268 for $C_{13}H_{10}F_8O_3SI$. However, treatment of sulfonic acid **305** with either phosphorus

pentachloride or a combination of phosphorous pentachloride and phosphoryl chloride showed only unreacted starting material and no sulfonyl chloride **310**. Therefore, attention turned to aqueous chlorination of sodium sulfite **309** which had been employed by Qiu and Burton in the generation of sulfonyl chlorides.[119] This proved more promising and after 20 minutes the CF_2SO_2Na signal seen at –127 ppm in the ^{19}F NMR spectrum had been completely replaced by a CF_2SO_2Cl signal at –104 ppm. Purification by distillation using a Kugelrohr bulb-to-bulb distillation apparatus yielded sulfonyl chloride **310** in 37% yield, confirmed by stretches at 1415 and 1220 cm^{-1} in the IR spectrum and molecular ions at m/z = 567 and 569 (3:1, $M+Na^+$) in the ES mass spectrum. Unfortunately sulfonyl chloride **310** proved unstable and was found to rapidly decompose before the accurate mass could be confirmed. Despite some stability problems, these reactions demonstrated the possibility of loading diiodoperfluoroalkanes onto alkenes and also showed that oxidation to sulfonic acids and sulfonyl chlorides was possible. Therefore, extending the established chemistry to eugenol **295** was investigated next. The free hydroxyl group of eugenol was attractive as it provided a means of attachment of a future linker unit to a solid support. Progress with eugenol is described in Section 2.1.2.

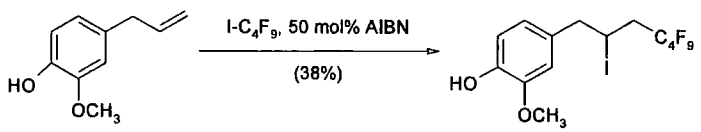


Scheme 2.5

2.1.2 Eugenol-derived Sulfonic Acids

2.1.2.1 Solution Phase Studies

It had been shown by de Sousa that a larger amount of AIBN was required for the radical addition of 1-iodononafluorobutane and 1,4-diiodooctafluorobutane to eugenol.[110] This was attributed to the presence of the free phenol group complicating the reaction and so reaction of 1-iodononafluorobutane in the presence of 50 mol% AIBN yielded iodide 296, Scheme 2.6. Monitoring of the reaction by ^{19}F NMR spectroscopy showed the complete disappearance of the CF_2-I peak at –59 ppm and the appearance of a CH_2-CF_2 multiplet at –111 - – 115 ppm after 16 h. Purification by flash chromatography gave iodide 296 in 38% yield and this was confirmed by a molecular ion at m/z = 509.9727 in EI HRMS which was in agreement with the calculated value of 509.9733 for $C_{14}H_{12}F_9O_2I$.

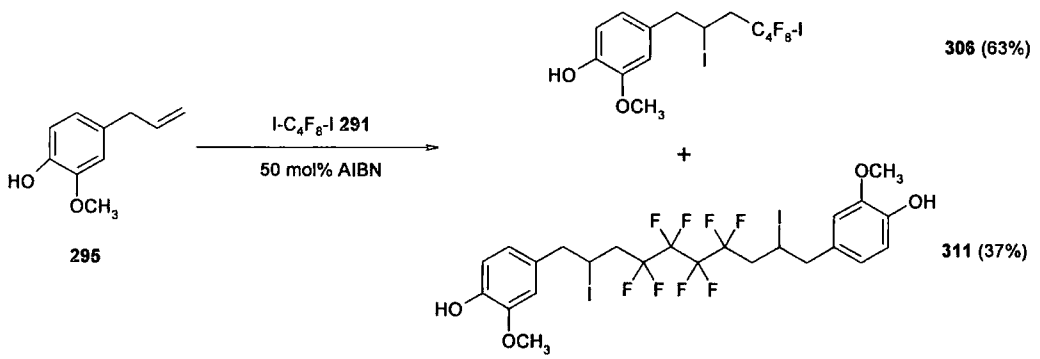


295 296

Scheme 2.6

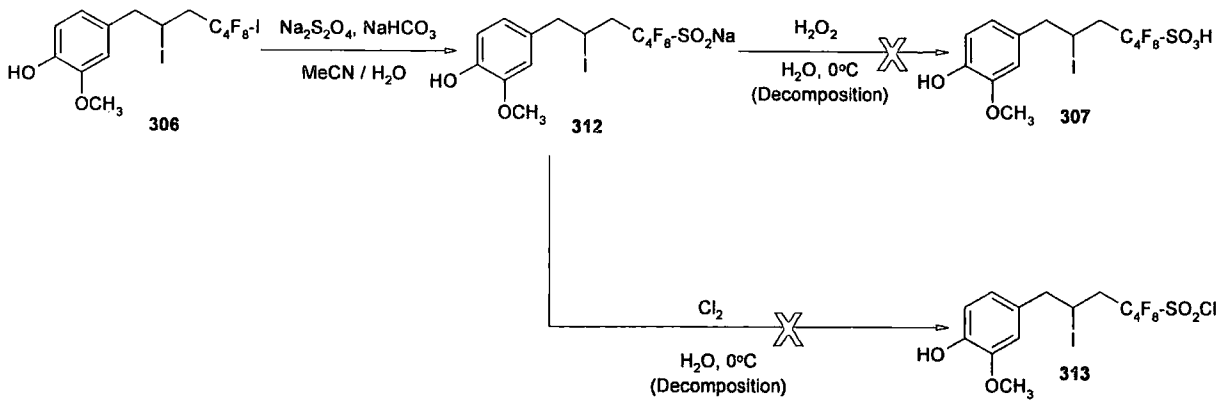
The reaction of 1,4-diiodooctafluorobutane 291 with eugenol also required 50 mol% AIBN. Monitoring the reaction by ^{19}F NMR spectroscopy showed it to be complete after 16 h and this was confirmed by four CF_2 peaks in the spectrum for iodide 306. However, an additional two peaks were also observed for the symmetrical bis-substituted compound 311. While the radical reaction of 1,4-diiodooctafluorobutane with allylbenzene yielded exclusively mono-coupled iodide, the reaction with eugenol yielded a 4:1 mixture of mono- 306 and bis- 311 coupled products, Scheme 2.7. This was due to the more nucleophilic nature of the alkene in eugenol when compared to allylbenzene. The increased reactivity resulting from the hydroxyl and methoxy groups on the aromatic ring led to the addition of a second molecule of eugenol giving bis-coupled product 311.

Separation of the mono- and bis-coupled compounds was not possible by distillation and therefore purification by flash chromatography was necessary. This gave iodide **306** in 63% yield, based upon eugenol, confirmed by a molecular ion at m/z = 617.8793 in the EI HRMS which was in agreement with the calculated value of 617.8786 for $C_{14}H_{12}F_8I_2O_2$. Further elution yielded bis-coupled compound **311** in 37% yield, based upon eugenol, and this was confirmed by a molecular ion at m/z = 781.9623 in EI HRMS which agreed with the calculated value of 781.9631 for $C_{24}H_{24}F_8I_2O_4$.



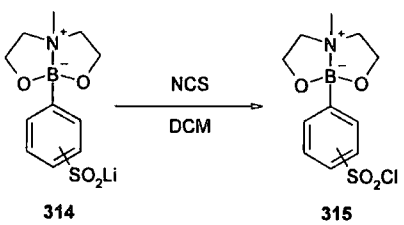
Scheme 2.7

With significant quantities of iodide **306** in hand, treatment with 2 equivalents of sodium dithionite resulted in some conversion into sodium sulfite **312**. However, ^{19}F NMR spectroscopy showed significant decomposition and a complex mixture of materials. It was thought that these complications were the result of excess sodium dithionite interfering with the free phenol. Therefore, the amount of sodium dithionite was reduced to 1.25 equivalents and this gave quantitative conversion into sodium sulfite **312** in 4 h, confirmed by the replacement of the CF_2-I signal at –59 ppm with a CF_2-SO_2Na at –127 ppm in the ^{19}F NMR spectrum. Subsequent treatment with hydrogen peroxide was expected to yield sulfonic acid **307** but this did not prove to be the case. The oxidation resulted in decomposition and gave a complex mixture from which none of the desired sulfonic acid could be isolated, Scheme 2.8. Similarly, aqueous chlorination of sodium sulfite **313** resulted in decomposition of material.



Scheme 2.8

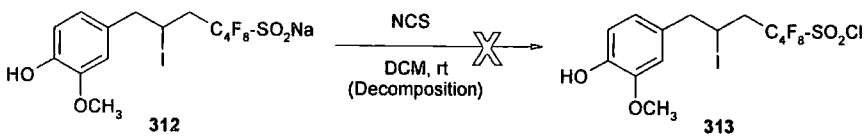
Concurrent with chlorination problems encountered in work described in Chapter 4 of this thesis, Vedsø *et al.* reported the conversion of lithium sulfites 314 into the corresponding sulfonyl chlorides 315 using *N*-chlorosuccinimide, Scheme 2.9.[123]



Scheme 2.9

Therefore, the chlorination of sodium sulfite 312 was attempted using 2.5 equivalents of *N*-chlorosuccinimide, Scheme 2.10, and the reaction was monitored by ^{19}F NMR spectroscopy. After 4 h the CF_2-SO_2Na signal at –127 ppm had been completely replaced by a CF_2-SO_2Cl signal at –104 ppm in the ^{19}F NMR spectrum which was a promising result. Unfortunately, sulfonyl chloride 313 was formed with significant quantities of iodine as a by-product. This was the result of the oxidation of sodium iodide, an inseparable by-product from the initial sulfonation reaction, to iodine. The initial attempt to remove this iodine using a reductive sodium thiosulfate work-up was unsuccessful, resulting in

decomposition of sulfonyl chloride 313. This was confirmed by the presence of many peaks in the ^{19}F NMR spectrum. Complications with all of these oxidations were thought to be due either to the presence of the free phenol or the unwanted secondary alkyl iodide which was an inevitable result of the initial radical addition. To overcome this, the first strategy was to remove the free phenol by protecting it as the acetate derivative.

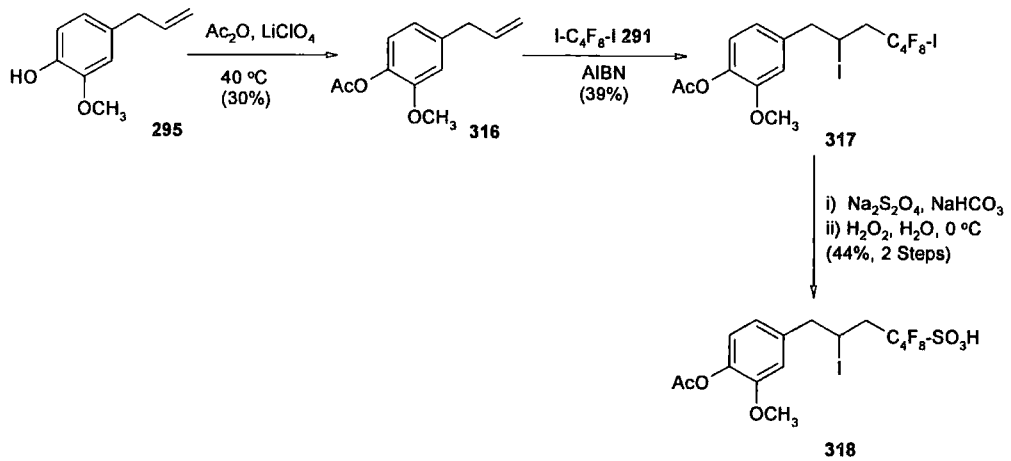


Scheme 2.10

2.1.2.2 Protected Eugenol Studies

Eugenol 295 was protected as the corresponding acetate using the procedure of Sato *et al.*.[124] Treatment with acetic anhydride and lithium perchlorate gave acetate 316 in a low but unoptimised 30% yield. Protection was confirmed by the disappearance of the OH absorption from the IR spectrum and the appearance of an ester C=O absorption at 1765 cm^{-1}. Furthermore, a molecular ion at m/z = 224.1282 ($M+NH_4^+$) in the ES HRMS agreed with the calculated value of 224.1287 for $C_{12}H_{18}NO_3$. Reaction of acetate 316 with 1,4-diiodooctafluorobutane 291 in the presence of 50 mol% AIBN gave iodide 317 in 39% yield following purification by flash chromatography. Iodide 317 was confirmed by a molecular ion at m/z = 677.9256 ($M+NH_4^+$) in the ES HRMS which was in agreement with the calculated value of 677.9248 for $C_{16}H_{18}F_8I_2NO_3$. Iodide 317 was then converted into the corresponding sodium sulfite salt by treatment with sodium dithionite. The conversion of the CF_2-I signal at –59 ppm into a CF_2-SO_2Na signal at –127 ppm in the ^{19}F NMR spectrum confirmed that the reaction was complete in 6 h. Subsequent oxidation with hydrogen peroxide gave sulfonic acid 318 in 16% yield, Scheme 2.11. The generation of sulfonic acid 318 was confirmed by a broad absorption at 3475 cm^{-1} in the IR spectrum and a molecular ion at m/z = 617 (M-H+) in the ES mass spectrum. However,

sulfonic acid 318 proved to be unstable and decomposition occurred before an accurate mass could be confirmed. Despite some stability problems, the protection of the free phenol did allow for the generation of a sulfonic acid. Therefore, at this stage it was desirable to see whether the chemistry was compatible with solid phase synthesis. The strategy was to immobilise the free phenol by using it as a point of attachment to a solid support and then generate sulfonic acids and sulfonyl chlorides directly on resin-bound substrates.

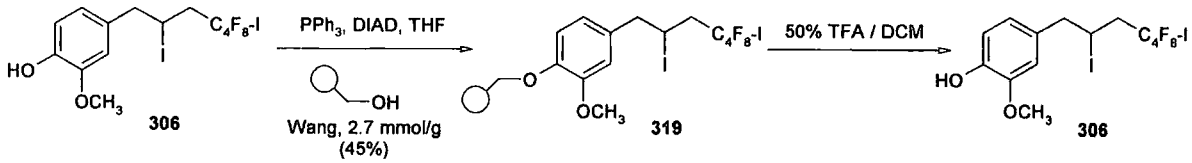


Scheme 2.11

2.1.2.3 Solid Phase Studies

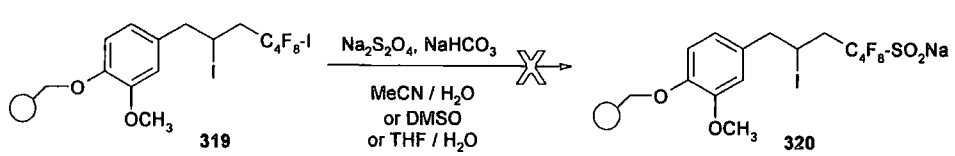
The generation of perfluoroalkanesulfonic acid 318 from protected eugenol discussed in the previous section demonstrated that it was possible to generate a bifunctional molecule which could function as a linker unit. However, perfluoroalkanesulfonic acid 318 was generated in 5% yield over 4 steps and so the chemistry required significant optimisation. Therefore, it was decided to immobilise eugenol onto a solid support and reattempt the oxidation on the solid phase. It was hoped that the use of large excesses of reagent in the solid phase reactions would drive the reactions to completion and improve the yield. Wang resin (loading = 2.7 mmol / g) was chosen for the polymer support as cleavage of materials with TFA / DCM allowed for the quick identification of substrates attached to the resin at any time. Iodide 306 was loaded onto Wang resin 319 using 5 equivalents of DIAD and triphenyl phosphine at room temperature using

a Mitsunobu reaction, Scheme 2.12. Cleavage of a small amount of resin with 50% TFA / DCM confirmed the loading of iodide 306 to be 45% based upon the maximum theoretical loading of the resin.



Scheme 2.12

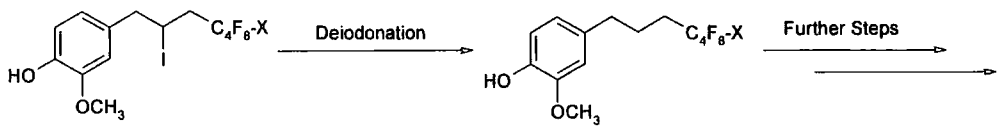
Resin-bound iodide 319 was treated with sodium dithionite in acetonitrile and water with the aim of generating resin-bound sodium sulfite 320. However, analysis of the material cleaved from a small amount of resin with 50% TFA / DCM following the sulfonation reaction indicated only starting iodide 306 by ^{19}F NMR spectroscopy. This indicated that the aqueous sulfonation reaction was unsuccessful and unsuitable for solid phase chemistry. It was speculated that this was due to the incompatibility of the resin with aqueous reaction conditions and so alternative solvents were sought. As described in Section 1.3.1, Long and Chen carried out analogous sulfonation reactions in DMSO. Therefore, the solid phase sulfonation reaction was repeated in DMSO as well as THF / water (1:1) but both reactions were unsuccessful and in each case only starting iodide 306 was recovered after cleavage, Scheme 2.13. At this stage, as solution phase oxidation was giving unstable sulfonic acids and solid phase oxidation had been unsuccessful, it was decided to reduce the secondary iodide. It was believed that this iodide was contributing to the instability of the system and that its removal would provide a more stable linker unit. The next section of this thesis describes attempts at deiodination.



Scheme 2.13

2.1.3 Deiodination Studies

It was decided to reduce the unwanted secondary iodide, Scheme 2.14, as it was thought to be complicating oxidations to sulfonic acids and sulfonyl chlorides. Furthermore, it was suspected that it may cause problems with future transition-metal-catalysed cross-coupling reactions. Initial efforts concentrated on zinc-mediated deiodination reactions as they are well known.

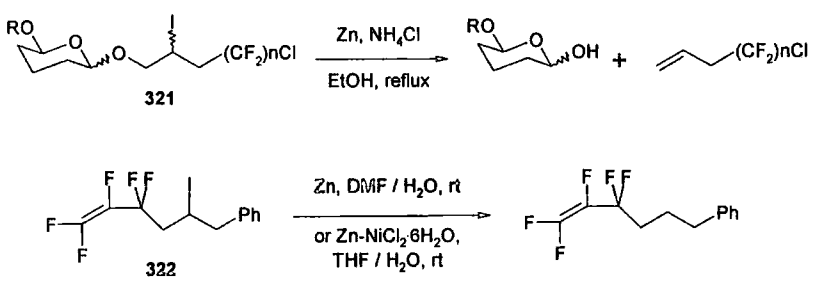


X = I, F, SO_3H, SO_2Cl etc.

Scheme 2.14

2.1.3.1 Zinc-mediated Deiodination

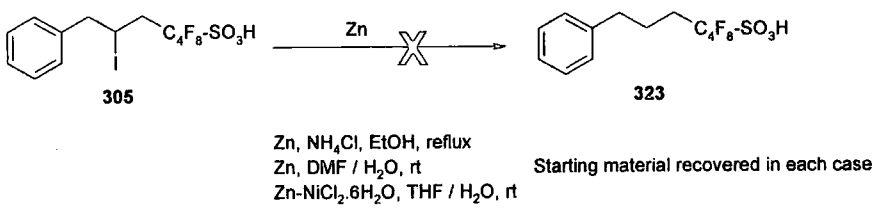
Zinc-mediated deiodination is well documented in the literature. For example, Yu *et al.* employed zinc powder and ammonium chloride to reduce iodide 321[125] while Burton *et al.* reduced iodide 322 using zinc or a combination of zinc and nickel (II) hexahydrate, Scheme 2.15.[126]



Scheme 2.15

These conditions were attempted using sulfonic acid 305 as a model system. However, in each case none of reduction product 323 was observed and starting material 305 was recovered, Scheme 2.16. No obvious explanation for this was forthcoming, but it quickly indicated that zinc-mediated reductions were not reactive enough to perform the desired deiodination on this system. Therefore

attention turned to alternative methods and to this end radical deiodination was chosen.



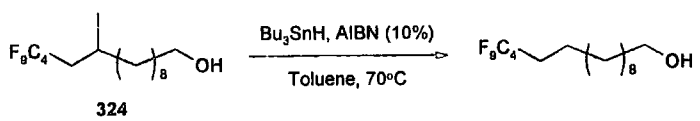
Scheme 2.16

2.1.3.2 Radical Deiodination

As zinc-induced deiodination had proved inactive, deiodination using radical methods were attempted as they are also common in the literature and it was hoped they would be more active. A number of possible radical methods for deiodination are known but the most common example by far is the combination of tributyltin hydride and AIBN.

Tributyltin Hydride

The use of tributyltin hydride to achieve deiodination is well documented.[127-130] For example it has been employed by Calas *et al.* to reduce iodide 324, Scheme 2.17.[127]

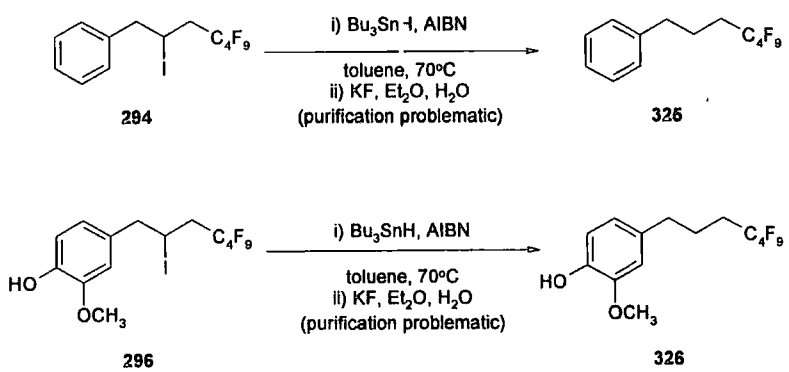


324

Scheme 2.17

With this literature precedent available, it was decided to explore this technique using model systems. For this purpose, iodides 294 and 296 derived from 1-iodononafluorobutane were chosen as they possessed no terminal iodide which could complicate the initial test reactions. Iodide 294 and 10 mol% AIBN were stirred together in toluene and then 1 equivalent of tributyltin hydride was added

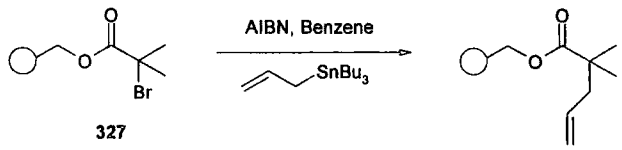
dropwise. The reaction was stirred at 80° C and after 16 h the iodide had been successfully reduced, Scheme 2.18. This was confirmed by EI GCMS which showed a molecular ion at m/z 338 corresponding to reduced compound **325**. Further analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy also showed the absence of the characteristic C*H*I signal at 4.4 ppm. The analogous reaction was also attempted using the eugenol-derived iodide **296**, Scheme 2.16. Analysis of the crude reaction mixture by EI GCMS confirmed that deiodination was again successful, seen as a molecular ion at m/z = 384 corresponding to reduction product **326**. However, purification of both reduced compounds proved to be extremely problematic. Initially, removal of tributyltin iodide was attempted using the procedure of Leibner and Jacobus.[131] The crude reaction mixture was partitioned between ether and water and treated with potassium fluoride. The resulting tributyltin fluoride was insoluble in both solvents and was removed by filtration. This was only partially successful and significant amounts of tin by-products were still present in the ^{1}H NMR spectrum. Further complications resulted as significant portions of the reduced material were lost in the aqueous KF layer and could not be recovered. Therefore, this was not a viable method for deiodination but it was hoped that these purification difficulties could be overcome by carrying out the reaction in the solid phase.



Scheme 2.18

Relatively few examples of solid phase radical reactions have been carried out.[12] However, the first example was reported by Sibi and Chandramouli.[132] They

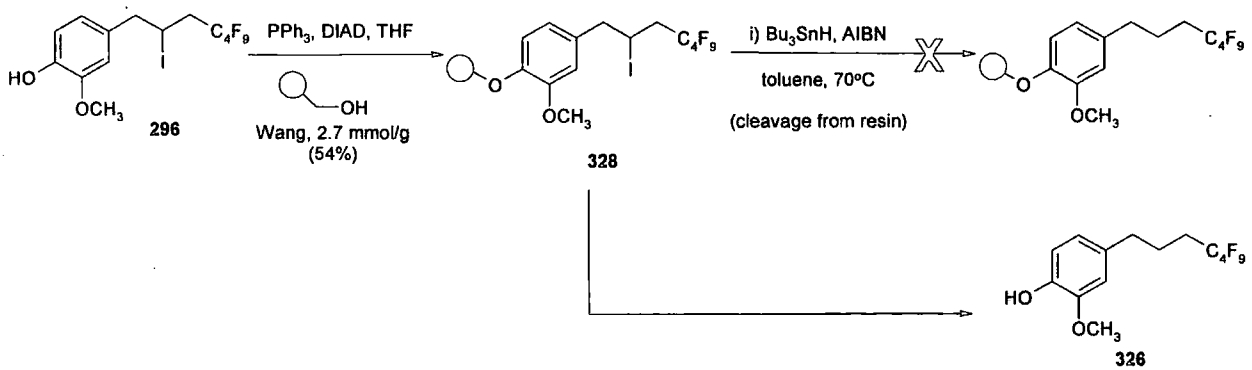
showed that solid-supported bromide 327 could be allylated in the presence of AIBN and allyltributyltin, Scheme 2.19.



327

Scheme 2.19

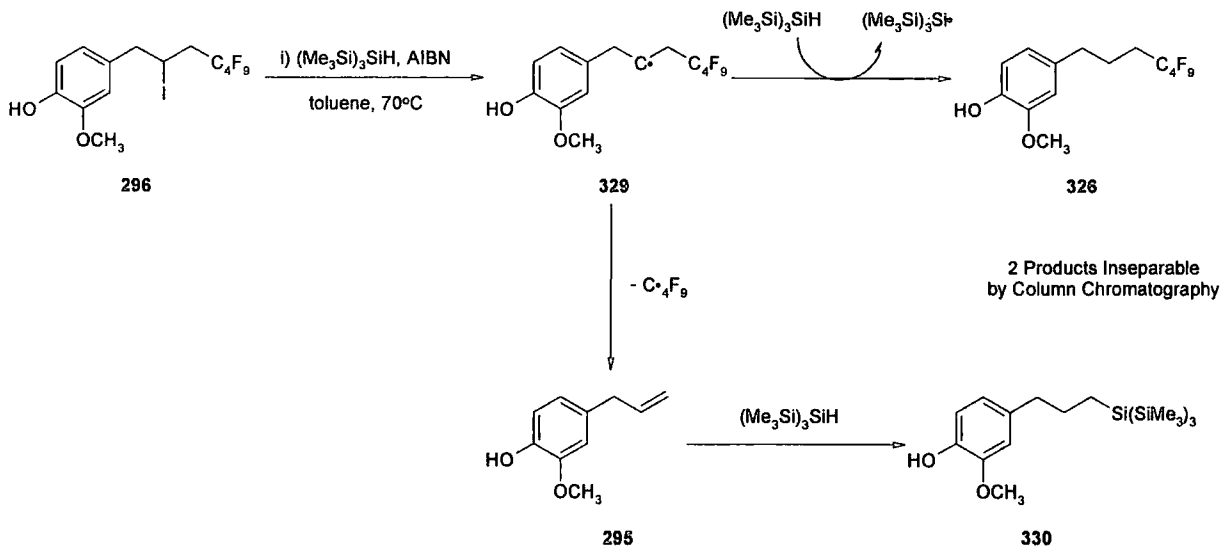
While this example represents an allylation reaction rather than hydrogen abstraction, it does demonstrate that radicals can be generated with solid-supported reagents. Therefore, it was speculated that if tributyltin hydride was used in place of allyltributyltin, then hydrogen abstraction would occur, resulting in a dehalogenation reaction. Furthermore, carrying out the deiodination reactions on a solid support was expected to simplify the removal of tin by-products. Simple filtration of the beads and subsequent washing with copious amounts of solvent should remove unwanted by-products. Therefore, iodide 296 was loaded onto Wang resin, Scheme 2.20, using an analogous Mitsunobu reaction to that previously described. Cleavage of a small portion of resin with 50% TFA/DCM confirmed loading to be 54% based upon the maximum possible loading of the resin. With resin-bound iodide 328 in hand, deiodination using tributyltin hydride was reattempted. However, while the deiodination reaction was successful, simultaneous cleavage of reduction product 326 occurred. This was confirmed by ^{1}H NMR spectroscopy and mass spectrometry as previously described but unfortunately meant that the same difficulties in purifying it from organostannane by-products were encountered. Deiodination using tributyltin hydride was abandoned at this stage as it had too many problems associated with it and instead efforts focussed upon the use of silyl radicals.



Scheme 2.20

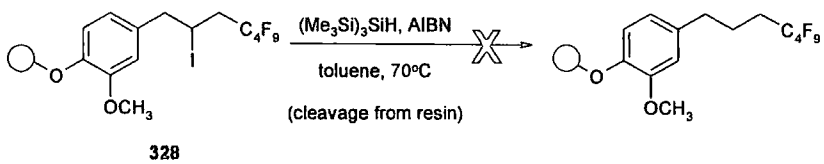
Tris(trimethylsilyl)silane

Silyl radicals appeared more attractive than their tin counterparts as the by-products are known to be water soluble. Furthermore their use in hydrogen abstraction reactions from organohalides has been known since the 1960s.[133] Solution phase deiodination of iodide 296 was attempted by adding 1 equivalent of tris(trimethylsilyl)silane to a solution of iodide 296 and 10 mol% AIBN in an analogous fashion to the tributyltin hydride reactions, Scheme 2.21. Analysis of the reaction mixture by EI GCMS showed the desired reduction product 326 after 24 h, confirmed by a molecular ion at m/z = 384. However, it was formed as a 4 : 1 mixture with a by-product showing a molecular ion at m/z = 411 in the EI GCMS. This indicated that silane 330 was formed in an unwanted side reaction. The mechanism for the formation of this by-product is not understood but it is speculated that abstraction of the iodide left a secondary radical 329 which could eliminate a perfluorobutyl radical to re-form eugenol 295. Final addition of tris(trimethylsilyl)silane to eugenol yielded silane 330 and separation of this silane from reduction product 326 was not possible by flash chromatography. It was thought that formation of silane 330 could be reduced in future reactions by controlling the quantities of reagents used. However, prior to optimisation of reaction conditions, it was desirable to determine if the reaction was applicable to solid phase synthesis.



Scheme 2.21

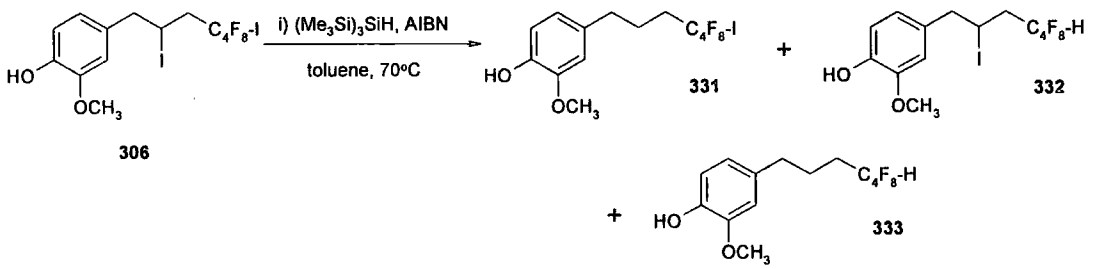
The analogous reaction was carried out on solid-supported iodide 328 to determine if purification was any easier. However, tris(trimethylsilyl)silane also cleaved material from the resin, Scheme 2.22. Analysis of the filtrate showed a complex mixture of products from which none of the desired reduction product could be obtained. This confirmed that it was necessary to carry out the deiodination reaction in solution phase and then attach the linker unit to a resin.



Scheme 2.22

Prior to optimisation of solution phase reaction conditions, it was necessary to attempt the deiodination reaction on iodide 306. This was in order to determine if the secondary iodide could be successfully reduced in the presence of a terminal difluoro-iodo-methyl unit. However, on attempting the deiodination reaction with 1 equivalent of tris(trimethylsilyl)silane on iodide 306, a complex mixture of products was formed, Scheme 2.23. Analysis of the crude reaction mixture by EI

GCMS showed the desired reduction product 331, confirmed by a molecular ion at m/z = 492. However, this was inseparable from the compound obtained from reduction of the terminal iodide 332 (m/z = 492) and the compound in which both iodides had been reduced 333 (m/z = 366). These two compounds were further confirmed by the presence of triplet of triplets at 6.0 ppm in the ^{1}H NMR spectrum corresponding to a CF_2H group. Therefore, it was decided to abandon deiodination employing silyl radicals at this stage as its use was hindered by complex mixtures of products and purification problems. Furthermore, incompatibility with a terminal difluoro-iodo-methyl unit meant that, while silyl radicals showed moderate potential on the test system, they could not be applied to the bifunctional linker unit. It was decided to explore phosphonyl radicals as an alternative means of deiodination.

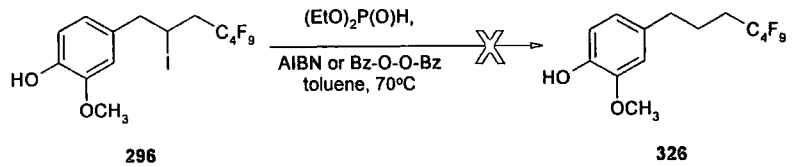


Scheme 2.23

Diethyl Phosphite

The problems associated with radical induced deiodination using tin and silyl reagents meant that another alternative was required. To this end attention turned to the use of phosphonyl radicals. Phosphonyl radicals ($R_2P(O)^{\cdot}$) are generated upon heating phosphites in the presence of radical initiators and they have been shown to abstract halogen atoms from organohalides.[134] Initially reduction of iodide 296 was attempted using AIBN as the initiator in toluene, Scheme 2.24. However, no reduction occurred and iodide 296 was recovered quantitatively. In order to try to overcome this problem, benzoyl peroxide was employed as an alternative radical initiator as it is known to show similar activity

to AIBN in generating phosphonyl radicals. Despite this, once more, no reduction was observed and the C*H*I signal was still present at 4.4 ppm in the ^{1}H NMR spectrum. Therefore, it was decided to abandon radical methods of deiodination as they had proved too problematic. The possibility of treating secondary iodides with base to eliminate HI was explored instead.

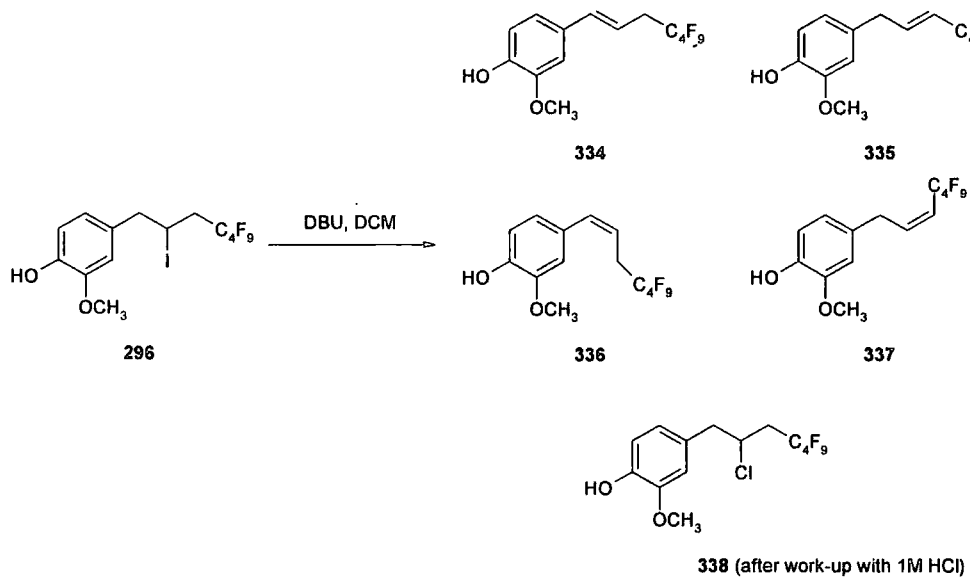


296 326

Scheme 2.24

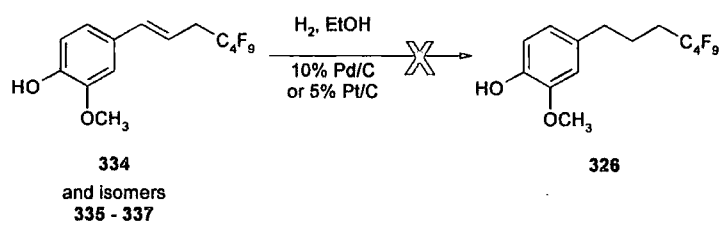
2.1.3.3 Base-mediated Deiodination

As radical approaches towards deiodination were complicated by complex mixtures of products and purification difficulties, it was decided to attempt the elimination of the secondary iodide using a base. It was hypothesised that treatment of iodide 296 with DBU would eliminate HI to give a mixture of 4 alkenes 334 - 337. *Trans* isomer 334 with the double bond in the benzylic position was expected to be the favoured isomer. Hydrogenation of the reaction mixture should then yield the single reduction product 326. Treatment of iodide 296 with 3 equivalents of DBU in DCM at room temperature, Scheme 2.25, was monitored by GC and GCMS. After 24 h, there were four signals at m/z = 490 in the ratio 6.1 : 2.6 : 1.4 : 1 in the EI GCMS. These corresponded to the elimination of HI and were thought to be alkenes 334 – 337. Following work-up (1M HCl) there was also a peak in the EI GCMS with a molecular ion at m/z = 526 : 528 (3 : 1). This suggested that addition of HCl across the double bond had occurred during work-up to give 338. The crude material was a complex mixture and so purification was not attempted at this stage. Instead it was decided to hydrogenate the double bonds to give a single reduction product which was expected to be easier to purify.



Scheme 2.25

Initially hydrogenation was attempted at atmospheric pressure in ethanol using 10% palladium on carbon as a catalyst, Scheme 2.26. However, monitoring the reaction by GC indicated that no reaction had occurred after 24 h at room temperature. Therefore, the reaction was repeated under pressure (Parr apparatus, 60 psi) and warmed to 60 °C but this was also unsuccessful. At this stage it was thought that the catalyst was not active enough and so it was changed to 5% platinum on carbon which has been shown to be a more active hydrogenation catalyst.[135] However, this also had no effect and once more starting material was recovered.



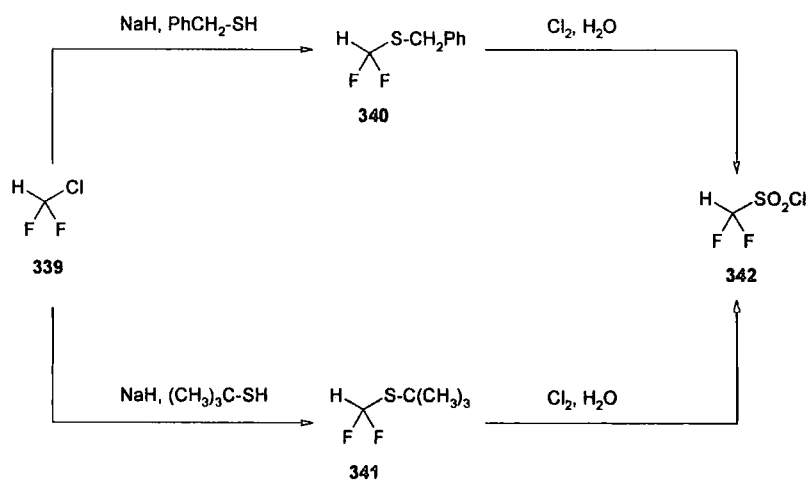
Scheme 2.26

At this stage it had not been possible to develop a reliable route to perfluorosulfonic acids and perfluorosulfonyl chlorides from eugenol that were

stable enough to function as a versatile linker unit. Furthermore, it had not been possible to improve the stability of the system by reducing the secondary iodide. Reluctantly it was decided not to pursue this route to a perfluorosulfonyl linker any further. Attention turned to alternative methods for the generation of perfluorosulfonyl chlorides and to this end reports in the literature of the oxidation of perfluoroalkyl benzyl thioethers to perfluorosulfonyl chlorides appeared promising.

2.2 Perfluorosulfonyl Chlorides from Thioethers

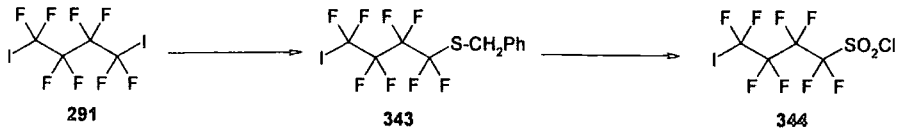
Since the synthesis of perfluorosulfonic acids and perfluorosulfonyl chlorides from sodium sulfite salts had proved extremely problematic, alternative strategies for the generation of sulfonyl chlorides were considered. For example, the work of Moore was particularly interesting as it was reported that difluoromethyl chloride **339** could be converted into difluoromethyl benzyl thioether **340** and difluoromethyl *tert*-butyl thioether **341**. Aqueous chlorination of **340** and **341** gave sulfonyl chloride **342**, Scheme 2.27.[136]



Scheme 2.27

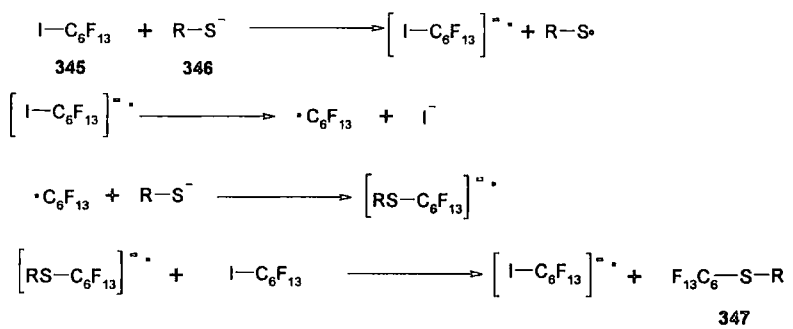
It was speculated that if 1,4-diiodooctafluorobutane **291** was converted into thioether **343**, then chlorination would provide a convenient route to iodosulfonyl chloride **344**. This would allow the other end to be coupled to an alkene using

previously described chemistry. It was hoped that this would offer a more practical route to a perfluorosulfonyl linker unit, Scheme 2.28.



Scheme 2.28

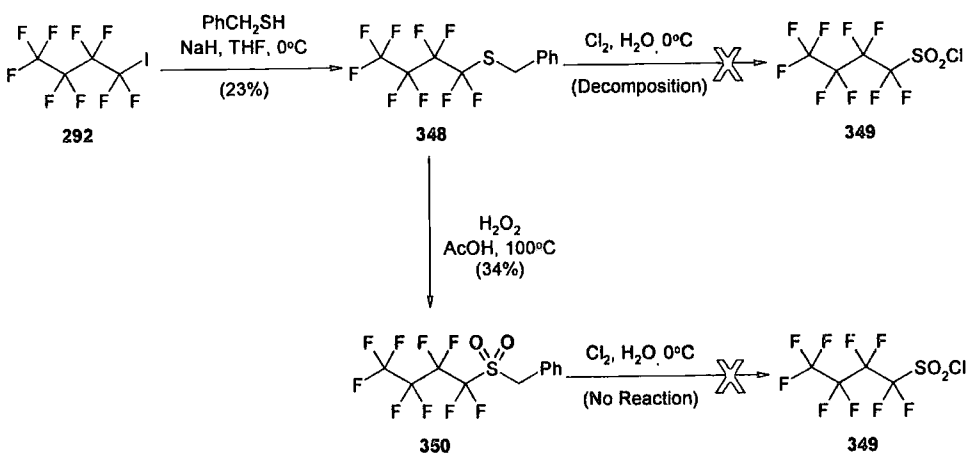
Initially it was decided to investigate the conversion of 1-iodononafluorobutane 292 to the corresponding perfluorobutyl benzyl and *tert*-butyl thioethers. To this end the report of Feiring that perfluoroalkylation of aromatic, heteroaromatic and aliphatic thiols with perfluoroalkyl iodides proceeded in the presence of sodium hydride was of interest.[137] Feiring reported that the first step was to preform the sodium thiolate 345 and add it to a solution of perfluorohexyl iodide 346. However, the reaction is not thought to go *via* a conventional S_N2 substitution as the blanket of electrons surrounding a perfluorobutyl group prevents the approach of a nucleophile. Therefore, what has been postulated is a radical chain mechanism resulting in perfluoroalkyl thioethers 347, Scheme 2.29.



Scheme 2.29

Therefore, treatment of 1-iodononafluorobutane 292 with benzyl thiolate yielded nonafluorobutyl benzyl thioether 348 in 23% yield, Scheme 2.30. ^{19}F NMR spectroscopy showed the disappearance of the CF_2-I signal at –59 ppm and the appearance of a CF_2-S signal at –88 ppm. The presence of thioether 348 was

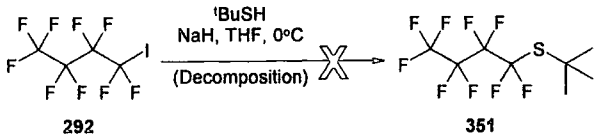
confirmed by a molecular ion at m/z = 342.0120 in the EI HRMS which was in agreement with the calculated value of 342.0125 for $C_{11}H_7F_9S$. However, aqueous chlorination of this material resulted in decomposition and no nonafluorobutanesulfonyl chloride 349 was observed. Therefore, it was decided to oxidise thioether 348 to the corresponding sulfone 350 and reattempt the chlorination. This was achieved using acetic acid and hydrogen peroxide following Moore's procedure.[136] The reaction was monitored by ^{19}F NMR spectroscopy and after 4 h the CF_2-S signal at –88 ppm had been completely replaced by a CF_2-SO_2 signal at –112.5 ppm in the NMR spectrum. Recrystallisation from petroleum ether gave sulfone 350 in 34% yield consistent with the appearance of a characteristic SO_2 stretch at 1144 cm^{-1} in the IR spectrum. Furthermore, a molecular ion at m/z = 372.9948 in the ES HRMS agreed with the calculated value of 372.9939 for $C_{11}H_6F_9SO_2$. Unfortunately, sulfone 350 proved unreactive to chlorination conditions and resulted in quantitative recovery of the starting material, Scheme 2.30.



Scheme 2.30

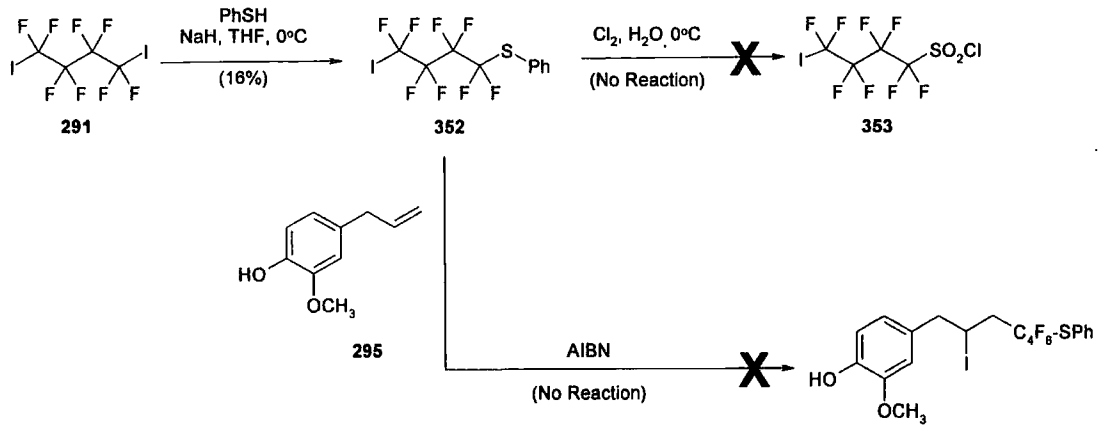
As it was not possible to oxidise the benzyl thioether to the desired sulfonyl chloride, attention was turned to synthesising the *tert*-butyl analogue. However, the reaction of 1-iodononafluorobutane with *tert*-butyl thiol resulted in

decomposition, indicated by the presence of many peaks in the ^{19}F NMR spectrum, and gave none of thioether 351, Scheme 2.31.



Scheme 2.31

Concurrent with these efforts, the possibility of selectively functionalising one end of 1,4-diiodooctafluorobutane with a thiol was also investigated. The analogous reaction to that described above using *tert*-butyl thiol was attempted but also resulted in decomposition, observed by many peaks in the ^{19}F NMR spectrum. Therefore, in an attempt to overcome these stability problems, it was decided to utilise thiophenolate as a more stable thiolate. Treatment of 1 equivalent of thiophenol with sodium hydride and subsequent addition of the resulting sodium thiolate to a solution of 1,4-diiodooctafluorobutane gave thioether 352 in 16% yield. This was monitored by the appearance of a CF_2S signal at –87 ppm in the ^{19}F NMR spectrum and confirmed by a molecular ion at m/z = 435.9032 which was in agreement with the calculated value of 435.9029 for $C_{10}H_5SF_8I$. Unfortunately, while iodooctafluorobutyl phenyl thioether 352 was easier to synthesise than the *tert*-butyl and benzyl analogues, it proved to be extremely unreactive. Attempts to generate sulfonyl chloride 353 merely resulted in the recovery of unreacted starting material as did efforts to add it to eugenol using AIBN, Scheme 2.32. Consequently, as the generation of perfluorosulfonyl chlorides from thioethers had shown little promise as a practical route towards a perfluorosulfonyl linker unit, it was abandoned at this stage. Attention was turned to other commercially available starting materials.

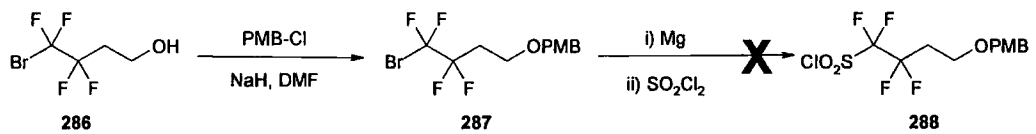


Scheme 2.32

2.2 Alternative Starting Materials

2.3.1 4-Bromo-3, 3, 4, 4-tetrafluorobutan-1-ol

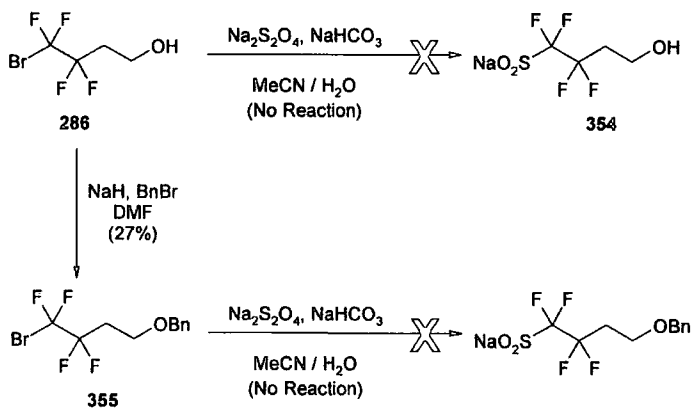
At this stage, the investigation of bromoalcohol **286** as a route to a perfluorosulfonyl linker was carried out because the alcohol provided a means of attachment to a solid support. In previous work, de Sousa had been unable to convert the bromide of protected bromoalcohol **287** into the corresponding sulfonyl chloride **288** using Grignard chemistry, Scheme 2.33.



Scheme 2.33

However, the possibility of reacting bromoalcohol **286** with sodium dithionite to yield the corresponding sodium sulfite salt **354** had not been investigated and so this was attempted. Unfortunately, no reaction occurred with 2 equivalents of sodium dithionite and starting material was recovered, Scheme 2.34. This was confirmed by the CF_2-Br signal that was still observed at –66 ppm in the ^{19}F NMR spectrum. It was speculated that this was due to either to complications resulting from the free alcohol or because the bromide was not sufficiently reactive.

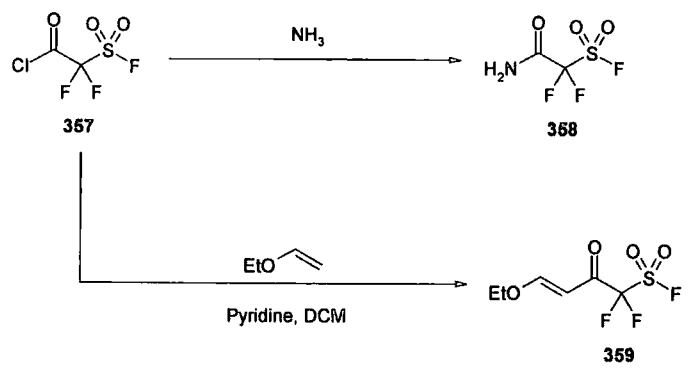
Therefore, it was decided to protect the alcohol as the benzyl derivative **355** and this was achieved in 27% yield using sodium hydride and benzyl bromide. Protection was confirmed by the disappearance of the OH stretch in the IR spectrum and a molecular ion of 332.0272 (M + NH_4) was in agreement with the calculated value of 332.0273 for $C_{11}H_{15}F_4NOBr$. The radical addition of sodium dithionite was attempted on the protected alcohol but once again only starting material was recovered after 24 h and the C*F*$_2$-Br signal was still present at –66 ppm in the ^{19}F NMR spectrum. Therefore the generation of a perfluorosulfonyl linker from bromoalcohol **286** was abandoned as it was not sufficiently reactive for conversion into the sulfonyl chloride. At this stage, it was necessary to change strategy and find an alternative starting material.



Scheme 2.34

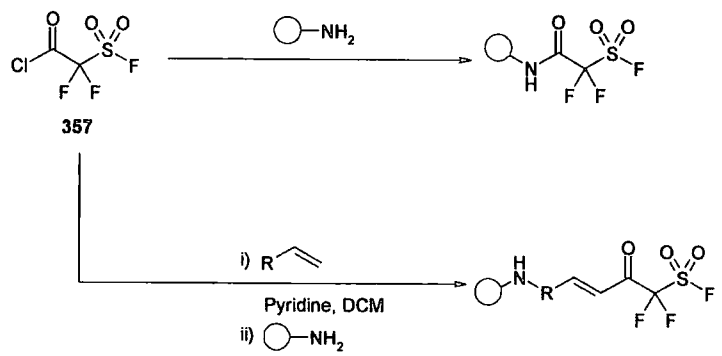
2.3.2 (Fluorosulfonyl)difluoroacetic Acid

As bromoalcohol **286** had proved unreactive towards sodium dithionite, the use of (fluorosulfonyl)difluoroacetic acid **356** as an alternative starting material was investigated. The acid chloride analogue **357** of (fluorosulfonyl)difluoroacetic acid is known in the literature. For example, Nazaretian *et al.* demonstrated that it reacted with ammonia to yield amide **358** without affecting the sulfonyl fluoride.[138] Alternatively, Gerus *et al.* showed that acid chloride **357** underwent addition to ethyl vinyl ether in the presence of pyridine to give **359**, again without any unwanted side reactions occurring at the sulfonyl fluoride, Scheme 2.35.[139]



Scheme 2.35

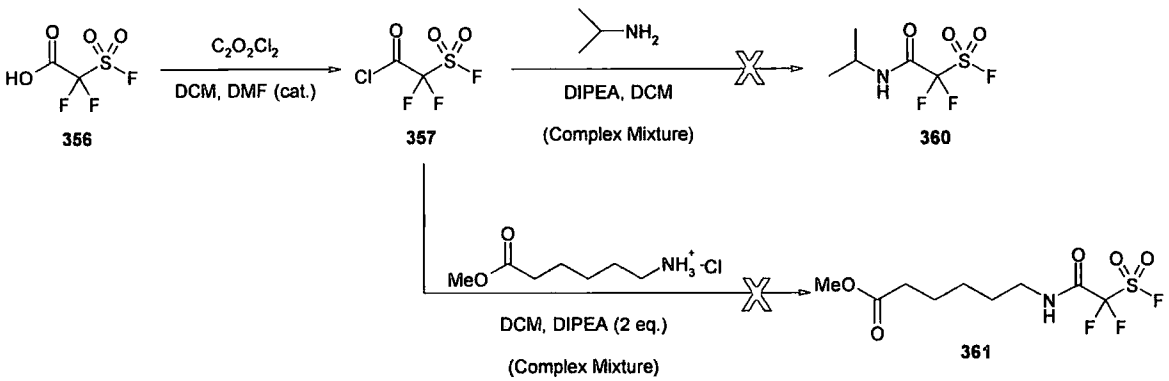
With this literature precedent available, it was speculated that if acid chloride 357 could be generated then it could either be loaded directly onto an amino resin or coupled to an alkene first and subsequently attached to a resin to provide a simple route to a perfluorosulfonyl linker unit, Scheme 2.36.



Scheme 2.36

Therefore, attention turned to treatment of (fluorosulfonyl)difluoroacetic acid 356 with oxalyl chloride. Reaction of 356 with 2 equivalents of oxalyl chloride resulted in complete conversion into acid chloride 357 after 4 h at 0 °C. This was confirmed by a shift in the CF_2 signal from –104 ppm to –100 ppm in the ^{19}F NMR spectrum and a shift in the SO_2F signal from +41 to +45 ppm, Scheme 2.37. However, as the boiling point of the acid chloride 357 is known to be 67 – 68 °C[139] it was decided not to try to isolate it but to react it with amines *in situ* as

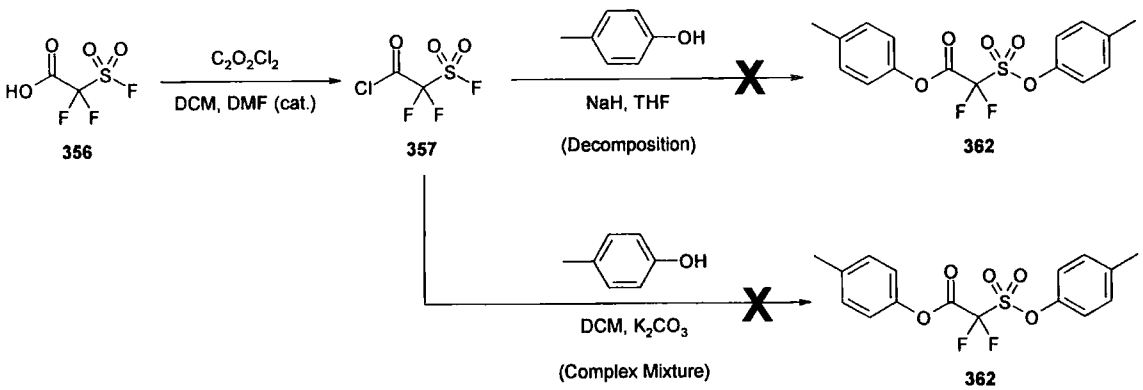
model studies for loading a potential linker unit onto amino resins. Therefore the reaction of acid chloride 357 with either 1 equivalent of isopropylamine or 1 equivalent of 6-aminocaproic acid methyl ester (as the hydrochloride salt to prevent cyclisation) were investigated. The reactions were monitored by EI GCMS and ^{19}F NMR spectroscopy but, in each case, decomposition resulted in complex mixtures of more than 8 components being formed. In the reaction with isopropylamine, EI GCMS indicated trace amounts of amide 360 (m/z = 219) but as a minor component of a complex mixture. None of amide 361 was formed in the reaction with 6-aminocaproic acid methyl ester.



Scheme 2.37

Concurrent with these efforts, the possibility of reacting phenols with the sulfonyl fluoride of acid chloride 357 was also investigated. As reactions using 1 equivalent of amine described above had given complex mixtures, it was decided initially to use 2 equivalents of phenol. It was hoped that 2 equivalents would react with the acid chloride and the sulfonyl fluoride in order to give the single bis-coupled product 362 and prevent further complex mixtures being formed. Initially the reaction was attempted by generating acid chloride 357 *in situ* as previously described and treating it with 2 equivalents of sodium phenoxide. However, this resulted in decomposition, confirmed by many peaks in the ^{19}F NMR spectrum. Therefore, the reaction was repeated using potassium carbonate but again a complex mixture of products was formed, Scheme 2.38.

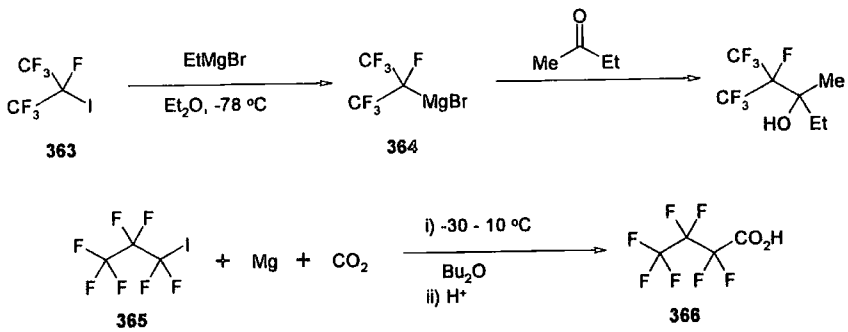
Therefore, the use of (fluorosulfonyl)difluoroacetic acid as a starting material was abandoned at this stage and the use of Grignard reagents as an alternative strategy was explored.



Scheme 2.38

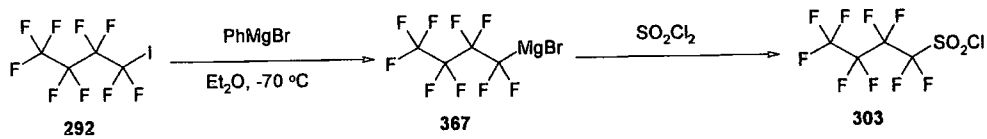
2.3 Fluorinated-Grignard Reagents

As attempts to derive a perfluorosulfonyl linker unit from commercially available starting materials had proved problematic, it was decided to investigate the generation of Grignard reagents from iodoperfluoroalkanes as an alternative route to perfluorosulfonyl chlorides. The use of fluorinated organometallics has been reviewed in the literature.[140, 141] For example, Chambers *et al.* demonstrated that perfluoroalkyl iodide **363** could be converted to the corresponding Grignard reagent **364** and in turn added to carbonyl compounds.[142] Furthermore, Haszeldine showed that if the Grignard reagent of 1-iodoperfluoropropane **365** was synthesised, then it could be added to carbon dioxide and subsequently acidified to yield a carboxylic acid **366**, Scheme 2.39.[143]



Scheme 2.39

Therefore it was speculated that if the Grignard of 1-iodononafluorobutane could be prepared then it could be added to sulfuryl chloride to yield sulfonyl chloride **303**. The synthesis of Grignard reagent **367** was attempted using phenyl magnesium bromide at –70 °C according to the procedure of Smith *et al.*[144] After stirring for 30 minutes at –70 °C, sulfuryl chloride was added and the reaction was allowed to warm to rt. However, analysis of the reaction by ^{19}F NMR spectroscopy and EI GCMS showed a complex mixture of products. There was no peak in the GCMS corresponding to sulfonyl chloride **303** (m/z = 318 : 320) and furthermore, the absence of a CF_2SO_2Cl signal at -104 ppm in the ^{19}F NMR spectrum indicated that the reaction was not successful.



Scheme 2.40

At this stage, an alternative route towards a perfluorosulfonyl linker unit using a bis-sulfonyl chloride was showing more promise and this work is described in Chapter 3 of this thesis. Therefore, fluorinated organometallic derivatives were abandoned at this stage.

2.4 Conclusions

- The reactions of allylbenzene and eugenol with 1-iodononafluorobutane and 1,4-diiodooctafluorobutane were scaled up to give significant quantities of alkene bound perfluoroalkyl iodides.

- Allylbenzene perfluoroalkyl iodide 304 was converted into the corresponding sulfonic acid 305 and sulfonyl chloride 310. However, the eugenol derivative required protection of the free phenol prior to oxidation.

- Eugenol perfluoroalkyl iodide 306 was loaded onto Wang resin 319 using a Mitsunobu reaction, but sulfonation and oxidation to the sulfonic acid or sulfonyl chloride was incompatible with solid phase chemistry.

- Attempts to solve problems with stability by reducing the secondary iodide were problematic and unsuccessful using zinc, radical methods or DBU.

- Perfluoroalkyl thioethers were generated from the corresponding thiols but it was not possible to oxidise them to sulfonyl chlorides.

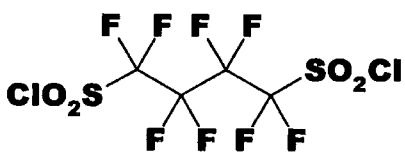
- Efforts to convert bromoalcohol 286 into the corresponding sulfonyl chloride was unsuccessful due to the poor reactivity of the bromo-difluoro-methyl group to sodium dithionite.

- (Fluorosulfonyl)difluoroacetic acid 356 was converted into the acid chloride 357 but attempts to react it with phenols and amines resulted in decomposition and complex mixtures.

- The generation of fluorinated Grignard reagents and subsequent reaction with sulfuryl chloride resulted in decomposition.

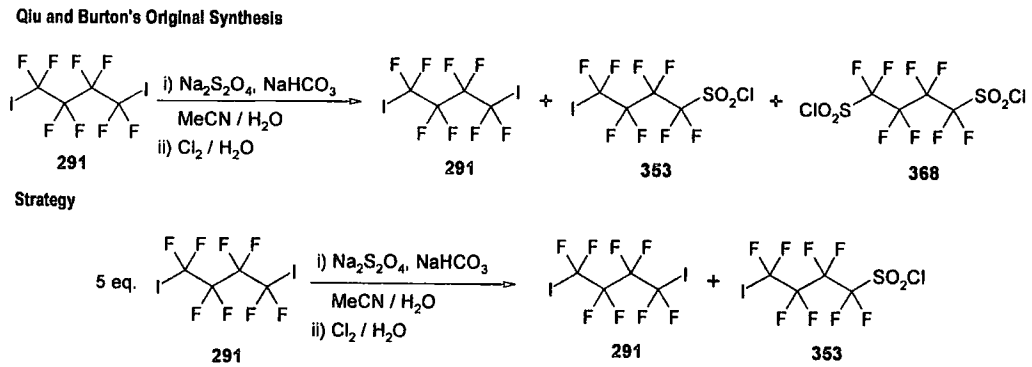
CHAPTER 3

BIS-SULFONYL CHLORIDE LINKER UNIT



3 General Introduction

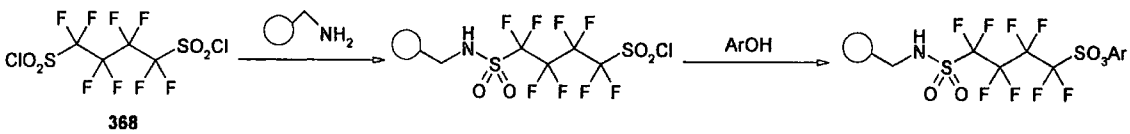
As attempts to generate bifunctional sulfonic acids and sulfonyl chlorides had proved unsuccessful, a different approach to a perfluoroalkanesulfonyl linker unit was sought. It was apparent that the original synthesis of perfluoroalkanesulfonyl chlorides reported by Qiu and Burton was simple and reliable but that attempts to couple diiodoperfluoroalkanes to alkenes prior to oxidation seemed to complicate the chemistry.[119] In the original sulfonation and chlorination of 1,4-diiodooctafluorobutane, Qiu and Burton obtained a statistical mixture of starting material, iodo-sulfonyl chloride **353** and bis-sulfonyl chloride **368** in the ratio 1 : 25 : 5 respectively, Scheme 3.1. It was decided to investigate the use of excess 1,4-diiodooctafluorobutane in order to obtain a mixture of iodo-sulfonyl chloride **353** and starting material which could easily be removed by distillation. It should then be simple to attach this iodosulfonyl chloride directly to a resin, or *via* radical addition to an alkene first, to give a perfluoroalkanesulfonyl linker unit.



Scheme 3.1

However, surprisingly and in contrast to the findings of Qiu and Burton, reaction of 5 equivalents of 1,4-diiodooctafluorobutane with 1 equivalent of sodium dithionite and subsequent chlorination gave exclusively bis-sulfonyl chloride **368** and unreacted starting material but none of the desired iodo-sulfonyl chloride **353**. Bis-sulfonyl chloride **368** was obtained in 10% yield based upon conversion of 1,4-diiodooctafluorobutane and this suggests that one molecule of sodium dithionite fragments to give one molecule of sulfur dioxide, one molecule of sodium iodide and one SO_2Na radical which undergoes reaction. The bis-

sulfonyl chloride was confirmed by 2 signals in the ^{19}F NMR spectrum at -119 ppm ($CF_2CF_2SO_2Cl$) and -104 ppm (CF_2SO_2Cl) and sulfonyl chloride stretches at 1220 and 1421 cm^{-1} in the IR spectrum, all of which agrees with the original data reported by Qiu and Burton.[114] There is no simple explanation for why these findings contradict the literature, but it does suggest that once a molecule of 1,4-diiodooctafluorobutane has undergone one sulfonation, it is highly activated to undergo a second. However, it was apparent that if it was possible to differentiate between the two sulfonyl chlorides then one could be used to attach the linker to a resin while keeping the other free for the loading of substrates, Scheme 3.2. Efforts were therefore turned to optimising the synthesis of bis-sulfonyl chloride 368 as it presented a simple and promising strategy to a perfluoroalkanesulfonyl linker unit.

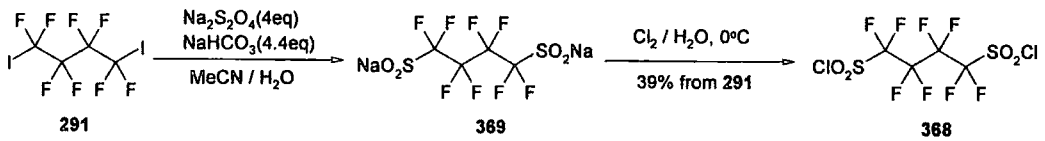


Scheme 3.2

3.1 Bis-sulfonyl Chlorides

The synthesis of bis-sulfonyl chloride 368 was re-attempted on a small scale using excess sodium dithionite to drive the initial sulfonation reaction to completion, Scheme 3.3. Monitoring the reaction by ^{19}F NMR spectroscopy showed that complete conversion of 1,4-diiodooctafluorobutane into bis-sodium sulfite 369 was achieved in 4 h. This was confirmed by the disappearance of the CF_2-I signal at -59 ppm and the CF_2CF_2-I peak at -112 ppm in the ^{19}F NMR spectrum of the reaction and the appearance of CF_2SO_2Na and $CF_2CF_2SO_2Na$ peaks at -127 ppm and -114 ppm respectively. Inorganic materials were removed by filtration and the solvent evaporated to give the crude material. This was dissolved in water and chlorine was bubbled through the solution at 0 °C. Initially the solution turned from clear to red and finally to green resulting in the precipitation of a white solid. Although it is not clear what these colour changes represent, the red colour is suggestive of the oxidation of sodium iodide, a by-product of the radical reaction with sodium dithionite, to iodine. Further oxidation

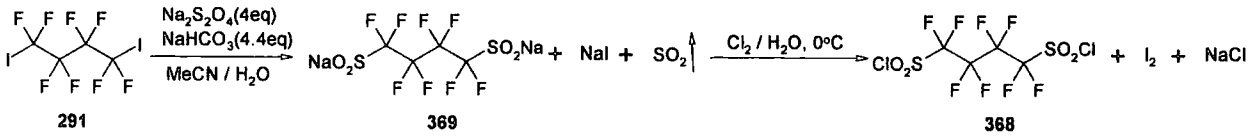
of iodine would account for the subsequent disappearance of the red colour. ^{19}F NMR spectroscopy indicated that the reaction was complete after 20 min, showing the previously described sulfonyl chloride signals at -104 and -119 ppm. Extraction with DCM gave bis-sulfonyl chloride in a reasonable 39% yield following re-crystallisation from petroleum ether. Analysis of this bis-sulfonyl chloride by mass spectrometry proved problematic and it was not possible to detect the molecular ion. However, a peak corresponding to M-Cl was observed by ES HRMS at m/z = 362.8794 and this agreed with the calculated mass of 362.8793 for $C_4F_8S_2O_4{}^{35}Cl$. Further confirmation of bis-sulfonyl chloride 368 was sought using elemental analysis. Experimental values of %C = 12.06% and %Cl = 17.85% agreed with the calculated values of 12.03% and 17.79% respectively. However, the experimental fluorine content of 38.10% was slightly out from the calculated value of 36.59% and this was because of the large percentage fluorine in the molecule complicating the analysis. Despite these minor anomalies, all data agreed with that published by Qiu and Burton[119] and so there was no doubt that the material was bis-sulfonyl chloride 368.



Scheme 3.3

With this chemistry established, it was necessary to scale up the reaction to produce significant quantities of bis-sulfonyl chloride 368 suitable for model solution phase studies and analogous solid phase chemistry. The sulfonation proceeded as above on a 20 mmol scale and complete conversion into bis-sodium sulfite 369 was seen in 4 h. The chlorination was again complete within 20 min but extracting into DCM, drying ($MgSO_4$) and evaporation gave bis-sulfonyl 368 chloride inseparable from large quantities of iodine. As sodium sulfite 369 was not purified following the initial sulfonation reaction, this iodine was thought to be the result of the oxidation of sodium iodide under chlorination

conditions. The purification of the bis-sulfonyl chloride from 20 mmol iodine represented a significant synthetic challenge.



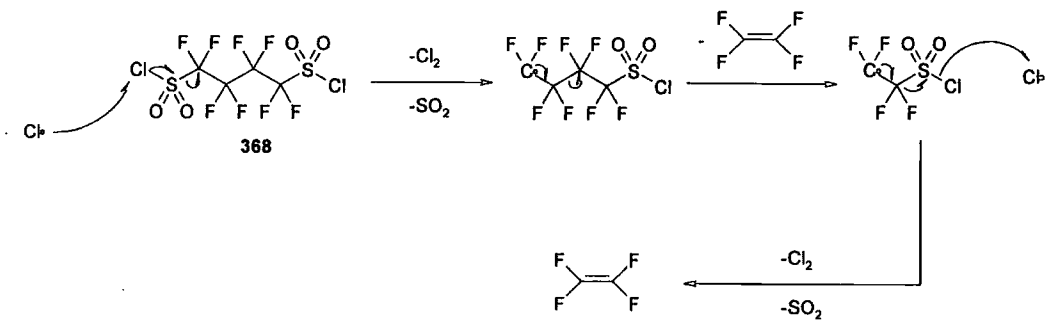
291 369 368

Scheme 3.4

The first attempt to solve the problem was a simple work-up with sodium thiosulfate following extraction of the bis-sulfonyl chloride into DCM. This proved efficient at removing most of the iodine, seen by the loss of the purple colour. However, several washings were required and this resulted in an unacceptably low 19% yield of bis-sulfonyl chloride. The poor yield was the result of decomposition caused by sodium thiosulfate and many peaks were seen in the ^{19}F NMR spectrum of the sodium thiosulfate solution following workup. Therefore, a sodium thiosulfate workup was not ideal and so purification of the bis-sodium sulfite 369 intermediate prior to chlorination was attempted. Simple solubility studies showed that while sodium iodide was soluble in acetonitrile the crude material was only very sparingly soluble. Washing with acetonitrile removed most of the sodium iodide, confirmed by elemental analysis. Elemental analysis of the crude material confirmed that the iodine content was 19% before washing with acetonitrile but this was reduced to 2% after washing. However, the mass balance was still greater than that corresponding to pure sodium sulfite and so continuous extraction with methanol was found to efficiently separate it from other unwanted inorganic materials. Chlorination of the purified bis-sodium sulfite resulted in a much cleaner reaction and recrystallisation of the crude material from petroleum ether gave bis-sulfonyl chloride 368 in a more acceptable 53% yield as a stable white solid.

At this stage an efficient method for the production of significant quantities of bis-sulfonyl chloride 368 in high purity had been developed. However, the reasonably high cost of 1,4-diiodooctafluorobutane meant that while the yield had been increased to 53%, it was still an uneconomical process with room for

improvement. It is not clear where material was being lost as ^{19}F NMR spectroscopy of both the sulfonation and chlorination steps showed 100% conversion with no decomposition. However, the initial sulfonation was regarded as quantitative as 100% of the mass balance was recovered and therefore decomposition was occurring during the chlorination step. In the presence of excess chlorine, bis-sulfonyl chloride 368 is ideally set-up to fragment into chlorine, sulfur dioxide and tetrafluoroethene, Scheme 3.5. This would account for the loss of material and as tetrafluoroethene is volatile it also explains why no decomposition was observed in the ^{19}F NMR spectra. In order to reduce decomposition and the loss of material, it was decided to optimise the chlorination step.

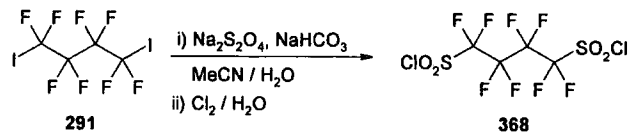


Scheme 3.5

In their original work Qiu and Burton bubbled chlorine through aqueous solutions of sodium sulfite salts until the red colour had disappeared but never quantified the experimental process any further.[119] Therefore, in order to optimise experiments, a number of variables were explored using the Design Expert 6® software.* Employing a 2 level factorial design the effects of reaction time, temperature, concentration and the rate of chlorine addition upon yield of bis-sulfonyl chloride were investigated. Qiu and Burton's original conditions were taken as the control, carrying out the reaction in 6 ml water at 0 °C and a concentration of 0.44 mol dm^{-3} for 20 min. The reaction temperature was varied between 10 °C and –10 °C as it was thought that decomposition of the bis-

* Stat-Ease Inc., 2021 East Hennepin Avenue, Suite 480, Minneapolis, MN55413, USA. www.statease.com

sulfonyl chloride would be quite significant at temperatures greater than 10 °C. – 10 °C was the lowest reaction temperature possible before the aqueous media froze preventing reaction. No literature information on the rate of chlorine addition was available and so it was chosen to control this *via* a flow meter allowing for addition from 1 – 10 ml/min. The central rate of addition of 5.5 ml/min was set as the control. Scheme 3.6 shows the array of chlorination experiments carried out and the yield of bis-sulfonyl chloride obtained in each case.



291 **368**

Experiment Number	Concentration M	Temperature °C	Reaction Time min	Rate of Cl_2 Addition ml/min	Yield %
1	0.22	10	10	10	58
2	0.66	10	10	1	36
3	0.66	10	30	10	59
4	0.22	-10	10	1	35
5	**0.66**	**-10**	**30**	**1**	**62**
6	0.44	0	20	5.5	58
7	0.66	-10	10	10	53
8	0.22	10	30	1	25
9	**0.22**	**-10**	**30**	**10**	**63**

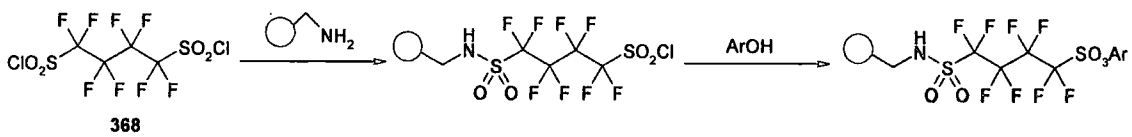
Scheme 3.6

Analysis of this data using the Design-Expert software® indicated that none of the reaction conditions varied had a statistically significant effect on the yield of bis-sulfonyl chloride. However, the optimum conditions were seen in experiments 5 and 9, giving bis-sulfonyl chloride **368** in 62% and 63% yield respectively. The high reaction concentration and low rate of chlorine addition seen in experiment 5

was the most promising, allowing for the chlorination of larger quantities of material and so these conditions were adopted for all future syntheses of the bis-sulfonyl chloride.

3.2 Model Solution Phase Studies

With the bis-sulfonyl chloride linker unit in hand, model solution phase studies of desired solid phase organic syntheses were explored. The two priorities were to obtain a method of attaching the linker unit to a solid support and develop a procedure for the loading of phenols. The strategy was to attach the bis-sulfonyl chloride linker unit to amino-functionalised resins through the formation of a sulfonamide bond. The use of excess bis-sulfonyl chloride should attach the linker to the resin through one sulfonyl chloride and minimise cross-linking, leaving the other sulfonyl chloride free for the loading of phenols, Scheme 3.7. To this end, reactions of bis-sulfonyl chloride 368 with amines and phenols were investigated. It was decided at this stage to use 2 equivalents of base or phenol and generate bis-sulfonamides and bis-sulfonate esters respectively. This was done in order to demonstrate that the chemistry worked without generating complex mixtures of mono- and bis-substituted compounds which were expected if 1 equivalent was used. These would be difficult and time consuming to purify



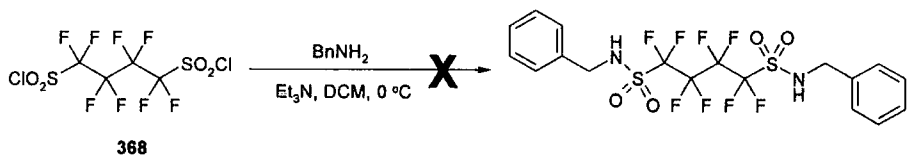
368

Scheme 3.7

3.2.1 Bis-perfluoroalkanesulfonamides

To explore the possibility of attaching the linker unit to amino resins, the generation of bis-perfluoroalkanesulfonamides was investigated using isopropylamine and benzylamine. Isopropylamine was chosen as a simple amine with a characteristic NMR signal and benzylamine was chosen as a solution phase mimic of a polystyrene based resin. Initially reactions with both amines were carried out at room temperature using triethylamine or pyridine as

the base. These conditions were chosen as they are simple and easily applicable to solid phase synthesis. Unfortunately, rapid decomposition of bis-sulfonyl chloride **368** was apparent as many peaks were observed in the ^{19}F NMR spectrum and no bis-sulfonan ' 'es were generated. Therefore the reaction temperature was reduced to 0 °C. In the case of benzylamine, carrying the reactions out at 0 °C with triethylamine or pyridine was no more promising and many peaks in the ^{19}F NMR spectrum indicated further decomposition in both cases, Scheme 3.8.

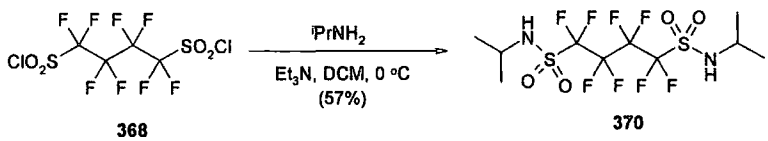


368

Scheme 3.8

The analogous reaction at 0 °C using isopropylamine with pyridine also resulted in decomposition but use of triethylamine proved more encouraging. Bis-sulfonyl chloride **368** was added to a stirred solution of isopropylamine and triethylamine at 0 °C. After 4 h bis-sulfonyl chloride **368** had been completely consumed by ^{19}F NMR spectroscopy and two new peaks had appeared at –124 and –132 ppm. Furthermore, a white solid had precipitated and recrystallisation from chloroform gave bis-perfluoroalkanesulfonamide **370** in 57% yield, Scheme 3.9. This was confirmed by an N-H stretch at 2966 cm^{-1} and an N-H bend at 1644 cm^{-1} in the IR spectrum as well as sulfonamide absorptions at 1150 and 1384 cm^{-1}. However, analysis by ES mass spectrometry was problematic and only an ion at m/z = 329 (SO_2-C_4F_8-SO_2+H^+) was detected. Further confirmation of bis-sulfonamide **370** was sought by elemental analysis but experimental values of %C = 25.56%, %H = 4.50%, %N = 5.85% and %F = 32.26% were slightly out from the calculated values of %C = 26.97%, %H = 3.60%, %N = 6.29% and %F = 34.16% for **370**. This was attributed to either the high fluorine content of the molecule or the possibility of forming the mono-hydrochloride salt which has calculated values of %C = 24.97%, %H = 3.50%, %N = 5.8% and %F = 31.63% . However, evidence suggested that bis-sulfonamide **370** had been generated and so it seemed

plausible that the linker unit could be attached to amino resins. Therefore, work turned to focus on a method for the loading of phenols.



368 370

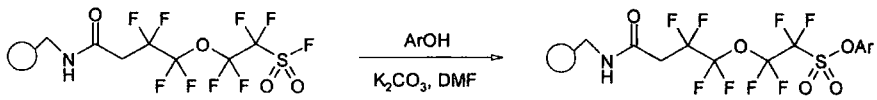
Scheme 3.9

3.2.2 Bis-perfluoroalkanesulfonate Esters

In order to identify suitable conditions for the loading of phenols on to the resin-bound linker unit, coupling reactions of bis-sulfonyl chloride 368 were investigated with *p*-cresol as it has a characteristic methyl group which can easily be tracked by ^{1}H NMR spectroscopy. Following the precedent for the formation of aryl perfluoroalkanesulfonate esters reported in Section 1.2.2.1,[82,83] triethylamine was used as the base in the reaction. However, triethylamine resulted in decomposition of bis-sulfonyl chloride 368 at room temperature and 0 °C observed as many peaks in the ^{19}F NMR spectrum. This was interesting as it had proved an effective base in the reaction with isopropylamine previously described. Therefore, reactions using potassium carbonate were investigated instead.

In the approach reported by Holmes, potassium carbonate was employed to load phenols onto the solid-supported sulfonyl fluoride linker.[68, 69] The analogous reaction was attempted using bis-sulfonyl chloride in DCM, THF or DMF but in each case no reaction was seen after 72 h at 0 °C. Allowing the reactions to warm up to room temperature resulted in decomposition of bis-sulfonyl chloride 368, observed as many signals in the ^{19}F NMR spectrum. It is not understood why reactions using triethylamine and potassium carbonate should have resulted in decomposition of bis-sulfonyl chloride 368 but there were obviously unwanted side-reactions taking place. Interestingly, Holmes did not report any decomposition using potassium carbonate and it is believed that the central

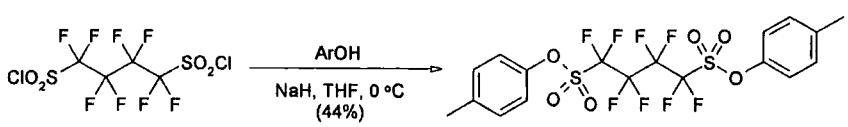
oxygen linkage in resin-bound sulfonyl fluoride 163 provided enhanced stability, preventing simple fragmentation to tetrafluoroethene, Scheme 3.10.[68, 69]



163 164

Scheme 3. 10

As the loading of phenols onto the bis-sulfonyl chloride linker unit using milder bases had been unsuccessful, it was decided to improve the nucleophilicity of the phenol by pre-forming the sodium phenoxide (NaOAr), Scheme 3.11. This was done by treating *p*-cresol with sodium hydride in THF at 0 °C, followed by addition of a solution of the bis-sulfonyl chloride. After 4 h, sulfonyl chloride peaks at –104 and –119 ppm were replaced by two new peaks at –109 and –120 ppm in the ^{19}F NMR spectrum corresponding to bis-perfluoroalkanesulfonate ester 371. Purification by flash chromatography afforded the product in a moderate 44% yield, confirmed by a molecular ion at m/z = 560.0441 in ES HRMS which agreed with the calculated mass of 560.0442 for $C_{18}H_{18}O_6NF_8S_2$ ($M+NH_4$). Once more ^{19}F NMR spectroscopy showed 100% conversion of bis-sulfonyl chloride 368 into bis-sulfonate ester 371. Therefore the relatively low yield is suggestive of base-mediated decomposition of bis-sulfonyl chloride 368 to tetrafluoroethene and sulfur dioxide as previously described. Decomposition appears to be an unavoidable drawback of chemistry using a perfluorobutyl unit. One solution may lie in the use of perfluoropropyl or perfluoropentyl analogues as the odd number of CF_2 groups will prevent fragmentation to tetrafluoroethene. Unfortunately the propyl and pentyl diiodoperfluroroalkanes are not commercially available and their synthesis is not trivial.



368 371

Scheme 3.11

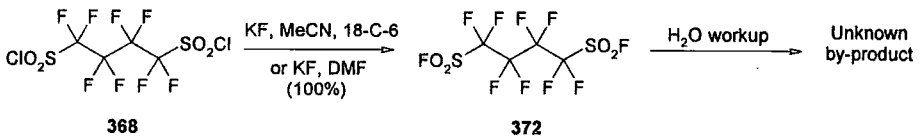
While the use of sodium hydride confirmed the possibility of loading phenols onto the bis-sulfonyl chloride linker unit, there still remained a need for milder conditions as sodium hydride is not an ideal base for solid phase organic synthesis. Pre-forming a solution of sodium phenoxide and transferring it *via* cannula to a suspension of resin-bound sulfonyl chloride was possible but much less appealing than shaking a suspension of resin, phenol and base directly. Therefore the use of other milder bases was further investigated and to this end reactions were attempted with pyridine and DBU. As in the case of triethylamine, pyridine resulted in decomposition of the bis-sulfonyl chloride confirming its intolerance to amine bases in the presence of weak nucleophiles. DBU gave the desired bis-sulfonate ester 371 in a poor 6% yield following flash chromatography but again mostly decomposition was observed. At this stage the bis-sulfonyl chloride offered a highly stable, easy to handle linker unit, but it was not electrophilic enough to allow loading of phenols under mild conditions. Therefore it was decided to convert it into a more reactive functional group. Sulfonyl fluorides are more reactive than sulfonyl chlorides due to the electron withdrawing influence of the fluorine and so the generation of a bis-sulfonyl fluoride linker unit was investigated.

3.3 Alternatives to the Bis-sulfonyl Chloride Linker Unit

3.3.1 Bis-sulfonyl Fluorides

Qiu and Burton showed that treatment of bis-sulfonyl chloride 368 with potassium fluoride in acetonitrile at room temperature gave quantitative conversion into the corresponding bis-sulfonyl fluoride 372. This reaction was repeated and ^{19}F NMR spectroscopy showed 75% conversion into bis-sulfonyl fluoride 372 in 24 h. This was observed by the shift of sulfonyl chloride signals at –104 (CF_2SO_2Cl) and –119 ppm ($CF_2CF_2SO_2Cl$) to sulfonyl fluoride signals at –108 (CF_2SO_2F) and –120 ppm ($CF_2CF_2SO_2F$) and the appearance of an SO_2F signal at +46 ppm, all of which agreed with published data.[119] Modification of reaction conditions improved the conversion into bis-sulfonyl fluoride 372. It was found that simple addition of 18-crown-6 to the reaction or heating to reflux gave complete conversion in 6 h. Alternatively, use of DMF as the solvent gave rapid

conversion into the bis-sulfonyl fluoride 372 at room temperature, Scheme 3.12. However, repeating Qiu and Burton's aqueous work-up procedure to remove unreacted potassium fluoride resulted in hydrolysis of bis-sulfonyl fluoride 372 to an unknown by-product, observed by loss of the SO_2F signal in the ^{19}F NMR spectrum. While it was suspected that this by-product was the bis-sulfonic acid, or the potassium salt thereof, it was not possible to confirm this by EI or ES mass spectrometry. To overcome this problem, the bis-sulfonyl fluoride linker unit was generated *in situ.*

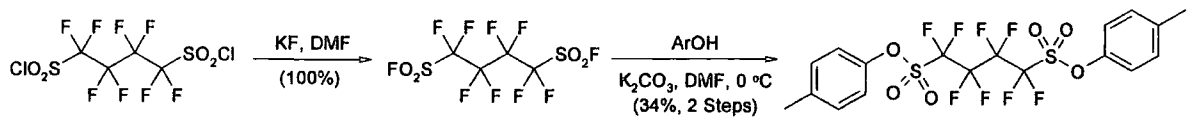


368 372

Scheme 3.12

To investigate the loading of phenols, the conversion of bis-sulfonyl chloride 368 into bis-sulfonyl fluoride 372 was monitored by ^{19}F NMR spectroscopy. Once complete, unreacted potassium fluoride was removed by filtration and the bis-sulfonyl fluoride was added directly to solutions of *p*-cresol and either triethylamine or potassium carbonate. Unfortunately, triethylamine again resulted in significant decomposition of material but did give some of the desired bis-perfluoroalkanesulfonate ester 371 in 8% yield. This is indicative of more rapid nucleophilic attack than at the sulfonyl chloride, but is still unacceptable for an effective linker unit. Potassium carbonate appeared more promising, yielding 34% following purification by flash chromatography, Scheme 3.13. The yield was lower than that obtained using sodium hydride and bis-sulfonyl chloride (44%), but the synthetic advantage was the possibility of loading phenols onto a sulfonyl fluoride based linker unit using milder conditions. This bis-sulfonyl fluoride showed promise as a possible linker unit, but did have some problems with stability. Therefore, it was speculated that the *p*-nitro phenol bis-sulfonate ester offered a more stable route to a perfluoroalkanesulfonyl linker unit. Bis-sulfonate esters appeared to be more stable than their bis-sulfonyl halide counterparts and

p-nitro phenoxide is a good leaving group due to resonance stabilisation by the nitro group. The next section reports research into this alternative linker unit.

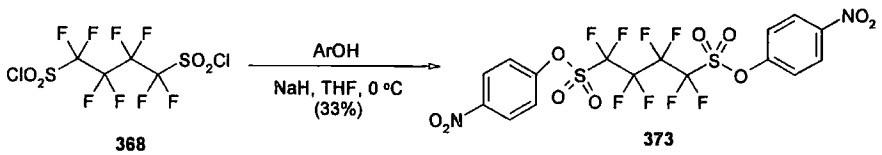


368 372 371

Scheme 3.13

3.3.2 Bis-*p*-nitro Phenol Perfluoroalkanesulfonate Ester

Whereas bis-sulfonyl chloride 368 was unreactive towards phenols unless the sodium phenoxide was preformed, in contrast bis-sulfonyl fluoride 372 was found to be too reactive to nucleophiles and prone to hydrolysis for use as a perfluoroalkanesulfonyl linker unit. Therefore, it was desirable to determine whether bis-*p*-nitro phenol perfluoroalkanesulfonate ester 373 offered a more stable perfluoroalkanesulfonyl linker unit where the nitro benzene group acts as a leaving group. It was synthesised from bis-sulfonyl chloride 368 and pre-formed sodium *p*-nitro phenoxide as previously described, Scheme 3.14. The replacement of sulfonyl chloride peaks at -104 and -119 ppm in the ^{19}F NMR spectrum with bis-sulfonate ester peaks at -108 and -120 ppm showed the reaction to be complete after 4 h at 0 °C. Recrystallisation from chloroform yielded 33% of bis-perfluoroalkanesulfonate ester 373 as a white solid. EI HRMS confirmed a molecular ion at 603.9492 consistent with the calculated mass of 603.9487 for $C_{16}H_8O_{10}N_2F_8S_2$ and characteristic NO_2 signals were observed at 1350 and 1537 cm^{-1} in the IR spectrum.

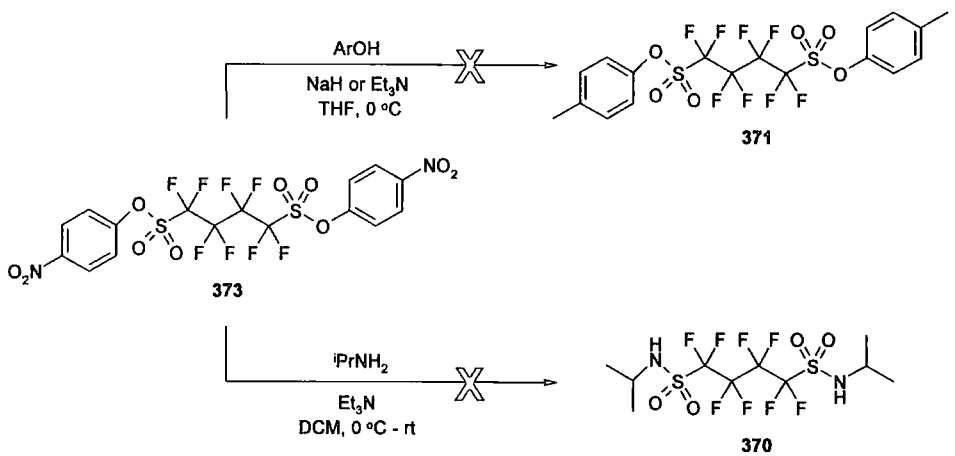


368 373

Scheme 3.14

With bis-*p*-nitro phenol perfluoroalkanesulfonate ester 373 in hand, analogous reactions with amines and phenols to those carried out using the bis-sulfonyl

halide substrates were attempted. Initially reaction with 2.4 eq of isopropylamine in the presence of triethylamine at 0 °C in DCM showed no reaction after 16 h and warming the reaction up to room temperature for a further 24 h still did not promote reaction, Scheme 3.15. Likewise, the replacement of the *p*-nitro phenol group with *p*-cresol employing either triethylamine in DCM or sodium hydride in THF resulted in no reaction. This is evidence that bis-*p*-nitro phenol perfluoroalkanesulfonate ester **373** is very stable and not prone to nucleophilic attack. Therefore, as this strategy demonstrated little promise as a linker unit it was not explored any further. It was decided to establish palladium-catalysed diversity cleavage conditions using the bis-sulfonate esters as a model system and then progress the bis-sulfonyl chloride and bis-sulfonyl fluoride linker units into solid phase trials.



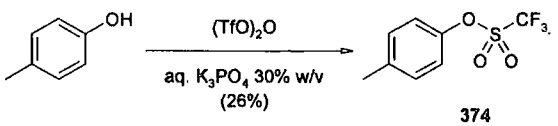
Scheme 3.15

3.4 Model Solution Phase Cleavage Studies

3.4.1 Suzuki Cross-coupling Reactions

With chemistry established for attaching the perfluoroalkanesulfonyl linker unit to a solid support and the subsequent loading of phenols, it was desirable to investigate model cleavage strategies. To this end, the Suzuki cross-coupling was chosen as a test reaction and in order to probe a wide range of possible cross-coupling conditions it was decided to screen parallel arrays of reaction conditions using a Radley Technologies Greenhouse Parallel Synthesiser®. The simple triflate of *p*-cresol was chosen as a model substrate and was prepared

according to a literature procedure using trifluoromethanesulfonic anhydride and aqueous tripotassium phosphate in toluene at 0 °C, Scheme 3.16.[145] Recrystallisation from chloroform yielded triflate 374 in moderate 26% yield.



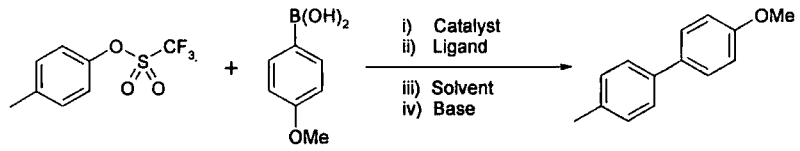
374

Scheme 3.16

An array of 24 Suzuki cross-coupling reactions were carried out using triflate 374 and 4-methoxyphenyl boronic acid 375 according to the protocol given in Appendix 1. Catalyst, ligand, base and solvent were varied to explore a wide range of possible reaction conditions and the results are shown in Scheme 3.17.

Highlights of the array were reactions 1 and 21 which indicated that the combination of caesium carbonate and DMF were promising cleavage conditions, giving yields of biphenyl from 40 – 50%. A reasonable 44% yield was also obtained employing tripotassium phosphate as the base in reaction 17. However, the most active Suzuki conditions were palladium acetate as the catalyst, DMF as solvent, triethylamine as the base and 1,4-bis(diphenylphosphino)butane (dppb) as the ligand (reaction 15). These conditions gave known biphenyl 376 in 79% yield following purification by flash chromatography and it was confirmed by a molecular ion at m/z = 198 in the EI mass spectrum. Furthermore all ^{1}H NMR and IR spectroscopic data agreed with that reported in the literature.[146]

Other interesting results from the array were that $Pd(PPh_3)_4$ seemed to be the most generally applicable catalyst, giving the desired biphenyl in fair yields (8 – 42%) using a variety of solvents and bases. Reactions 8 – 11 showed that the system was completely unresponsive to palladium acetate and tri-*o*-tolyl phosphine.



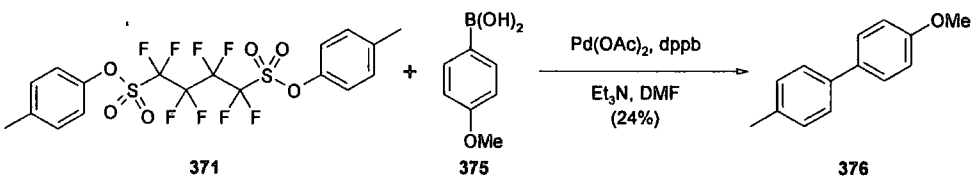
374 375 376

Experiment	Catalyst	Ligand	Base	Solvent	Yield *
1	**$Pd(PPh_3)_4$**		**Cs_2CO_3**	**DMF**	**42%**
2	$Pd(PPh_3)_4$		K_3PO_4	DMF	8%
3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O	25%
4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O	9%
5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O	No Reaction
6	$Pd(PPh_3)_4$		NaOH	DME / H_2O	21%
7	$Pd(OAc)_2$		K_2CO_3	DME / H_2O	12%
8	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Toluene	No Reaction
9	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	DMF	No Reaction
10	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	MeCN	No Reaction
11	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Dioxane / H_2O	No Reaction
12	$Pd(OAc)_2$	Dppm	Et_3N	DMF	7%
13	$Pd(OAc)_2$	(2-furan)$_3$P	Et_3N	DMF	No Reaction
14	$Pd(OAc)_2$	Dppe	Et_3N	DMF	No Reaction
15	**$Pd(OAc)_2$**	**Dppb**	**Et_3N**	**DMF**	**79% §**
16	$Pd(OAc)_2$	Dppf	Et_3N	DMF	20%
17	**$Pd(OAc)_2$**	^{t}Bu$_2$P(BiPh)	**K_3PO_4**	**EtOH / H_2O**	**44%**
18	$Pd(OAc)_2$	^{t}Bu$_2$P(BiPh)	K_3PO_4	Toluene	No Reaction
19	$Pd_2(dba)_3$		KOAc	Toluene/EtOH	No Reaction
20	$Pd_2(dba)_3$	Dppm	Cs_2CO_3	Dioxane	No Reaction
21	**$Pd_2(dba)_3$**	**Dppf**	**Cs_2CO_3**	**DMF**	**49%**
22	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O	No Reaction
23	$PdCl_2$(Binap)		K_3PO_4	DMF	7%
24	$PdCl_2$(Binap)		CsF	THF / H_2O	No Reaction

Reactions were carried out using triflate **374** (0.1 mmol), 4-methoxyphenyl boronic acid **375** (0.1 mmol), catalyst (0.003 mmol), ligand (0.006 mmol) and base (0.3 mmol) and heated at 80 °C for 16 h. * Yields reported are GC yields using diethylene glycol di-*t*-butoxy ether as the standard except § which is the isolated yield following flash chromatography.

Scheme 3.17

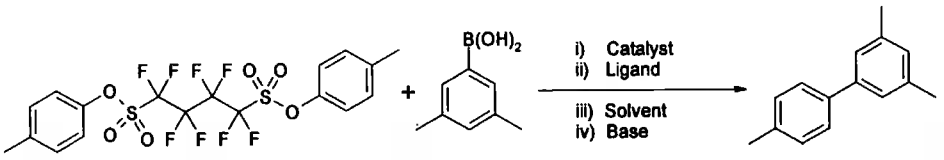
With acceptable conditions for Suzuki cleavage in hand for triflate 374, a model experiment was attempted using bis-sulfonate ester 371 to confirm that the conditions were equally applicable to a C_4F_8 nonaflate unit, Scheme 3.18. The reaction did proceed but disappointingly the good yield observed for the triflate was not reflected, and biphenyl 376 was only obtained in 24% yield based upon both perfluoroalkanesulfonate esters undergoing reaction. It was speculated that the low yield was the result of only one sulfonate ester undergoing a Suzuki cross-coupling reaction although it was not possible to confirm this by GCMS.



371 375 376

Scheme 3.18

Therefore it was decided to screen cross-coupling conditions using bis-sulfonate ester 371 with the aim of optimising cleavage conditions for the nonaflate system. An array of Suzuki reactions was carried out using bis-sulfonate ester 371 and the results are reported in Scheme 3.19.



371 377 378

Experiment	Catalyst	Ligand	Base	Solvent	Yield *
1	$Pd(PPh_3)_4$		Cs_2CO_3	DMF	33%
2	$Pd(PPh_3)_4$		K_3PO_4	DMF	20%
3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O	No Reaction
4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O	No Reaction
5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O	No Reaction
6	$Pd(PPh_3)_4$		NaOH	DME / H_2O	No Reaction
7	$Pd(OAc)_2$		K_2CO_3	DME / H_2O	No Reaction
8	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Toluene	No Reaction
9	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	DMF	No Reaction
10	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	MeCN	No Reaction
11	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Dioxane / H_2O	No Reaction
12	$Pd(OAc)_2$	Dppm	Et_3N	DMF	No Reaction
13	$Pd(OAc)_2$	(2-furan)$_3$P	Et_3N	DMF	No Reaction
14	$Pd(OAc)_2$	Dppe	Et_3N	DMF	No Reaction
15	$Pd(OAc)_2$	Dppb	Et_3N	DMF	24%
16	$Pd(OAc)_2$	Dppf	Et_3N	DMF	No Reaction
17	$Pd(OAc)_2$	(BiPh)P^{t}Bu$_2$	K_3PO_4	EtOH / H_2O	No Reaction
18	$Pd(OAc)_2$	(BiPh)P^{t}Bu$_2$	K_3PO_4	Toluene	No Reaction
19	$Pd_2(dba)_3$		KOAc	Toluene/EtOH	No Reaction
20	$Pd_2(dba)_3$	Dppm	Cs_2CO_3	Dioxane	No Reaction
21	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	DMF	No Reaction
22	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O	No Reaction
23	$PdCl_2$(Binap)		K_3PO_4	DMF	15%
24	$PdCl_2$(Binap)		CsF	THF / H_2O	No Reaction

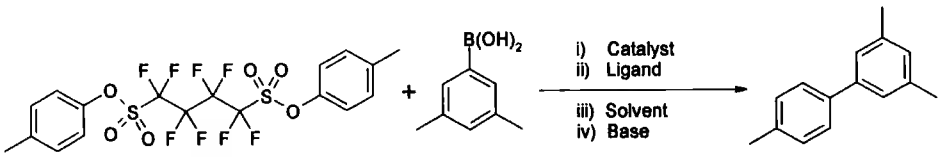
Reactions were carried out using bis-sulfonate ester **371** (0.025 mmol), 4-methoxyphenyl boronic acid **377** (0.05 mmol), catalyst (0.002 mmol), ligand (0.003 mmol) and base (0.15 mmol) and heated at 80 °C for 16 h.

*GC yields reported using diethylene glycol di-*t*-butoxy ether as the standard.

Scheme 3.19

While half of the Suzuki reactions screened for using aryl triflate 374 yielded the desired biphenyl, albeit in only moderate yields, disappointingly these results were not duplicated for bis-sulfonate ester 371, Scheme 3.19. Only reactions 1, 2, 15 and 23 resulted in known biphenyl 378, confirmed by a molecular ion at m/z = 196 in the EI GCMS, while all others gave homo-coupled boronic acid as the major product. Interestingly, the most active cross-coupling conditions seen for triflate 374, using palladium acetate, triethylamine and dppb in DMF, were active for bis-sulfonate ester 371 giving biphenyl 378 in 24% yield. However, the best conditions were found to be $Pd(PPh_3)_4$ and caesium carbonate in DMF, giving biphenyl 378 in 33% yield. Employing tripotassium phosphate as a base in DMF with either $Pd(PPh_3)_4$ or $PdCl_2$(Binap) as catalysts yielded the biphenyl in 20 and 15% yield respectively.

Therefore, as DMF was the solvent of choice and K_3PO_4 or Cs_2CO_3 were the most active bases for Suzuki reactions using bis-sulfonate ester 371, it seemed advantageous to screen an array around these conditions with the aim of further reaction optimisation. DME was chosen as an alternative solvent so that results could be compared to the control using DMF and the results are summarised in Scheme 3.20.



371 377 378

Experiment	Catalyst	Ligand	Base	Solvent	Yield *
1	$Pd(PPh_3)_4$		K_3PO_4	DMF	28%
2	$Pd(OAc)_2$		K_3PO_4	DMF	12%
3	$Pd_2(dba)_3$		K_3PO_4	DMF	No Reaction
4	$PdCl_2$(Binap)		K_3PO_4	DMF	27%
5	$Pd(PPh_3)_4$		K_3PO_4	DME	No Reaction
6	$Pd(OAc)_2$		K_3PO_4	DME	No Reaction
7	$Pd_2(dba)_3$		K_3PO_4	DME	No Reaction
8	$PdCl_2$(Binap)		K_3PO_4	DME	No Reaction
9	$Pd(PPh_3)_4$		Cs_2CO_3	DMF	30%
10	$Pd(OAc)_2$		Cs_2CO_3	DMF	8%
11	$Pd_2(dba)_3$		Cs_2CO_3	DMF	No Reaction
12	$PdCl_2$(Binap)		Cs_2CO_3	DMF	13%
13	$Pd(PPh_3)_4$		Cs_2CO_3	DME	No Reaction
14	$Pd(OAc)_2$		Cs_2CO_3	DME	No Reaction
15	$Pd_2(dba)_3$		Cs_2CO_3	DME	No Reaction
16	$PdCl_2$(Binap)		Cs_2CO_3	DME	No Reaction
17	$Pd(PPh_3)_4$	IMES	K_3PO_4	DMF	6%
18	$Pd(PPh_3)_4$	$(2\text{-furan})_3P$	K_3PO_4	DMF	No Reaction
19	$Pd(PPh_3)_4$	Dppf	K_3PO_4	DMF	19%
20	$Pd(PPh_3)_4$	Dppb	K_3PO_4	DMF	No Reaction
21	$Pd(PPh_3)_4$	Buchwald	K_3PO_4	DMF	7%
22	$Pd(OAc)_2$	IMES	Cs_2CO_3	DMF	No Reaction
23	$Pd_2(dba)_3$	IMES	Cs_2CO_3	DMF	No Reaction

Reactions were carried out using bis-sulfonate ester **371** (0.025 mmol), 4-methoxyphenyl boronic acid **377** (0.05 mmol), catalyst (0.002 mmol), ligand (0.003 mmol) and base (0.15 mmol) and heated at 80 °C for 16 h.

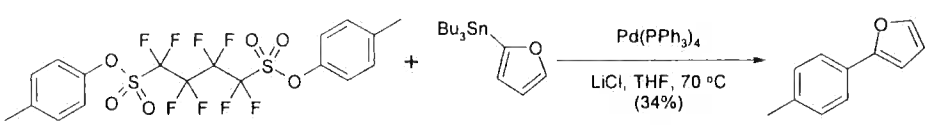
*GC yields reported using diethylene glycol di-*t*-butoxy ether as the standard.

Scheme 3.20

Screening this second array of Suzuki cross-coupling reactions for bis-sulfonate ester **371** did not improve yields of biphenyl **378**. The best conditions were identified from the first array as $Pd(PPh_3)_4$ and K_3PO_4 or Cs_2CO_3 in DMF and no further improvements were to be made by changing the catalyst or using additional ligands. Concurrent with investigations into Suzuki reactions, bis-sulfonate ester **371** was also explored as a substrate in a Stille cross-coupling reaction to provide an alternative strategy for diversity cleavage.

3.4.2 Stille Cross-coupling Reactions

To further investigate possible diversity cleavage strategies for the bis-sulfonyl chloride linker unit, bis-sulfonate ester **371** was employed in a simple Stille reaction, Scheme 3.21. Reaction with 2-(tributylstannyl)furan **379** employing $Pd(PPh_3)_4$ and lithium chloride yielded known 2-tolyl furan **380** in 34% yield, confirmed by a molecular ion at m/z = 158 in the EI mass spectrum. Furthermore, ^1H NMR and IR spectroscopic data agreed with that reported by Narasaka *et al.*[147] Homo-coupled furan was also observed as a significant by-product in the reaction and accounted for the poor yield.



371 379 380

Scheme 3.21

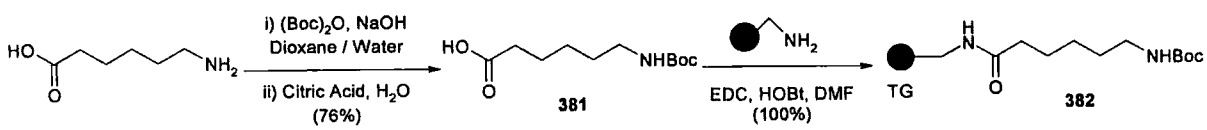
At this stage, model solution phase chemistry was in place for attaching the bis-sulfonyl chloride linker onto amino resins and subsequent loading of phenols to generate solid-supported aryl triflates. Furthermore, it had been demonstrated that bis-sulfonate ester **371** could be used as a component in cross-coupling reactions. However, considerable optimisation and generalisation of the procedure is still required in future work but at this stage, it was decided to investigate the possibility of transferring the chemistry onto a solid support.

3.5 Perfluoroalkanesulfonyl Diversity Linker Unit

3.5.1 Bis-sulfonyl Chloride Linker Unit

The strategy was to attach the bis-sulfonyl chloride and fluoride linker units to an amino resin through the formation of a sulfonamide bond. The solid support chosen was amino TentaGel® as it offered the possibility of magic angle ^{1}H NMR spectroscopy of resin-bound substituents as described in Section 1.1.3.3. Furthermore, ^{19}F spectroscopy does not require locking the signal to a deuterated solvent and therefore it was possible to obtain gel-phase ^{19}F NMR spectra of resin-bound material by swelling some resin in DCM in an NMR tube.

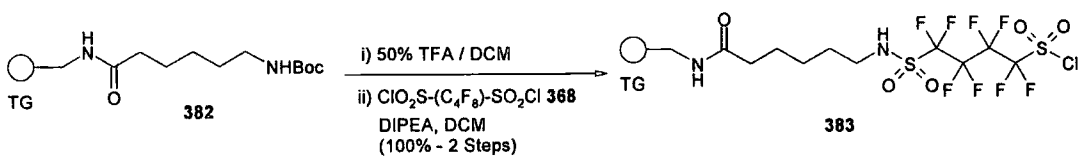
It was decided to add a spacer unit to the amino resin which contained protons which would provide characteristic ^{1}H NMR spectra. To this end, 6-aminohexanoic acid was chosen for its long alkyl chain and the ease of attaching it to amino TentaGel® *via* a peptide bond. Initially 6-aminohexanoic acid was Boc protected **381** in 76% yield using Boc anhydride according to a literature procedure, Scheme 3.22.[148] Boc protection was confirmed by the presence of a *tert*-butyl signal at 1.43 ppm in the ^{1}H NMR spectrum and the presence of acid (1715 and 3367 cm^{-1}) and carbamate (1683 cm^{-1}) absorptions in the IR spectrum. Boc protected 6-aminohexanoic acid was loaded onto amino TentaGel® **382** using EDC and HOBt in DMF. The reaction was monitored by bromophenol blue indicator and after 16 h at room temperature a green colour indicated no more primary amine confirming quantitative loading. Furthermore, analysis of a small portion of resin by IR spectroscopy confirmed loading was successful as amide carbonyl (1648 cm^{-1}) and carbamate (1683 cm^{-1}) absorptions were present in the IR spectrum.



Scheme 3.22

With resin-bound 6-aminohexanoic acid in hand, the Boc protecting group was removed by treatment with 50% TFA in DCM for 4 h. After this time, a small portion of resin was tested with bromophenol blue and a blue colour confirmed deprotection had occurred. In addition, the carbamate absorption (1683 cm^{-1}) was no longer present in the IR spectrum.

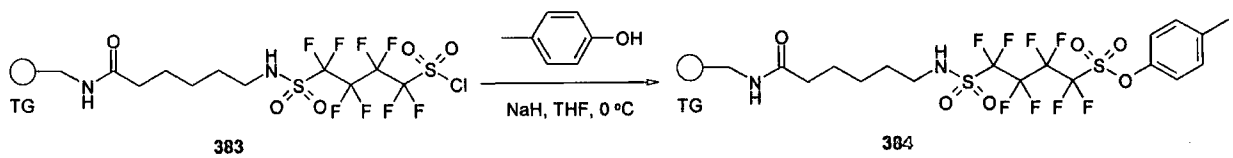
Bis-sulfonyl chloride 368 was loaded onto the resin using DIPEA in DCM, Scheme 3.23, and after 16 h all amines had reacted (green colour by bromophenol blue indicator). This was confirmed by signals at -104 and -119 ppm in the ^{19}F NMR spectrum which indicated a resin-bound sulfonyl chloride. Furthermore, sulfonamide absorptions at 1152 and 1354 cm^{-1} and sulfonyl chloride absorptions at 1174 and 1368 cm^{-1} in the IR spectrum indicated resin-bound sulfonyl chloride . With a novel perfluoroalkanesulfonyl linker unit 383 in hand, all that remained was to develop a protocol for the loading of phenols.



Scheme 3.23

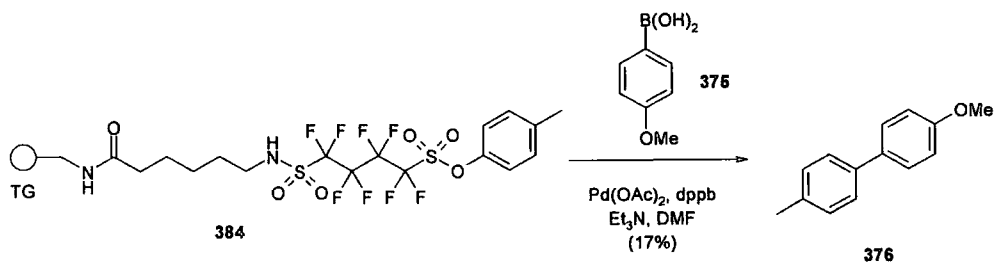
3.5.2 Resin-bound Perfluoroalkanesulfonate Esters

Treatment of resin-bound sulfonyl chloride 383 with 10 equivalents of sodium *p*-methyl-phenoxide yielded resin-bound perfluoroalkanesulfonate ester 384, Scheme 3.24. Analysis of a small portion of resin by ^{19}F NMR spectroscopy indicated a resin-bound perfluoroalkanesulfonate ester, confirmed by signals at -108 and -120 ppm in the ^{19}F NMR spectrum.



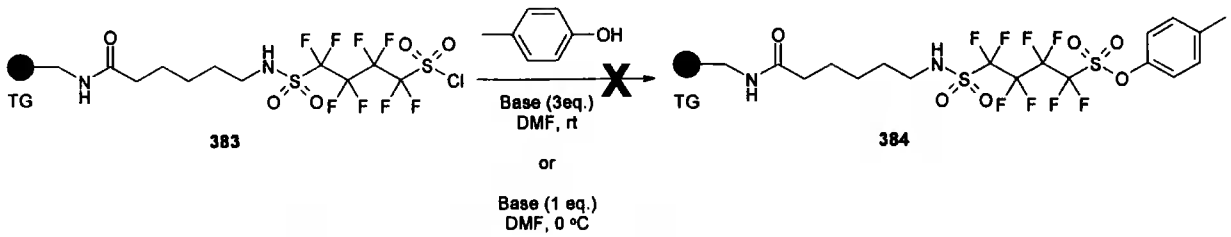
Scheme 3.24

At this stage it was desirable to investigate whether solid-supported perfluoroalkanesulfonate ester 384 could undergo diversity cleavage. To this end, a Suzuki reaction was attempted using palladium acetate, triethylamine and dppb in DMF, Scheme 3.25. Biphenyl 376 was formed in 17% GC yield based upon the original loading of bis-sulfonyl chloride and confirmed by a molecular ion at m/z = 198 in the EI GCMS but was inseparable from large amounts of homo-coupled boronic acid. This showed proof of concept of diversity cleavage, but the poor yield suggested problems with the generation of solid-supported perfluoroalkanesulfonate esters. This step required major improvement and therefore it was decided to investigate it further.



Scheme 3.25

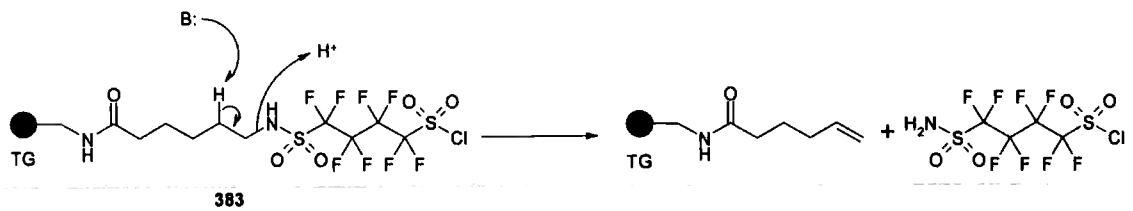
Attempts to repeat the loading of phenols using sodium hydride showed no resin-bound perfluoroalkanesulfonate esters. Analysis of the resin and filtrate following the solid phase reaction by ^{19}F NMR spectroscopy indicated that treatment with sodium phenoxide had completely cleaved the linker unit from the resin. The mechanism of cleavage is not presently understood but this does account for the low yields obtained above. Therefore, it was decided to screen an array of milder bases in order to investigate alternative conditions for the loading of phenols onto resin-bound sulfonyl chloride 383. Initially reactions were shaken for 24 h at rt using 3 equivalents of base and 1.5 equivalents of *p*-cresol in DMF and the results are shown in Scheme 3.26.



Experiment	Base	Result
1	DIPEA	Linker cleaved from resin
2	DBU	Linker cleaved from resin
3	CsF	Linker cleaved from resin
4	Cs_2CO_3	Linker cleaved from resin
5	BEMP	Linker cleaved from resin
6	K_2CO_3	Linker cleaved from resin

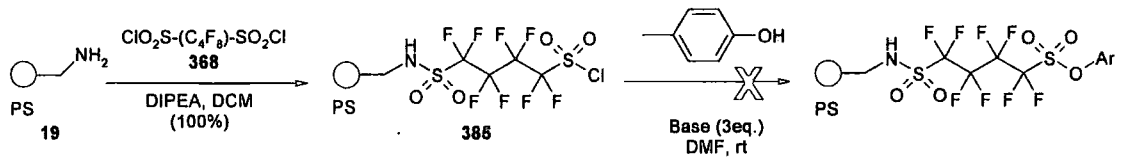
Scheme 3.26

Unfortunately, all of these bases resulted in cleavage of the perfluoroalkanesulfonyl linker unit from the solid support. This cleavage may have been the result of excess base or from carrying the reactions out at room temperature. Consequently, the array was repeated at 0 °C using 1 equivalent of base but this made no difference and once again the linker unit was completely cleaved from the resin. The ^{19}F NMR spectrum of the cleaved material contained peaks at -124 and -132 ppm. These are similar to those reported in Section 3.2.1 for bis-sulfonamide **370** and is suggestive of base mediated elimination of a sulfonamide, Scheme 3.27. However, it was not possible to confirm this as the fluorinated compound was undetectable by GCMS.



Scheme 3.27

In order to test this hypothesis, it was decided to attach bis-sulfonyl chloride 368 to basic amino-methyl polystyrene resin 19, Scheme 3.28. Resin-bound sulfonyl chloride 385 had no protons β to the sulfonamide and so if the base was cleaving the material as illustrated in Scheme 3.27, this should solve the problem. An analogous array to those described above was carried out to load *p*-cresol but unfortunately the polystyrene resin made no difference and once more the linker unit was cleaved from the resin. Therefore, the hypothesis about the mechanism of cleavage was incorrect and it is not known how the linker unit is being cleaved from the resin. The instability of the sulfonamide bond as the point of attachment limited the practicality of this linker unit. Therefore, at this stage it was decided to investigate alternative strategies for the loading of bis-sulfonyl chloride 368 onto a solid support.



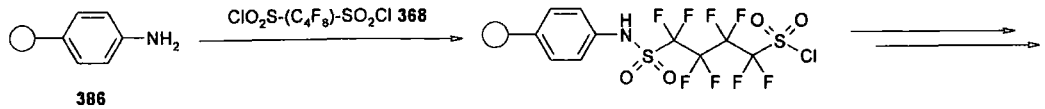
Experiment	Base	Result
1	DIPEA	Linker cleaved from resin
2	DBU	Linker cleaved from resin
3	CsF	Linker cleaved from resin
4	Cs_2CO_3	Linker cleaved from resin
5	BEMP	Linker cleaved from resin
6	K_2CO_3	Linker cleaved from resin

Scheme 3.28

3.5.3 Alternative Routes to Load Bis-sulfonyl Chloride

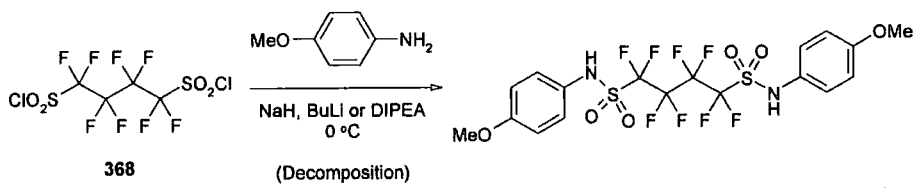
3.5.3.1 Reactions with Anilines

The alternative strategy was to attach bis-sulfonyl chloride 368 to a resin-bound aniline 386, Scheme 3.29. It was speculated that a sulfonamide derived from an aniline would be more stable to subsequent basic reaction conditions.



Scheme 3.29

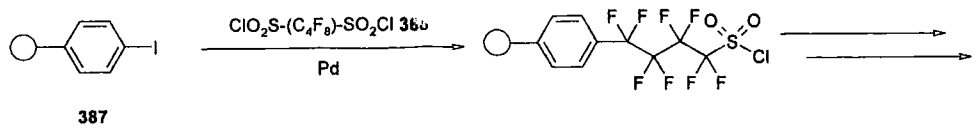
To this end, the solution phase reaction of bis-sulfonyl chloride 368 with *p*-anisidine was investigated as a model study, Scheme 3.30. Initially, it was attempted using DIPEA at 0 °C but this resulted in decomposition, confirmed by many peaks in the ^{19}F NMR spectrum. Therefore, as phenols required prior salt formation to improve reactivity it was decided to employ the same strategy for the reactions of anilines. The reaction was repeated using butyl lithium or sodium hydride but again decomposition occurred and in each case complex polymeric materials were formed. Consequently, the concept of loading bis-sulfonyl chloride 368 onto a solid-supported aniline was abandoned at this stage. Attention turned to the possibility of loading the bis-sulfonyl chloride linker unit using a cross-coupling reaction.



Scheme 3.30

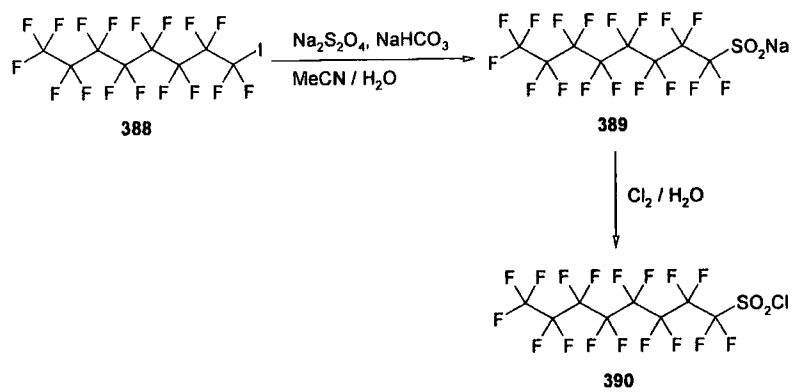
3.5.3.2 Cross-coupling Reactions with Perfluoroalkanesulfonyl Chlorides

Following the report by Vogel that aryl sulfonyl chlorides undergo Suzuki reactions,[100] it was decided to determine whether perfluoroalkanesulfonyl chlorides could also undergo cross-coupling reactions. If so, then it was speculated that bis-sulfonyl chloride 368 could undergo a Suzuki reaction with a resin-bound aryl iodide 387 to provide a stable perfluoroalkanesulfonyl linker unit, Scheme 3.31.



Scheme 3.31

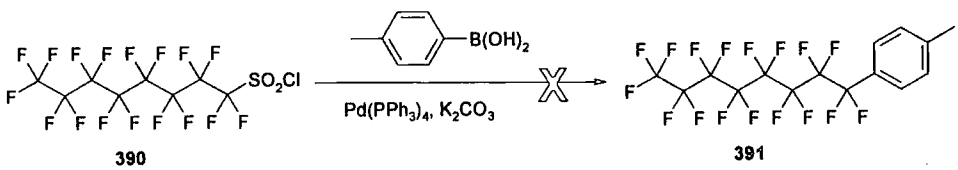
As attempts to generate perfluoroalkanesulfonyl chloride 303 from 1-iodononafluorobutane had been unsuccessful in Chapter 2, it was decided to use 1-iodoperfluorooctane 388 as a model system in the hope that the increased chain length would provide greater stability. Initially it was converted to sodium sulfite 389 using 2 equivalents of sodium dithionite. Complete conversion of the CF_2-I signal at -59 ppm to the CF_2-SO_2Na signal at -127 ppm in the ^{19}F NMR spectrum confirmed that the reaction was complete after 6 h. Sodium sulfite 389 was then oxidised to sulfonyl chloride 390, Scheme 3.32, using aqueous chlorination conditions previously described. After bubbling chlorine through the reaction for 20 min, the CF_2-SO_2Na signal at -127 ppm in the ^{19}F NMR spectrum had been completely converted to a CF_2-SO_2Cl signal at -104 ppm indicating that the reaction was complete. Recrystallisation from petroleum ether gave sulfonyl chloride 390 in 59% yield.



Scheme 3.32

With sulfonyl chloride 390 in hand, attention turned to employing it in a Suzuki cross-coupling reaction with *p*-tolyl boronic acid using $Pd(PPh_3)_4$, Scheme 3.33. After refluxing in THF for 16 h, the sulfonyl chloride peak seen at -104 ppm in the ^{19}F NMR spectrum had shifted to a doublet at -138 ppm, indicating that a reaction

had occurred. However, after aqueous work-up the fluorinated material was found in the aqueous layer suggesting that phenyl 391 had not been formed as this would have been in the organic layer. Upon evaporation of the aqueous layer, a white solid was obtained which was insoluble in even polar organic solvents (MeOH, EtOAc) and consequently could not be identified by EI GCMS, ES mass spectrometry or NMR spectroscopy. Therefore, these reactions were not investigated any further as a straightforward Suzuki cross-coupling was not occurring.



Scheme 3.33

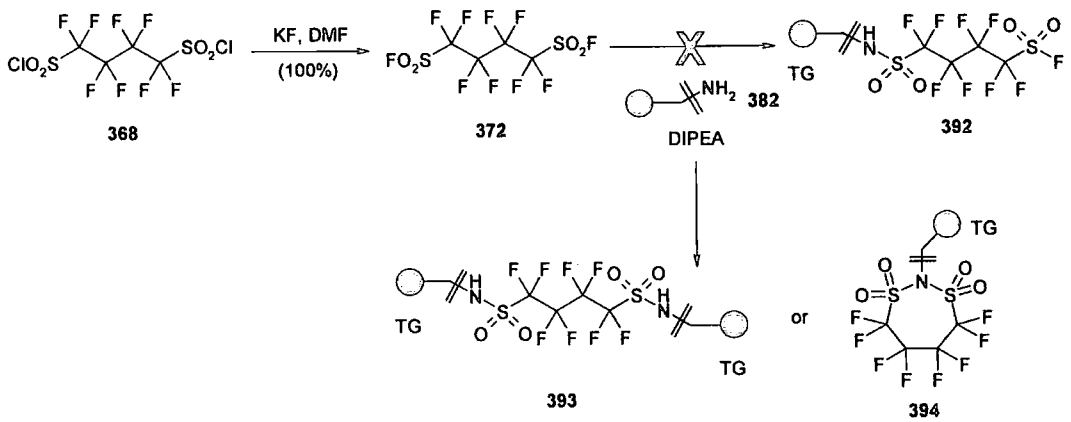
At this stage it was decided to abandon the bis-sulfonyl chloride linker unit as loading on to a solid support was too problematic. Instead the possibility of attaching the bis-sulfonyl fluoride linker unit 372 to a solid support was investigated. It was envisaged that the more rapid nucleophilic attack of the phenol at the sulfonyl fluoride would favour formation of a solid-supported perfluoroalkanesulfonate ester over cleavage of material.

3.5.4 Bis-sulfonyl Fluoride Linker Unit

Bis-sulfonyl fluoride 372 represented an alternative linker unit on to which it might be easier to load phenols. It was hoped that the use of milder bases and more rapid nucleophilic attack of the phenol would prevent cleavage of the linker unit from the resin and provide solid-supported perfluoroalkanesulfonate esters suitable for cleavage studies.

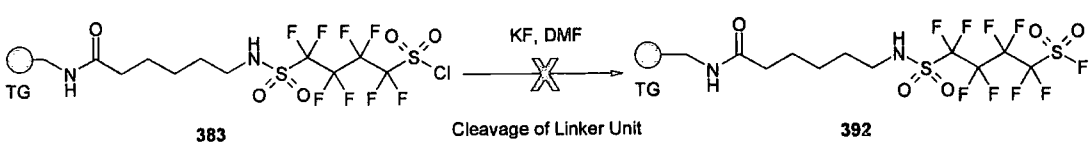
Initially, bis-sulfonyl fluoride 372 was generated *in situ* in DMF as previously described. After filtration to remove excess potassium fluoride, it was loaded directly onto resin 382 using DIPEA in DCM. However, following the reaction

only two CF_2 signals were observed at -116 and -121 ppm in the ^{19}F NMR spectrum and no sulfonyl fluoride signals were seen. This indicated that the more reactive bis-sulfonyl fluoride had cross-linked to give **393** or formed a cyclic tertiary sulfonamide system **394** and that resin-bound sulfonyl fluoride **392** was not generated, Scheme 3.34.



Scheme 3.34

As this was not a viable route for obtaining a resin-bound sulfonyl fluoride, attention turned to an alternative strategy. It was felt that treatment of resin-bound sulfonyl chloride **383** with potassium fluoride would generate the sulfonyl fluoride directly on the solid support. As potassium fluoride was basic, there was a risk that it would just cleave the linker unit from the resin as other bases had done. In attempt to minimise this, 1 equivalent was used with 18-crown-6 in the hope that it would react with the sulfonyl chloride first leaving no excess to cause cleavage. Disappointingly, no resin-bound sulfonyl fluoride **392** was generated and ^{19}F NMR spectroscopy once more showed cleavage of the linker unit from the resin, Scheme 3.30.



Scheme 3.35

Reluctantly it was decided to abandon this route to a perfluoroalkanesulfonyl linker unit. Despite getting so close to a novel perfluoroalkanesulfonyl linker unit, the sulfonamide linkage was too unstable to be of practical use and the loading of phenols was poor and unrepeatable. Therefore, attention was turned to generating a sulfonyl chloride with a more stable means of attaching it to a solid support. To this end, reactions with alkenes discussed in Chapter 2 were re-addressed. They provided a quick and simple means to sulfonyl chlorides possessing a range of additional functionalities which could be used to attach linker units to solid supports. It was decided to screen a wide range of alkenes and apply the chemistry developed in Chapters 2 and 3 towards developing a second generation perfluoroalkanesulfonyl linker unit with improved stability. Progress is discussed in Chapter 4.

3.6 Conclusions

- Synthesis of bis-sulfonyl chloride **368** was optimised and scaled up, providing multigram quantities in 60 – 70% yield.

- Generation of bis-perfluoroalkanesulfonamides and bis-perfluoroalkane sulfonate esters established model solution phase chemistry for the loading of the linker unit onto an amino resin and the subsequent loading of phenols.

- Bis-sulfonyl fluoride and *p*-nitro phenol bis-sulfonate ester linker units were also synthesised. The *p*-nitro phenol derivative was unreactive and was progressed no further. Bis-sulfonyl fluoride **372** was highly reactive and required generation *in situ*.

- Prototypical Suzuki and Stille reactions were demonstrated for a simple aryl triflate and bis-perfluoroalkanesulfonate esters.

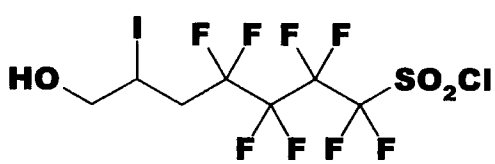
- Bis-sulfonyl chloride **368** was loaded onto amino TentaGel® giving a novel perfluoroalkanesulfonyl linker unit. Phenols were loaded using sodium

hydride but the loading was unrepeatable. Other bases resulted in cleavage of the linker unit from the resin.

- The solid-supported perfluoroalkanesulfonate ester underwent diversity cleavage using Suzuki conditions, but the sulfonamide bond proved insufficient to give the linker unit stability. Therefore this route was abandoned at this stage.

CHAPTER 4

ALLYL ALCOHOL LINKER UNIT



4 General Introduction

The bis-sulfonyl chloride linker unit described in Chapter 3 of this thesis demonstrated that it was possible to generate perfluorosulfonyl chlorides with which phenols and amines could be coupled. Furthermore, cleavage reactions using Suzuki and Stille conditions had been demonstrated as feasible, albeit with scope for optimisation of reaction conditions. However, attaching the bis-sulfonyl chloride directly to a solid support was problematic and provided a linker unit with insufficient stability to be of practical use. It was speculated that an additional spacer unit was required to enhance the stability of the system. However, previous work described in Chapter 2 of this thesis demonstrated that aromatic spacer units (eugenol and allylbenzene) underwent unwanted side reactions making them unsuitable candidates. Therefore, it was decided to develop a second generation linker unit possessing a simple alkyl spacer unit offering some means of attachment to a solid support. To this end reaction of 1,4-diiodooctafluorobutane with a number of commercially available alkenes was investigated and initial efforts are described in Section 4.1.

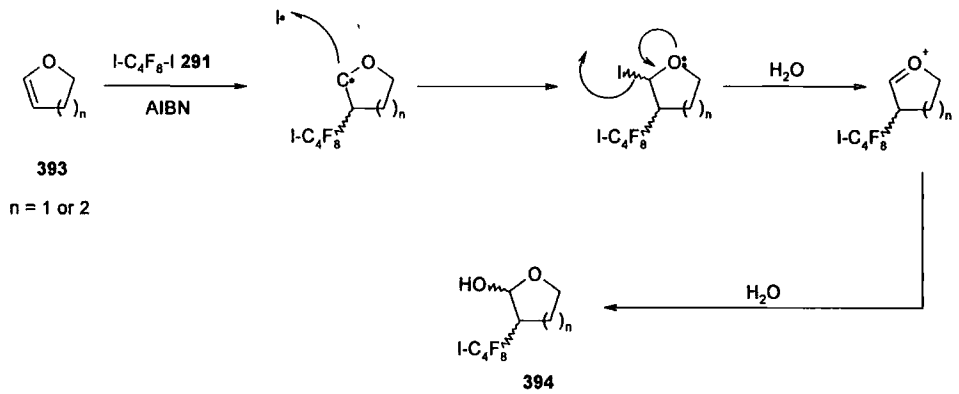
4.1 Reactions with Commercially Available Alkenes

It was decided to screen the reaction of 1,4-diiodooctafluorobutane with a range of alkenes in order to find an alternative spacer unit which could be used to attach a perfluorosulfonyl linker unit to a solid support. De Sousa had shown in early work that due to the electron-deficient nature of the radical generated from 1,4-diiodooctafluorobutane, it was necessary to react it with electron-rich alkenes. Therefore dihyrdropyrans and dihydrofurans were chosen for the initial investigations and work in this area is discussed below.

4.1.1 Dihydro-Pyrans and Dihydro-Furans

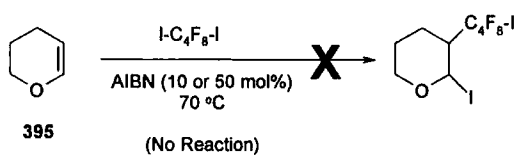
To this end, it was speculated that the reaction of 1,4-diiodooctafluorobutane **291** with a dihydropyran or dihydrofuran **393** would yield hemiacetal **394**. This could undergo spontaneous elimination to remove the unwanted iodine and leave an

alcohol following work-up, Scheme 4.1. The resulting hemiacetal could then be used as a point of attachment to a solid support.



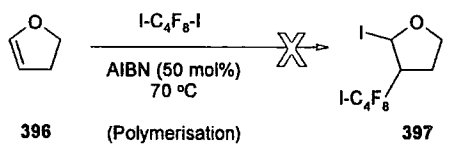
Scheme 4.1

With this strategy in mind, the reaction of 3,4-dihydro-2H-pyran **395** with 1,4-diiodooctafluorobutane was investigated, Scheme 4.2. It was carried out neat using 10 mol% AIBN at 70 °C and monitored by ^{19}F NMR spectroscopy. However, after 24 h only the 2 signals for 1,4-diiodooctafluorobutane were observed in the ^{19}F NMR spectrum at –59 and –112 ppm indicating that no reaction had occurred. Therefore, as some of the previous reactions of this type required a larger amount of AIBN to proceed, it was decided to reattempt the reaction using 50 mol%. Once more no reaction with 1,4-diiodooctafluorobutane occurred but on this occasion the larger quantity of AIBN appeared to promote the oligomerisation of 3,4-dihydro-2H-pyran with itself resulting in a complex polymeric by-product.



Scheme 4.2

Concurrent with these reactions, the analogous reaction was attempted with 2,3-dihydro-2H-furan 396, Scheme 4.3. As in the case of the pyran, polymerisation of the furan occurred and none of iodide 397 was observed. Therefore, pyrans and furans were abandoned as potential starting materials as they were unreactive to 1,4-diiodooctafluorobutane and attention was turned to alternative alkenes.

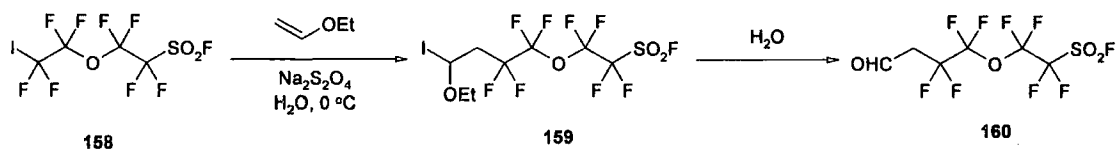


396 397

Scheme 4.3

4.1.2 2-Methoxypropene

As the reactions of 1,4-diiodooctafluorobutane with pyrans and furans had proved unsuccessful, attention was turned to alternative alkenes. Holmes reacted iodosulfonyl fluoride 158 with ethyl vinyl ether to give iodide 159 in the generation of the perfluorosulfonyl linker unit described in Chapter 1. This underwent elimination to generate aldehyde 160 upon work-up, Scheme 4.4, which was used to attach the linker unit to a resin as described in Chapter 1.[68, 69]

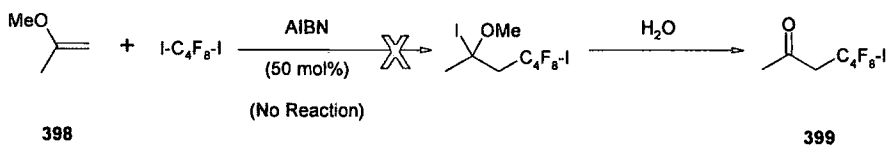


158 159 160

Scheme 4.4

Adapting this approach for the current project, the reaction of 1,4-diiodooctafluorobutane with 2-methoxypropene 398 was investigated, Scheme 4.5. 2-Methoxypropene was used in preference to ethyl vinyl ether as it was speculated that the resulting methyl ketone 399 would prove more stable than an aldehyde. The reaction of 2-methoxypropene with 1,4-diiodooctafluorobutane

was attempted using 10 mol% AIBN at a range of temperatures ranging from 36 °C to 70 °C. However, in each case there was no change in the ^{19}F NMR spectrum after 24 h indicating that no reaction had occurred. At lower reaction temperatures (< 60 °C) the lack of reactivity was due to higher temperatures being required to activate AIBN (typically 66 – 72 °C[149]). In contrast, it was speculated that the lack of reactivity at 70 °C was due to 2-methoxypropene refluxing as it has a low boiling point (36 °C). These problems of reactivity could possibly be overcome by carrying out reactions in a sealed tube. However, work described in Section 4.2 using allyl alcohol was proving more promising and so 2-methoxypropene was abandoned as a starting material at this stage. The use of simple dienes as starting materials was also investigated as they offered a number of different ways of loading a linker unit onto a solid support.

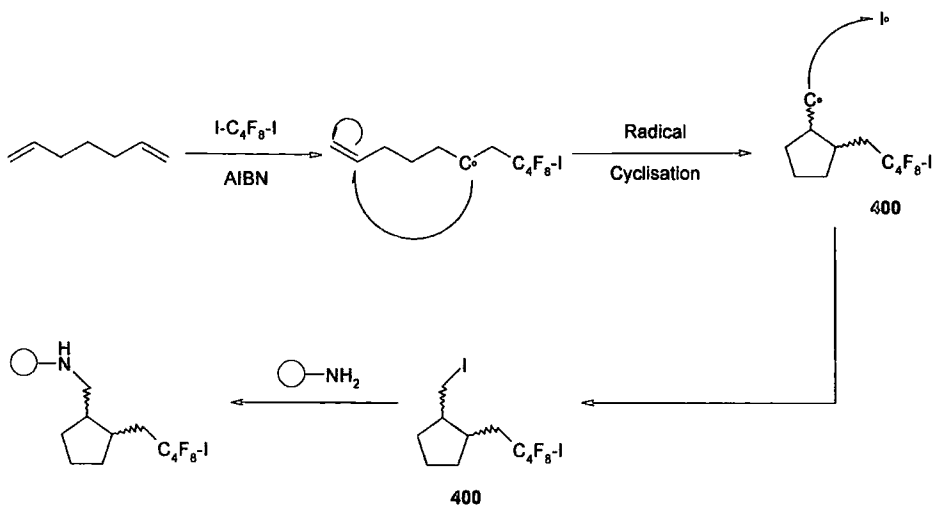


398 399

Scheme 4.5

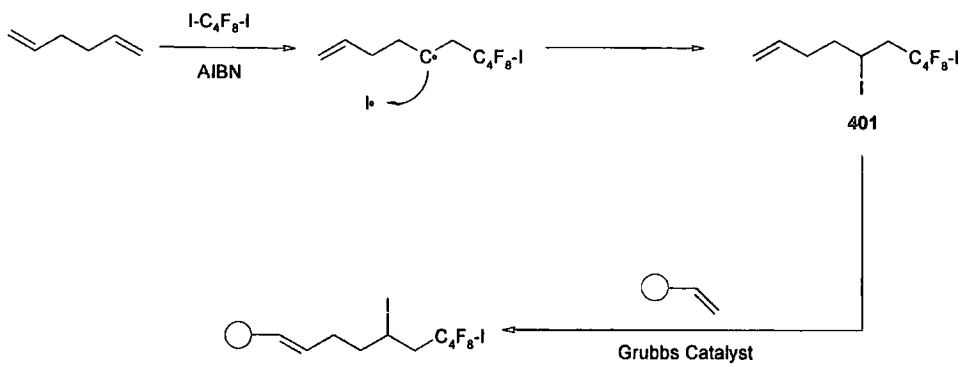
4.1.3 Dienes

The reactions of diiodoperfluoroalkanes were investigated with simple dienes as it was speculated that reaction with 1,6-heptadiene and subsequent cyclisation to yield a 5-membered ring 400 would be favoured. The terminal alkyl iodide could then be used to attach the linker unit to a nucleophilic resin, Scheme 4.6.



Scheme 4.6

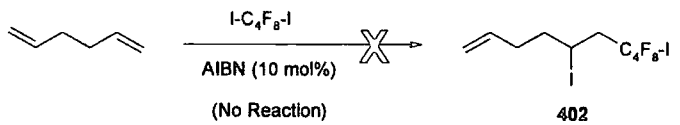
Alternatively, if 1,5-hexadiene were used then cyclisation to give a 4-membered ring would not be favoured and so it should be possible to isolate iodide 401. This iodide could then be attached to a resin using the free alkene in a cross-metathesis reaction, Scheme 4.7.



Scheme 4.7

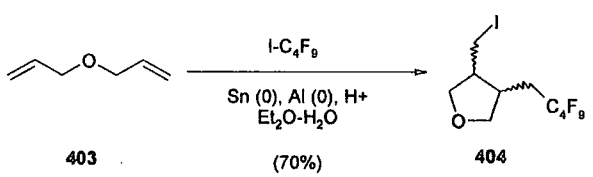
Initially the reaction of 1,4-diiodooctafluorobutane with 1,5-hexadiene was investigated using 10 mol% AIBN, Scheme 4.8. 1,5-Hexadiene boils at 60 °C and so it was necessary to carry out the reaction at 55 - 60 °C. After 24 h only 1,4-diiodooctafluorobutane was observed in the ^{19}F NMR spectrum and iodide 402 had not been generated. It is not clear as to why there should be no reaction

but, as in the case of 2-methoxypropene possibly the reaction temperature was too low to activate AIBN.



Scheme 4.8

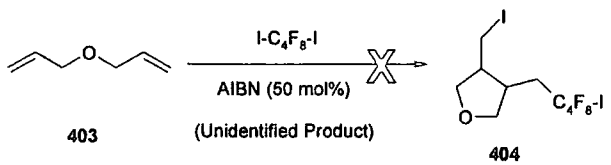
At this stage it was decided to investigate reactions with a longer diene in the hope that cyclisation would be the favoured process. As the reaction with 1,5-hexadiene was unsuccessful, it was decided not to use 1,6-heptadiene. Instead, in a separate section of work which will be described in detail in Section 4.2, it had been shown that 1,4-diiodooctafluorobutane was able to react with allyl alcohol in the presence of AIBN. Therefore, it was decided to investigate the reaction of 1,4-diiodooctafluorobutane with allyl ether 403. Allyl ether was chosen as an analogue of 1,6-heptadiene which was expected to favour cyclisation to give a 5 membered ring and furthermore there was also a literature precedent for this reaction. Kuroboshi and Ishihara had reacted allyl ether with 1-iodononafluorobutane to yield substituted tetrahydrofuran 404, Scheme 4.9.[150]



Scheme 4.9

The reaction of 1,4-diiodooctafluorobutane 291 with allyl ether 403 was carried out at 70 °C for 24 h and monitored by ^{19}F NMR and ^{1}H NMR spectroscopy. However, after this time many peaks in the ^{19}F NMR and ^{1}H NMR spectra indicated a complex mixture of products and attempts to isolate tetrahydrofuran 404 using flash chromatography were unsuccessful. At this stage it seemed apparent that only limited substrates were reactive towards

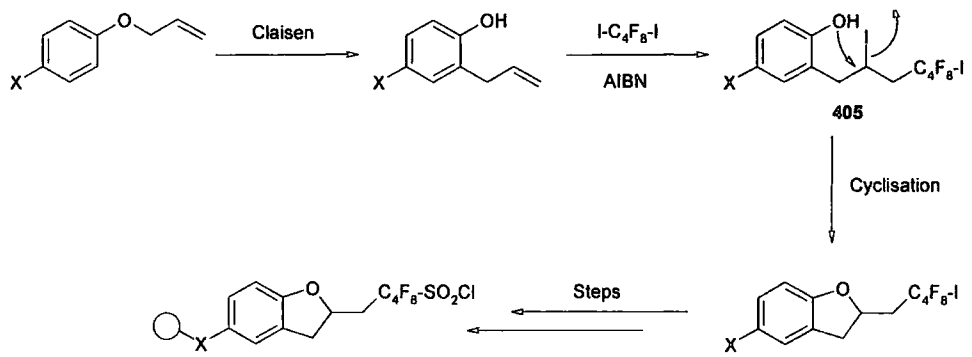
diiodoperfluoroalkanes under radical conditions. The most reactive seemed to be allylbenzene and the phenolic analogue eugenol as discussed in Chapter 2. Therefore, attention turned to the synthesis of analogues of allylbenzene which could be used as a spacer unit in a perfluorosulfonyl linker.



Scheme 4.10

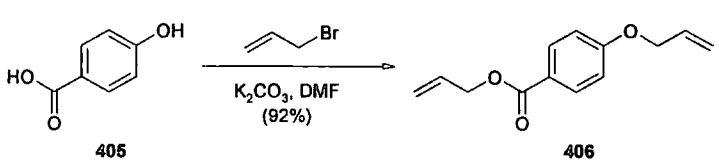
4.1.4 Analogues of Allylbenzene

The radical reactions of 1,4-diiodooctafluorobutane with allylbenzene and eugenol described in Chapter 2 were the most successful reactions with alkenes developed at this stage. However, 1,4-diiodooctafluorobutane was noticeably unreactive towards other alkenes. Unfortunately, allylbenzene possessed no functionality which could be used to attach a linker unit to a solid support and the hydroxyl group of eugenol caused too many problematic side reactions. Therefore it was decided to use a Claisen rearrangement to synthesise phenolic analogues of allylbenzene which possessed some functionality X which could be used to attach a linker unit to a resin. It was speculated that if 1,4-diiodooctafluorobutane was added to the allyl group 405 then the phenol resulting from the Claisen rearrangement would be set up to cyclise, Scheme 4.11. This would remove the unwanted secondary iodide and protect the phenol in a single step. This would provide a more stable linker unit which could be attached to a solid support through X.



Scheme 4.11

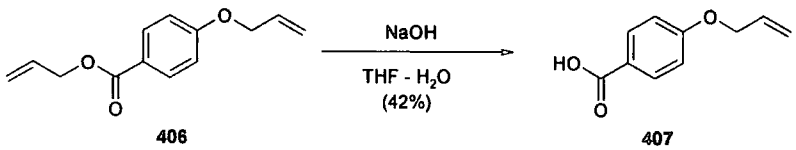
In order to test this synthetic strategy, 4-hydroxy benzoic acid 406 was selected as the starting material. It was necessary to convert the phenol to the allyl ether but rather than risk competing reactions with the acid, it was decided to use excess allyl bromide and generate the allyl ester as well. The ester could then be subsequently hydrolysed at a later date without touching the ether. Reaction of 4-hydroxy benzoic acid with 3 equivalents of allyl bromide was carried out in DMF at 50 °C using potassium carbonate, Scheme 4.12. Following aqueous work-up, excess allyl bromide and DMF were removed *in vacuo* to give known 4-allyloxybenzoic acid allyl ester 406 in 92% yield without need for further purification. The product was confirmed by a molecular ion at m/z = 218 in the EI mass spectrum and furthermore by IR spectroscopy. The phenol stretch of 4-hydroxy benzoic acid 405 seen at 3354 cm^{-1} was no longer observed in the IR spectrum and the acid C=O absorption seen at 1667 cm^{-1} had been completely replaced by an ester C=O absorption at 1713 cm^{-1}.



Scheme 4.12

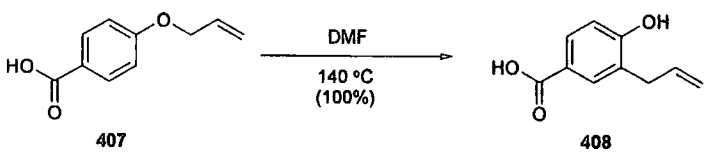
With 4-allyloxy-benzoic acid allyl ester 406 in hand, attention turned to hydrolysis of the allyl ester. This was achieved in THF / Water [1 : 1] using 5 equivalents of

sodium hydroxide, Scheme 4.13. Analysis by TLC showed no more starting material after 24 h and acidic work-up gave acid 407 in 42% yield without need for further purification. Known acid 407 was confirmed by a molecular ion at m/z = 178 in the EI mass spectrum and analysis by IR spectroscopy showed that the ester C=O absorption seen at 1713 cm^{-1} had been replaced by an acid C=O absorption at 1666 cm^{-1} in the IR spectrum. Furthermore, a broad carboxylic acid OH absorption was seen at 2957 cm^{-1}.



Scheme 4.13

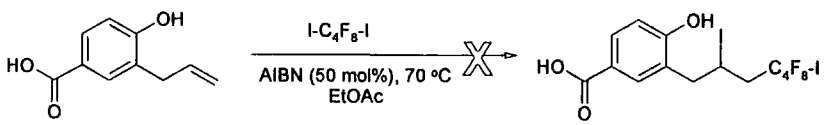
Attention then turned to the Claisen rearrangement of acid 407. This was achieved by heating in DMF at 140 °C, Scheme 4.14, and analysis of the reaction mixture by TLC showed that complete conversion occurred overnight. Removal of DMF *in vacuo* gave phenol 408 in 100% yield without need for further purification. This was confirmed by the presence of a phenolic OH absorption at 3379 cm^{-1} in the IR spectrum. Furthermore, the O-CH_2 signal of acid 407 seen at 4.60 ppm in the ^{1}H NMR spectrum had been completely replaced by the C-CH_2 signal of phenol 408 at 3.40 ppm.



Scheme 4.14

The reaction of 1,4-diiodooctafluorobutane with phenol 408 was then investigated. This reaction was different to the reactions of this type previously described, as all previous reactions had been carried out neat. In this case, phenol 408 was a solid and so a solvent was required. The free phenol and acid

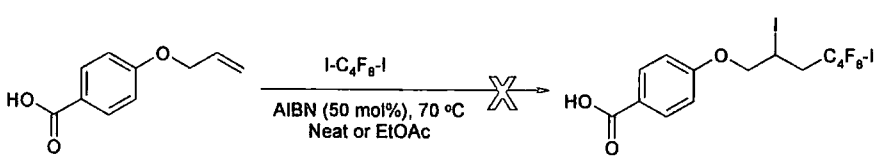
groups made it very insoluble in typical solvents for radical reactions, such as toluene, and so ethyl acetate was chosen for the reaction as its boiling point of 77 °C made it ideal for initiating AIBN. The reaction was carried out at 70 °C using 50 mol% AIBN, Scheme 4.15, and monitored by ^{19}F NMR spectroscopy. However, after 24 h only 2 peaks at -59 and -112 ppm corresponding to unreacted 1,4-diiodooctafluorobutane were observed in the ^{19}F NMR spectrum indicating that no reaction had occurred. As this reaction was unsuccessful, the analogous reaction was attempted on acid 407.



408 (No Reaction)

Scheme 4.15

It was hoped that the allyl ether group in acid 407 would prove more reactive to 1,4-diiodooctafluorobutane and the acid group still provided a means of attachment to a solid support. As acid 407 was an oil, the reaction was attempted both neat and in ethyl acetate using 50 mol% AIBN. Unfortunately monitoring both reactions by ^{19}F NMR spectroscopy showed no reaction after 24 h and only unreacted 1,4-diiodooctafluorobutane was observed in the NMR spectrum. Therefore, as this approach was showing little promise as a route to a perfluorosulfonyl linker unit and simultaneous work with allyl alcohol was proving more successful, it was decided to abandon this route at this stage. A perfluorosulfonyl linker unit based upon allyl alcohol is described in Section 4.2.

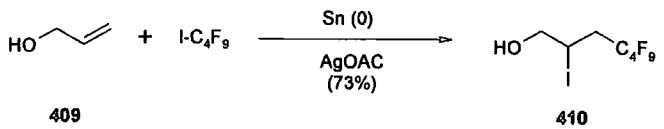


407 (No Reaction)

Scheme 4.16

4.2 Allyl Alcohol Linker Unit

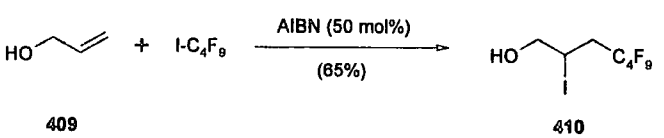
While 1,4-diiodooctafluorobutane was unreactive to the wide range of alkenes detailed in Section 4.1, the reaction of 1-iodononafluorobutane with allyl alcohol 409 was demonstrated by Kuroboshi and Ishihara. They carried out the transformation using metallic tin(0) and silver(I) acetate to yield iodide 410, Scheme 4.17.[150]



409 410

Scheme 4.17

With this literature precedent available, it was useful to determine whether the reaction could be promoted using AIBN instead of tin. Reaction of 1 equivalent of 1-iodononafluorobutane with allyl alcohol in the presence of 50 mol% AIBN, Scheme 4.18, was monitored by ^{19}F NMR spectroscopy. After 16 h the CF_2-I peak at -59 ppm had been completely replaced by a CH_2-CF_2 multiplet at -112 ppm in the ^{19}F NMR spectrum and purification by distillation using a Kugelrohr bulb-to-bulb distillation apparatus gave known iodide 410 in 65% yield. This was a promising result as the alcohol provided a means of attachment to a solid support and so it was decided to investigate the reaction with 1,4-diiodooctafluorobutane. This work is described in Section 4.2.1.

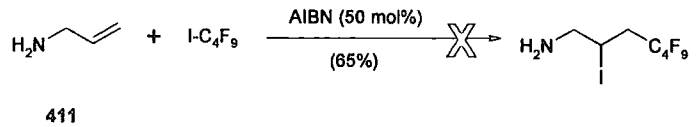


409 410

Scheme 4.18

The analogous reaction of 1-iodononafluorobutane with allylamine 411 was also investigated, Scheme 4.19. If this reaction could be promoted then it offered an alternative linker unit which could be attached to a solid support through an

amine. This was desirable as it was speculated that an amide linkage would be more stable than an ester linkage under basic conditions required to load phenols onto a linker unit. However, on attempting the reaction at 70 °C in the presence of 50 mol% AIBN, no reaction occurred and only peaks corresponding to 1,4-diiodooctafluorobutane were observed in the ^{19}F NMR spectrum. Therefore, it was decided to develop a linker unit from allyl alcohol.



411

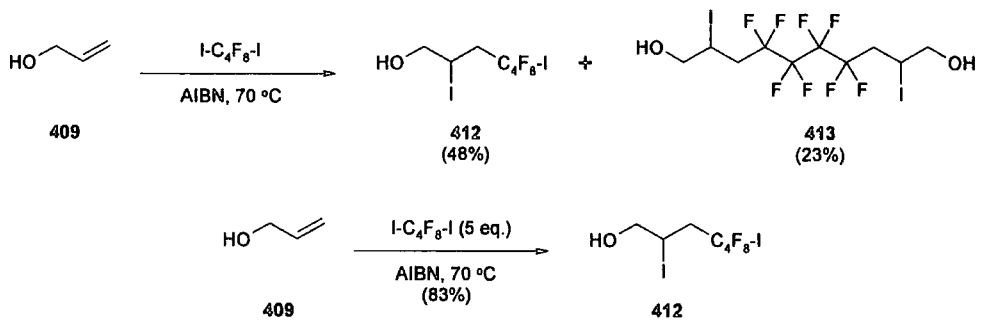
Scheme 4.19

4.2.1 Solution Phase Studies

Allyl alcohol 409 represented a desirable spacer unit as the alcohol could be used as a point of attachment to a solid support. In order to investigate this, allyl alcohol was reacted with 1 equivalent of 1,4-diiodooctafluorobutane in the presence of 50 mol% of AIBN at 70 °C. The reaction was monitored by ^{19}F NMR spectroscopy and was complete after 16 h. Four CF_2 peaks in the ^{19}F NMR spectrum confirmed mono-coupled iodide 412, including a CF_2-I peak at –59 ppm and a CH_2-CF_2 multiplet at –112 ppm. However, two further peaks were observed at –124 and –113 ppm corresponding to bis-coupled alcohol 413. Purification by flash chromatography yielded a 2:1 mixture (based upon allyl alcohol) of mono 412 and bis 413 coupled iodides, Scheme 4.20. Mono-coupled iodide 412 was confirmed by a molecular ion at m/z = 511.8375 in the EI HRMS which agreed with the calculated value of 511.8370 for $C_7H_6F_8I_2O$. A molecular ion at m/z = 569.8792 was in agreement with the calculated value of 569.8793 for $C_{10}H_{12}F_8I_2O_2$ and confirmed bis-coupled iodide 413.

The formation of bis-coupled iodide 413 as an unwanted by-product was uneconomical. Therefore, the reaction was repeated using 5 equivalents of 1,4-diiodooctafluorobutane and this yielded exclusively mono-coupled alcohol 412 in

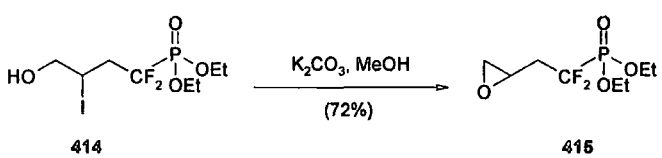
83% yield following purification of flash chromatography. The use of a large excess of expensive 1,4-diiodooctafluorobutane was initially considered undesirable. However, full recovery of unreacted 1,4-diiodooctafluorobutane using flash chromatography proved to be extremely simple and efficient as it was eluted very rapidly and cleanly using 100% petroleum ether. With large quantities of iodide 412 in hand, it was interesting to try and convert it into the epoxide as this could be used to attach the linker unit to a solid support and would also remove the unwanted secondary iodide.



Scheme 4.20

4.2.1.1 Epoxide Generation

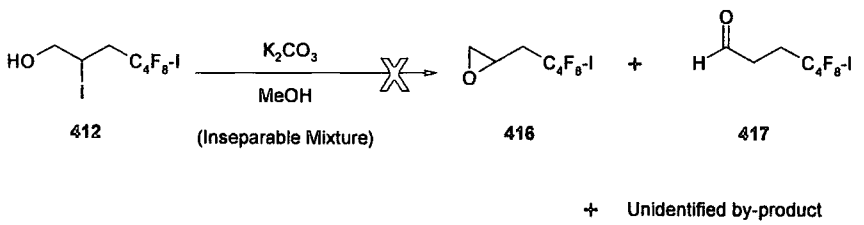
It was speculated that treatment of iodide 412 with a base would eliminate the secondary iodide to form epoxide 416. An example of an analogous reaction was demonstrated by Xu and Prestwich. They treated iodide 414 with potassium carbonate to give the corresponding epoxide 415, Scheme 4.21.[151]



Scheme 4.21

This reaction was attempted using iodide 412, Scheme 4.22, and monitored by TLC. After 16 h no starting material remained and analysis of the crude reaction mixture by EI GCMS showed a peak at m/z = 384 which may have indicated epoxide 416. However, attempts to purify this material by flash chromatography

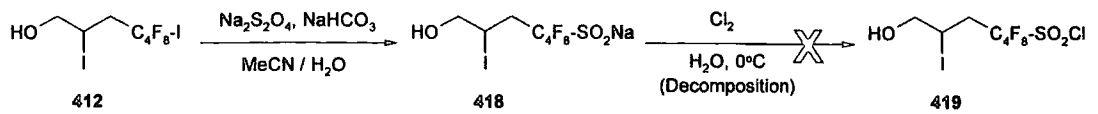
were problematic and epoxide 416 was obtained as an inseparable mixture containing two other components. Signals at 5.9 and 6.4 ppm in the ^{1}H NMR spectrum indicated alkene protons which suggested elimination of HI to give alkene 417 as one by-product and this was seen as a second peak with a molecular ion at m/z = 383 in the GCMS. The other by-product had a molecular ion at m/z = 399 but it was not possible to identify it. Therefore, as epoxide generation was resulting in complex mixtures, it was decided to investigate the use of iodide 412 itself as a linker unit and use the alcohol as a point of attachment to a resin.



Scheme 4.22

4.2.1.2 Sulfonyl Chloride Generation

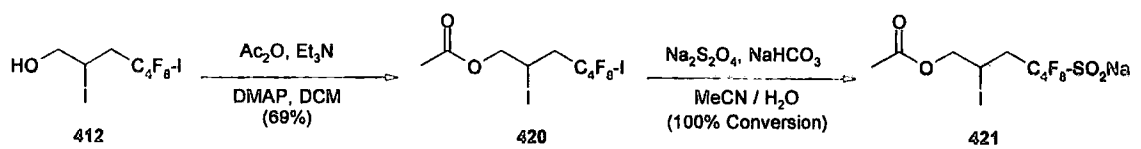
As it was decided to progress iodide 412 as a potential linker unit, it was necessary to generate the corresponding sulfonyl chloride. Therefore attention turned to the sulfonation reaction using 2 equivalents of sodium dithionite. ^{19}F NMR spectroscopy showed the replacement of a CF_2-I peak at –59 ppm with a CF_2-SO_2Na signal at –127 ppm indicating that the reaction was complete after 4 h. Inorganic materials were removed by filtration and sodium sulfite 418 was used without further purification. Unfortunately, aqueous chlorination resulted in a complex mixture of materials and decomposition, seen as many unidentifiable peaks in the ^{19}F NMR spectrum, and none of sulfonyl chloride 419 was formed, Scheme 4.23.



412 418 419

Scheme 4.23

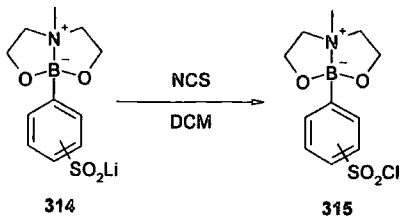
Decomposition was thought to be due to the free alcohol complicating the chlorination reaction. It is oxidisable and chlorine can act as an oxidising agent leading to unwanted side reactions in the chlorination step resulting in complex mixtures of products. Therefore, it was decided to protect it as the acetate 420. This was achieved using acetic anhydride, triethylamine and DMAP, Scheme 4.24, and analysis by TLC showed no more starting material after 16 h. Purification by flash chromatography gave acetate 420 in 69% yield and this was confirmed by the presence of an ester carbonyl stretch at 1745 cm^{-1} in the IR spectrum and the absence of a broad alcohol stretch. In addition, a molecular ion at m/z = 553.8477 (EI) was in agreement with the calculated value of 553.8488 for $C_9H_8F_8I_2O_2$. With acetate 420 in hand, reaction with 2 equivalents of sodium dithionite gave quantitative conversion to sodium sulfite 421, Scheme 4.24. Once more, replacement of the C*F*$_2$-I peak at -59 ppm with a C*F*$_2$-SO_2Na signal at -127 ppm in the ^{19}F NMR spectrum indicated that the reaction was complete after 4 h.



412 420 421

Scheme 4.24

At this stage it was intended to carry out the aqueous chlorination on protected sodium sulfite 421. However, before attempting that reaction, Vedsø *et al.* reported the conversion of lithium sulfites 314 into sulfonyl chlorides 315 using *N*-chlorosuccinimide as described in Chapter 2, Scheme 4.25.[123]



314 315

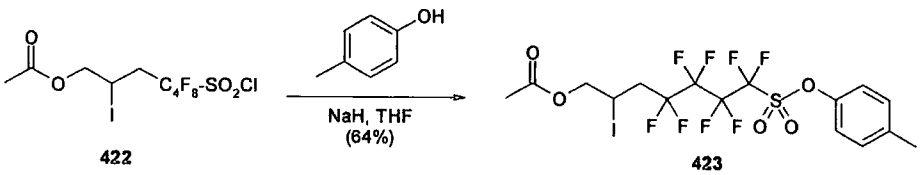
Scheme 4.25

This appeared a very attractive method of generating sulfonyl chlorides using much milder conditions to the elemental chlorine employed throughout the current research. It was decided to attempt this reaction on protected sodium sulfite 421, Scheme 4.26, and so it was suspended in DCM and treated with 1 equivalent of *N*-chlorosuccinimide at room temperature. This resulted in the appearance of a purple colour suggesting the oxidation of sodium iodide to iodine and chlorine as previously described in Chapter 3. After 4 h only a small amount of perfluorosulfonyl chloride was formed, confirmed by a C*F*$_2$-SO_2Cl signal at –104 ppm in the ^{19}F NMR spectrum. Nevertheless, encouraged by these initial results it was decided to add a further equivalent of *N*-chlorosuccinimide to the reaction. The complete replacement of the C*F*$_2$-SO_2Na signal at –127 ppm with a C*F*$_2$-SO_2Cl signal at –104 ppm in the ^{19}F NMR spectrum showed that the reaction had gone to completion after a further 4 h. Reductive work-up using saturated sodium thiosulfate solution removed the iodine formed and purification by flash chromatography gave sulfonyl chloride 422 in 73% yield. As with previous sulfonyl chlorides described in this thesis it was not possible to detect the molecular ion using mass spectrometry. However, a peak at 491 corresponded to loss of chloride from the molecular ion and further confirmation of sulfonyl chloride 422 was obtained from sulfonyl chloride stretches at 1210 and 1415 cm^{-1} in the IR spectrum.

421 422

Scheme 4.26

The acetate protecting group provided a solution phase analogue of a linker unit bound to a solid support through an ester linkage. Following stability problems with the sulfonamide linkage of the bis-sulfonyl chloride linker unit described in Chapter 3, it was desirable to determine the stability of the ester linkage in the presence of sodium phenoxide. To this end, treatment of sulfonyl chloride 422 with a solution of preformed sodium phenoxide at 0 °C gave sulfonate ester 423 in 64% yield following flash chromatography, Scheme 4.27. The reaction was monitored by ^{19}F NMR spectroscopy and after 4 h the CF_2-SO_2Cl signal at –104 ppm had been completely replaced by a CF_2-SO_3Ar signal at –108 ppm in the ^{19}F NMR spectrum. Sulfonate ester 423 was also confirmed by ES HRMS, a molecular ion at m/z = 615.9895 ($M+NH_4$) being identical to the calculated value for $C_{16}H_{19}O_5NF_8IS$.

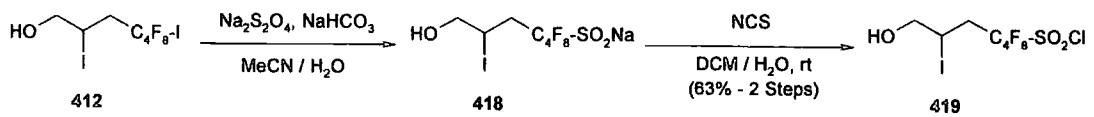


422 423

Scheme 4.27

With this chemistry established, all that remained was to generate sulfonyl chloride 419 possessing a free alcohol which could be attached to a solid support. While attempts to do so using elemental chlorine had resulted in decomposition, it was hoped that the reaction using *N*-chlorosuccinimide offered a solution to the problem. Reaction of iodide 412 with 2.5 equivalents of *N*-chlorosuccinimide in DCM was monitored by ^{19}F NMR spectroscopy. After 4 h, the CF_2-SO_2Na signal at –127 ppm had been replaced by a CF_2-SO_2Cl signal at –104 ppm in the ^{19}F NMR spectrum. Work-up with saturated sodium thiosulfate

solution and subsequent purification by flash chromatography gave sulfonyl chloride 419 in 25% yield. Sulfonyl chloride 419 was confirmed by mass spectrometry which showed a peak at m/z = 449 corresponding to the loss of chloride from the molecular ion. Furthermore, sulfonyl chloride stretches at 1212 and 1422 cm^{-1} and an alcohol stretch at 3302 cm^{-1} were observed in the IR spectrum. In order to justify the low yield, the sodium thiosulfate solution was analysed by ^{19}F NMR spectroscopy and it was found to contain unreacted sodium sulfite. Therefore, as sodium sulfite 418 was only sparingly soluble in DCM the reaction was reattempted in a biphasic solvent system. Repeating the reaction in DCM : H_2O [5 : 1] improved the yield of bis-sulfonyl chloride 419 to 63%, Scheme 4.28. The next objective was to load it on to a solid support.



Scheme 4.28

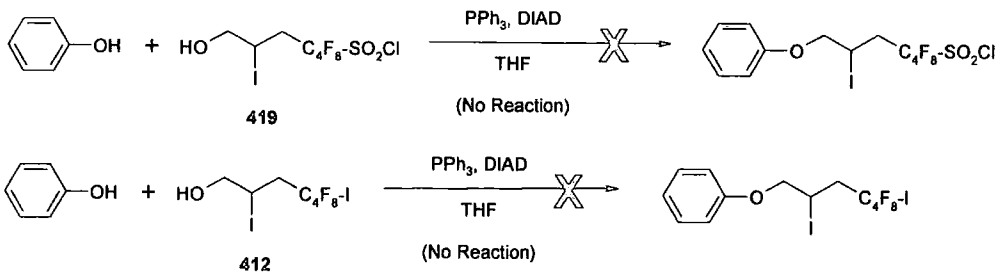
4.2.2 Solid Phase Studies

With a second generation perfluorosulfonyl linker unit in hand, it was necessary to load it onto a solid support. The Mitsunobu reaction was selected first as it was speculated that the mild reaction conditions would not be detrimental to the perfluorosulfonyl chloride.

4.2.2.1 Resin Loading using Mitsunobu Reactions

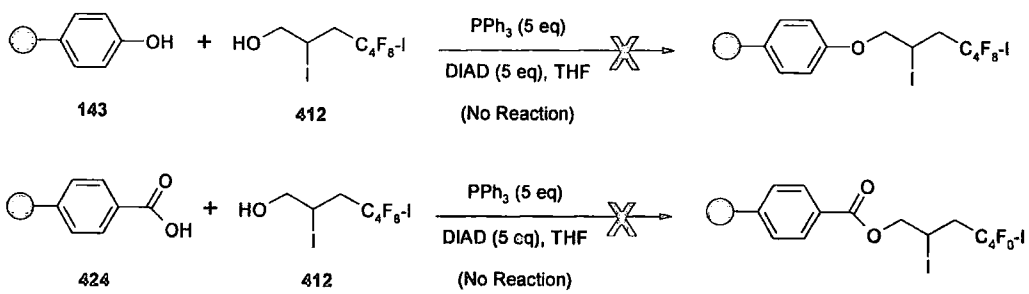
Initially a model solution phase experiment was attempted using a standard Mitsunobu reaction. Sulfonyl chloride 419 was reacted with phenol using triphenyl phosphine and DIAD in THF, Scheme 4.29. Unfortunately, no reaction occurred and sulfonyl chloride 419 was recovered quantitatively. No obvious explanation for the failure of this reaction was forthcoming but it was possibly due to the sulfonyl chloride interfering with the reaction. Therefore the reaction was attempted again using iodide 412 but once more no reaction occurred and starting material was recovered. In order to overcome the problem of poor

reactivity, it was decided to attempt the reactions on the solid phase so that large excesses of triphenyl phosphine and DIAD could be used.



Scheme 4.29

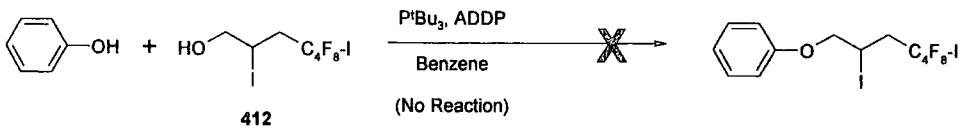
The advantage of solid phase Mitsunobu reactions was that 5 equivalents of triphenyl phosphine and DIAD could be employed in order to promote the reaction. The reactions of iodide 412 with phenol on polystyrene 143 or carboxy polystyrene 424 resins were investigated, Scheme 4.30. However, no reaction was seen in either case and no fluorinated material was loaded onto the solid supports.



Scheme 4.30

The reason for the failure of these Mitsunobu reactions is not clear but it may have been due to the pKa's of the phenol / acid being incompatible for reaction with iodide 412.[152] In an attempt to overcome this, attention turned to a more active version of the Mitsunobu reaction using tributyl phosphine and 1,1'-(azodicarbonyl) dipiperidine (ADDP) reported by Tsunoda *et al.*.[153] These

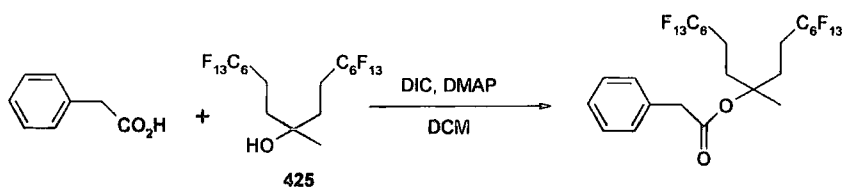
conditions were employed in the reaction of phenol with iodide **412** but once more no reaction occurred and starting material was recovered unchanged, Scheme 4.31. Therefore as Mitsunobu chemistry was clearly ineffective, loading the linker unit onto a polymer support using peptide coupling techniques was attempted.

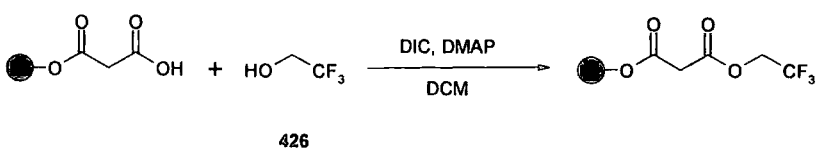


Scheme 4.31

4.2.2.2 Resin Loading using Peptide Coupling Techniques

Peptide coupling techniques were originally developed for the generation of amides from amines and carboxylic acids. However, their use in the reactions of alcohols with carboxylic acids to give esters has also been reported frequently in the literature. For example, Cobas *et al.* reported the coupling of fluorinated alcohol **425** with phenyl acetic acid using DIC and DMAP[154] and Hamper *et al.* loaded 1,1,1-trifluoroethanol **426** onto an acid resin using the same conditions, Scheme 4.32.[155]

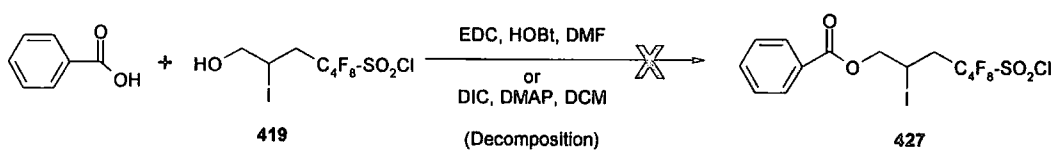




426

Scheme 4.32

With this attractive literature precedent available, it was decided to investigate the use of these strategies to couple sulfonyl chloride 419 with carboxylic acids. The solution phase reaction with benzoic acid was chosen as a mimic of carboxy polystyrene resin and the reaction was attempted using DIC and DMAP in DCM and EDC and HOBt in DMF, Scheme 4.33. However, in both cases none of the desired coupling product 427 was formed and many peaks in the ^{19}F NMR spectrum showed that the linker unit had been decomposed and was unstable to the reaction conditions. As sulfonyl chlorides investigated in Chapter 3 were unstable to amines, it seemed likely that the presence of DMAP or DMF was responsible for the observed decomposition. Therefore, it was decided to investigate the attachment of iodide 412 to a resin as it was known to be more stable. It was hoped that this could then be converted to the sulfonyl chloride while attached to a solid support.



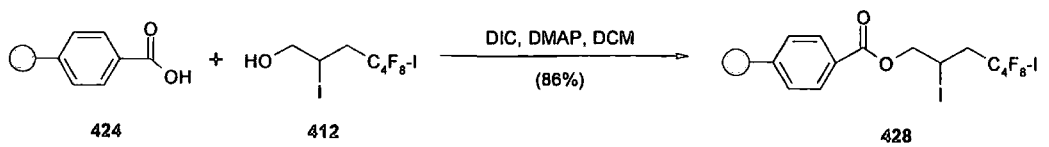
419 (Decomposition) 427

Scheme 4.33

4.2.2.3 Building up Resin-bound Sulfonyl Chlorides

As attempts to load sulfonyl chloride 419 onto resins directly had proved unsuccessful, it was decided to load iodide 412 instead and try and generate the corresponding sulfonyl chloride on the solid support. This had the advantage that iodide 412 was known to be more stable to a range of reaction conditions when compared to the sulfonyl chloride. The reaction with acetyl chloride described in Section 4.2.2.2 indicated that iodide 412 was tolerant of DMAP and triethylamine. Thus, repeating the coupling reaction using DIC and DMAP yielded resin-bound iodide 428, Scheme 4.34. The reaction was monitored by IR spectroscopy and after shaking for 16 h, the acid C=O stretch of the starting resin seen at 1680 cm^{-1} had been completely replaced by an ester C=O stretch at

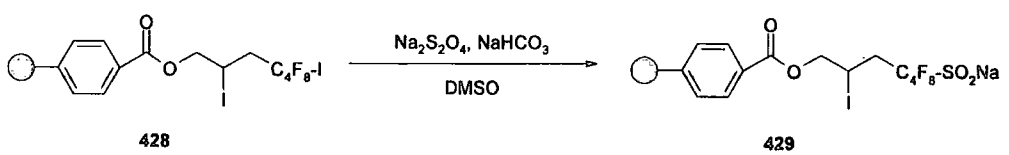
1720 cm^{-1} in the IR spectrum. The increase in mass of the resin indicated a loading of 86% based upon the maximum theoretical loading of the resin.



424 412 428

Scheme 4.34

With resin-bound iodide 428 in hand, attention turned to the sulfonation reaction. This reaction was incompatible with solid phase synthesis when attempted on eugenol derived iodide 319 bound to Wang resin, as described in Section 2.1.2.3. However, on this occasion the solid phase sulfonation proved more promising. Treatment of resin-bound iodide 428 with 10 equivalents of sodium dithionite in DMSO, Scheme 4.35, resulted in 25% conversion to resin-bound sodium sulfite 429 in 24 h. The reaction was monitored by ^{19}F NMR spectroscopy and the appearance of a CF_2-SO_2Na signal at –127 ppm confirmed that the reaction was proceeding. In order to drive it to completion, the reaction was warmed to 40 °C for a further 24 h and after this time complete conversion to sodium sulfite 429 had occurred. Only the CF_2-SO_2Na signal was observed in the ^{19}F NMR spectrum and the CF_2-I signal at –59 ppm had completely disappeared.

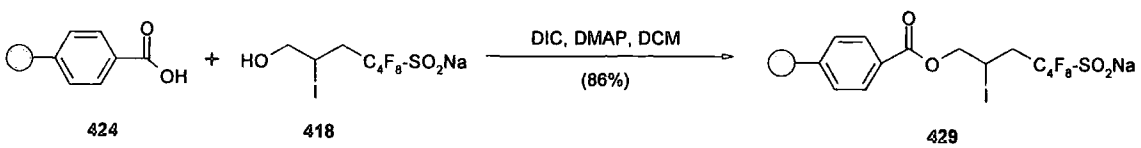


428 429

Scheme 4.35

Alternatively, resin-bound sodium sulfite 429 could also be obtained by loading sodium sulfite 418 onto carboxy polystyrene using analogous coupling conditions to those previously described, Scheme 4.36. This was confirmed by analysis of

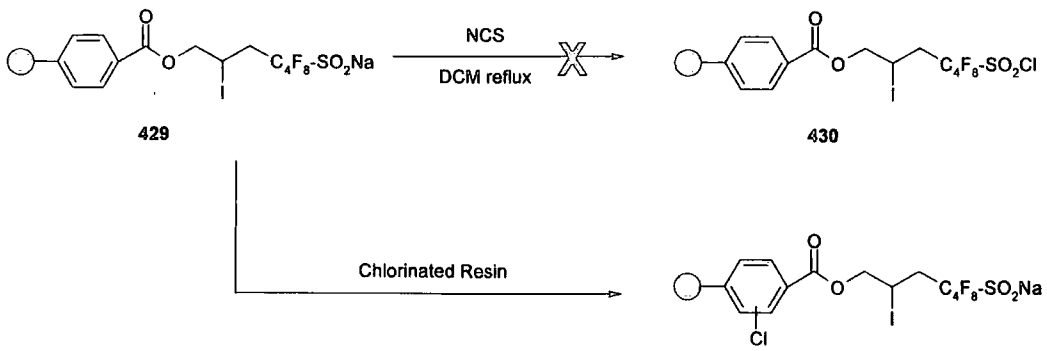
the resin by ^{19}F NMR spectroscopy which showed a CF_2-SO_2Na signal at –127 ppm.



424 418 429

Scheme 4.36

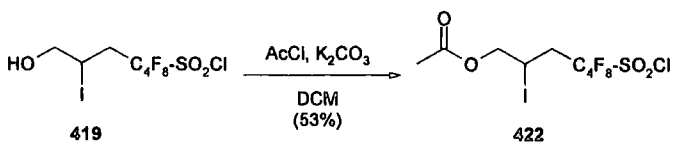
With significant quantities of resin-bound sodium sulfite 429 in hand, attention turned to its conversion to the corresponding sulfonyl chloride 430, Scheme 4.37. Initially this was attempted using 2 equivalents of *N*-chlorosuccinimide and shaking the reaction at rt. However, after 24 h no reaction had occurred and no CF_2-SO_2Cl signal was seen in the ^{19}F NMR spectrum. Therefore an additional 5 equivalents of *N*-chlorosuccinimide was added and the reaction was heated to reflux. Unfortunately, after a further 24 h there was still no sulfonyl chloride signal present in the ^{19}F NMR spectrum. It was decided to analyse the resin by IR spectrometry at this stage but there were no sulfonyl chloride stretches present. However, when comparing the IR spectrum to that of resin-bound sodium sulfite 429, it was noticed that a stretch had appeared at 875 cm^{-1}. This signal corresponded to a C-Cl bond which is suggestive of *N*-chlorosuccinimide preferentially chlorinating the aromatic groups on the resin over the sodium sulfite salt and accounted for the failure of the reaction. Therefore, this was not a viable route to resin-bound sulfonyl chloride 430 and so it was decided once more to focus efforts upon loading the sulfonyl chloride directly onto a solid support.



Scheme 4.37

4.2.2.4 Resin-bound Acid Chlorides

As attempts to load sulfonyl chloride 419 onto resins using Mitsunobu chemistry and peptide coupling techniques had been unsuccessful and it was not possible to build up the sulfonyl chloride on a solid support, an alternative strategy was required. From previous experience with sulfonyl chlorides in Chapter 3, it was known that they are intolerant of amine bases and so it was beneficial to attempt to functionalise the alcohol of sulfonyl chloride 419 using mild inorganic bases. Initially this was attempted in solution phase and treatment of sulfonyl chloride 419 with acetyl chloride in the presence of potassium carbonate, Scheme 4.38, gave protected sulfonyl chloride 422 in 53% yield. Monitoring the reaction by ^{19}F NMR spectroscopy showed no decomposition and the sulfonyl chloride remained intact, confirmed by the CF_2-SO_2Cl signal at –104 ppm. All other spectroscopic data agreed with that already reported for this compound in Section 4.2.1.



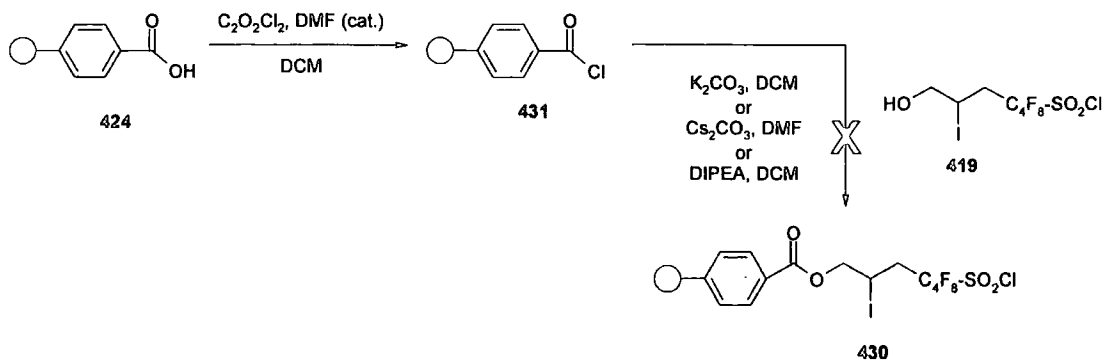
Scheme 4.38

This was a promising result and indicated that if a resin-bound acid chloride could be generated then it would be possible to load the linker unit onto a resin using mild conditions. Hamper *et al.* were able to generate resin-bound acid

chlorides by simple treatment of resin-bound carboxylic acids with oxalyl chloride.[155]

Carboxypolystyrene Resin

Carboxypolystyrene 424 was treated with 2 equivalents of oxalyl chloride and 1 drop of DMF and stirred overnight at room temperature, Scheme 4.39. After this time the resin was analysed by IR spectroscopy and the reaction was complete giving resin-bound acid chloride 431. The acid C=O stretch of the starting resin seen at 1680 cm^{-1} had been completely replaced by an acid chloride C=O stretch at 1770 cm^{-1} in the IR spectrum. There was also a second signal at 1735 cm^{-1} in the IR spectrum resulting from Fermi resonance. This second signal was due to an overtone of the C-Cl stretch observed at 875 cm^{-1} in Fermi resonance with the C=O signal. The signal at 1735 cm^{-1} is approximately 2 x 875 cm^{-1} as overtones occur at multiples of the normal frequency. With this resin-bound acid chloride in hand, attention turned to loading the sulfonyl chloride linker unit. However, treatment of acid chloride resin 431 with 5 equivalents of sulfonyl chloride 419 and potassium carbonate resulted in no significant loading of the linker unit. Analysis of the resin by ^{19}F NMR spectroscopy suggested that some sulfonyl chloride had been loaded, but there was no increase in the mass of the resin and there was no ester C=O stretch observed in the IR spectrum. This suggested that a very small amount of sulfonyl chloride was loaded, sufficient to be detected by ^{19}F NMR spectroscopy, but not enough for this to be a general route to a perfluorosulfonyl linker. To try to improve the loading, the reaction was repeated using caesium carbonate in DMF as it was more soluble than potassium carbonate, but again no loading was seen. Changing to DIPEA in the hope that sulfonyl chloride 419 would react before decomposition could occur was also unsuccessful and decomposition was observed by many peaks in the ^{19}F NMR spectrum. It was thought that possibly the poor reactivity was due to acid chloride 431 being too close to the polystyrene matrix of the resin. Therefore, to obtain a more reactive acid chloride it was decided to functionalise amino TentaGel with a carboxylic acid.

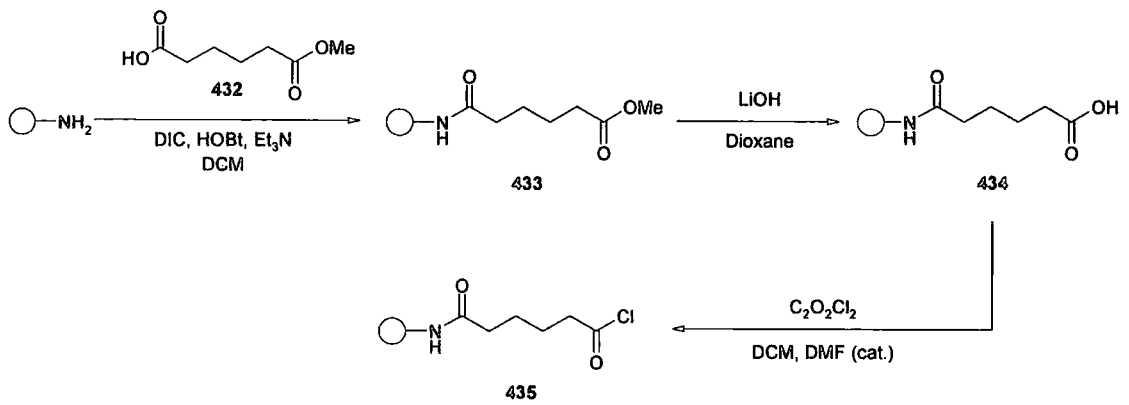


424 431 419 430

Scheme 4.39

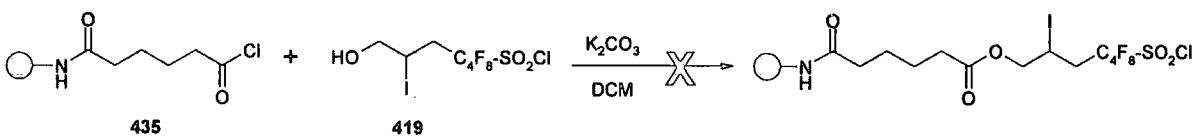
Adipic Acid Functionalised TentaGel Resin

The PEG grafts on amino TentaGel are known to hold reactive sites on the resin away from the polystyrene matrix and improve reactivity as discussed in Chapter 1. To this end, the work of Stieber and Waldmann was investigated as they had shown that it was possible to functionalise amino TentaGel with carboxylic acids.[156] Therefore TentaGel was functionalised with adipic acid methyl ester 432 using diisopropyl azodicarboxylate (DIC), hydroxybenzotriazole and triethylamine, Scheme 4.40. Analysis of a small amount of resin-bound ester 433 by IR spectroscopy showed an amide C=O stretch at 1654 cm^{-1} and an ester C=O stretch at 1740 cm^{-1} in the IR spectrum confirming that loading was successful. Hydrolysis of ester 433 was achieved using lithium hydroxide in dioxane and the ester C=O signal was replaced by and acid C=O signal at 1735 cm^{-1} in the IR spectrum. Subsequent treatment of resin-bound acid 434 with 2 equivalents of oxalyl chloride yielded acid chloride resin 435, confirmed by a shift of the acid C=O signal to an acid chloride C=O absorption at 1823 cm^{-1} in the IR spectrum.



Scheme 4.40

With acid chloride functionalised TentaGel 435 in hand, attention turned to the loading of sulfonyl chloride 419. The analogous reaction to that previously attempted using potassium carbonate was carried out but as before no reaction occurred. This was monitored by ^{19}F NMR spectroscopy which showed that no fluorinated material had been loaded onto the resin and analysis by IR spectroscopy indicated that the acid chloride had not reacted. No obvious explanation was apparent as to why sulfonyl chloride 419 was unreactive towards these resin-bound acid chlorides but future work will need to address this issue. It was decided to turn attention to functionalising the alcohol of alcohol 419 with another group which could be used as a point of attachment to a solid support.



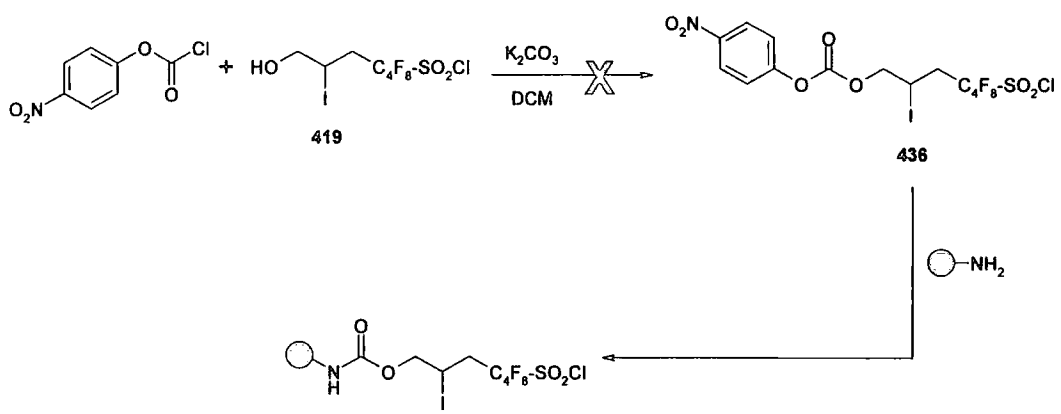
Scheme 4.41

4.2.2.5 Functionalising Sulfonyl Chloride 419

The loading of sulfonyl chloride onto solid supports through the alcohol group had proved unsuccessful. Therefore it was decided to functionalise this alcohol with an another group that possessed reactivity suitable for loading onto a solid support.

p-Nitro Phenol Carbonate

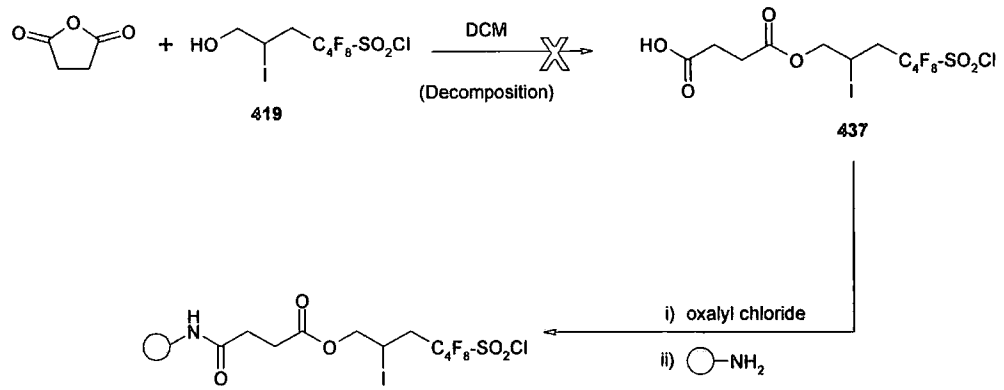
It was speculated that if the *p*-nitro phenol carbonate 436 of alcohol 419 could be prepared then this could be reacted with an amino resin resulting in displacement of *p*-nitro phenoxide, Scheme 4.43. To this end, alcohol 419 was treated with *p*-nitro phenol chloroformate in the presence of potassium carbonate. However, no reaction occurred and the sulfonyl chloride was recovered. Therefore it was decided to try to react sulfonyl chloride 419 with succinic anhydride in order to generate a carboxylic acid.



Scheme 4.42

Succinic Anhydride

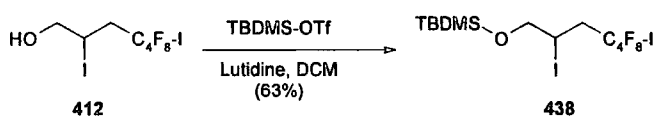
The reaction of sulfonyl chloride 419 was expected to yield carboxylic acid 437, Scheme 4.43. It was thought that this carboxylic acid could then be converted to the corresponding acid chloride and loaded onto an amino resin. However, reacting sulfonyl chloride 419 with succinic anhydride in THF resulted in decomposition observed as many peaks in the ^{19}F NMR spectrum. At this stage time restraints prevented further investigation of strategies for the loading of sulfonyl chloride 419 onto a resin. Therefore it was decided to demonstrate that it represented a viable linker motif in solution using the silyl-protected analogue. This work is described in Section 4.2.3.



Scheme 4.43

4.2.3 Silyl Protected Linker Unit

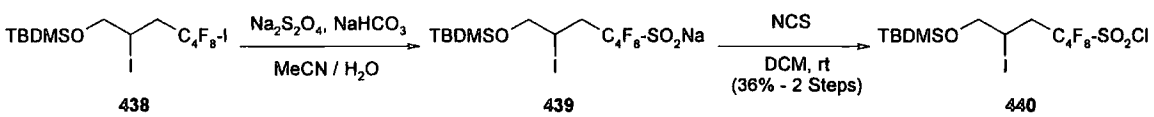
As the loading of sulfonyl chloride 419 onto a resin and subsequent solid phase chemistry was proving problematic, it was decided to demonstrate the viability of the system in solution phase using the silyl protected linker unit. To this end iodide 412 was protected with a TBDMS group by reacting it with *tert*-butyldimethylsilyl triflate in the presence of lutidine, Scheme 4.44. The reaction was monitored by TLC and after 16 h no starting material remained. Purification by flash chromatography gave protected iodide 438 in 63% yield and this was confirmed by the lack of an OH absorption observed in the IR spectrum and a molecular ion at m/z = 625 in the EI mass spectrum. An accurate mass could not be obtained for iodide 438 due to the poor resolution of the low resolution spectrum resulting from fragmentation of the TBDMS group.



Scheme 4.44

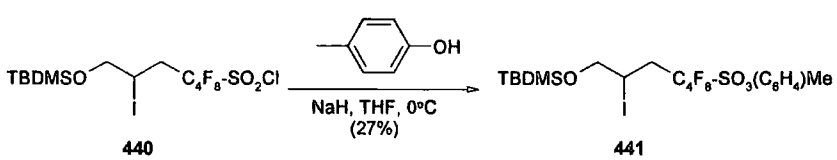
Sulfonation of protected iodide 438 was carried out using 2 equivalents of sodium dithionite to generate sodium sulfite 439, Scheme 4.45, and monitored using ^{19}F NMR spectroscopy. After stirring overnight at room temperature, the CF_2-I signal at –59 ppm in the ^{19}F NMR spectrum had been completely replaced by a CF_2-SO_2Na signal at –127 ppm indicating that the reaction had gone to completion.

Sodium sulfite 439 was then treated with *N*-chlorosuccinimide to generate sulfonyl chloride 440. The reaction was monitored by ^{19}F NMR spectroscopy and the CF_2-SO_2Na signal at –127 ppm was replaced by a CF_2-SO_2Cl signal at –104 ppm in the NMR spectrum and purification by flash chromatography gave sulfonyl chloride 440 in 36% yield. Sulfonyl chloride 440 was confirmed by sulfonyl chloride stretches at 1213 and 1419 cm^{-1} in the IR spectrum and molecular ions at m/z = 541 and 543 (3 : 1) in the EI mass spectrum corresponding to the loss of a *tert*-butyl group from the molecular ion.



Scheme 4.45

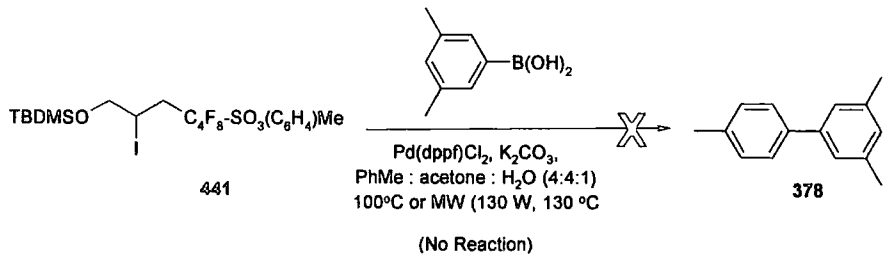
With sulfonyl chloride 440 in hand, attention turned to generation of the corresponding perfluorosulfonate ester 441. This was achieved by treatment of a solution of sulfonyl chloride 440 with a pre-formed solution of sodium phenoxide at 0 °C, Scheme 4.46. The reaction was monitored by ^{19}F NMR spectroscopy and after 4 h the CF_2-SO_2Cl signal at –104 ppm had been completely replaced by a CF_2SO_3Ar signal at –108 ppm in the NMR spectrum. Purification by flash chromatography gave sulfonate ester 440 in 27% yield, confirmed by a molecular ion at m/z = 613 in the EI mass spectrum (M -*t*-Bu).



Scheme 4.46

It was then necessary to test the viability of sulfonate ester 441 in a Suzuki cross-coupling reaction. Conditions chosen were those recently reported by Zhang *et al.* for the Suzuki reactions of perfluoroctanesulfonates but the use of $Pd(dppf)Cl_2$ and potassium carbonate in toluene, acetone and water were not active for

sulfonate ester 441, Scheme 4.47.[157] After 24 h at 100 °C only starting material was observed in the ^{19}F NMR spectrum. Therefore the reaction was repeated in a microwave at 130 °C and 150 W but this was no more successful and biphenyl 378 was not generated. Time restraints did not permit the synthesis of any more of sulfonate ester 441 and so a recommendation for future work is to screen it in an array of Suzuki reactions analogous to those described in Chapter 3.



Scheme 4.47

4.3 Conclusions

- The reactions of 1,4-diiodooctafluorobutane with a range of alkenes were screened to find a simple spacer unit which could be used to attach a linker to a solid support. However, reactions were problematic and no suitable spacer unit was developed.

- A second generation perfluorosulfonyl chloride linker unit 412 was derived from allyl alcohol following a novel oxidation of sodium sulfite salts to sulfonyl chlorides using *N*-chlorosuccinimide.

- The loading of this linker unit onto a solid support using a range of different methods was unsuccessful. The poor reactivity is not understood and future work is required in this area to develop solid phase chemistry.

- The viability of generating perfluorosulfonate esters using this linker unit was demonstrated using the silyl-protected analogue. At this stage diversity cleavage has not been demonstrated and future work will screen this system in arrays of Suzuki cross-coupling reactions.

CHAPTER 5

CONCLUSIONS AND FUTURE WORK

5 Conclusions

In conclusion, this thesis has reported a number of different approaches towards a perfluorosulfonyl diversity linker unit:

- Eugenol was shown to react with diiodoperfluoroalkanes in the presence of AIBN. The resulting iodide could be oxidised to a perfluorosulfonic acid provided that the free phenol was protected. The phenol was also used as a point of attachment to a solid support. However, the generation of a solid supported perfluorosulfonic acid was not feasible.

- A range of commercially available alternative starting materials were investigated. However, attempts to derive a perfluorosulfonyl linker unit from thiols, (fluorosulfonyl)difluoroacetic acid, bromotetrafluorobutan-1-ol and fluorinated Grignard reagents all proved problematic and were abandoned.

- A bis-sulfonyl chloride linker unit was derived from diiodoperfluoroalkanes. This was converted to bis-sulfonamides and bis-sulfonate esters to demonstrate the feasibility of generating solid supported perfluorosulfonate esters on amino-resins. Arrays of Suzuki reaction conditions were screened on the bis-sulfonate esters to determine optimum conditions for diversity cleavage. The bis-sulfonyl chloride linker was loaded onto TentaGel but the sulfonamide bond proved unstable and the linker was cleaved during attempts to load phenols.

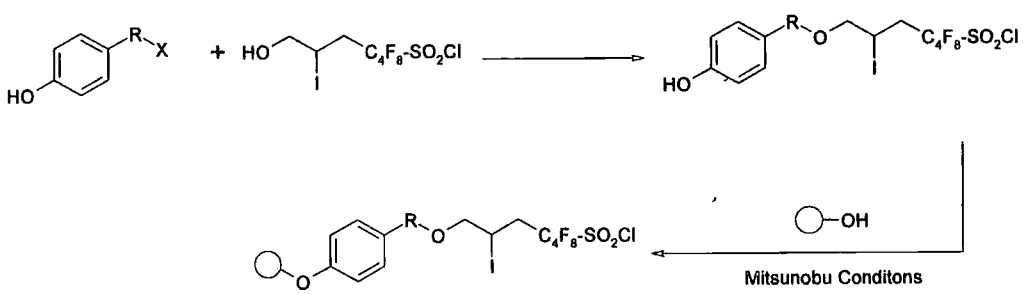
- Alternative spacer units were sought to improve the stability of the perfluorosulfonyl chlorides. However, diiodoperfluoroalkanes proved unreactive to a range of alkenes.

- A second generation linker unit has been derived from allyl alcohol. The feasibility of loading phenols onto this linker unit has been demonstrated

using the silyl protected linker. However, at this stage loading it onto a solid support has proved problematic and further work is required in this area.

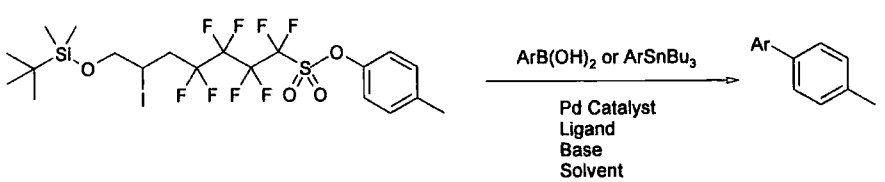
5.1 Future Work

Future work on this project should concentrate on developing conditions to load the allyl-alcohol-derived linker unit described in Chapter 4 onto a solid support. To this end, it may be advantageous to protect the alcohol with some group bearing a phenol. Time restraints prevented investigation of this route but it is speculated that the phenol could be loaded onto a solid support using Mitsunobu chemistry developed in Chapter 2, Scheme 5.1.



Scheme 5.1

In order to develop diversity cleavage conditions for this system, it is also recommended that the synthesis of the silyl protected linker unit, which at present has been formed in only 9% overall yield, be optimised. With significant quantities in hand it can then be screened in arrays of Suzuki and Stille cross-coupling reactions, Scheme 5.2.



Scheme 5.2

CHAPTER 6

EXPERIMENTAL PROCEDURES

6 General Procedures

Reactions were carried out under an atmosphere of argon in dry glassware unless otherwise stated.

Reagents

Reagents were used as supplied unless otherwise stated. *p*-Cresol was recrystallised from petroleum ether prior to use. Triethylamine was distilled from sodium hydroxide. Palladium catalysts were obtained from the Aldrich Chemical Company, except palladium acetate which was obtained from Lancaster, and all were used as received. Sodium hydride was obtained in powder form from the Aldrich Chemical Company and used as received. AIBN was obtained from Acrōs Organics and stored in a refrigerator.

Solvents

Dry DMF was obtained from the Aldrich Chemical Company and used as received. THF was distilled from sodium benzophenone ketyl and dry DCM was distilled over calcium hydride under an atmosphere of nitrogen. 40-60 Petroleum ether refers to the fraction of petroleum ether which boils between 40 and 60 °C and was redistilled prior to use. Solvents for cross-coupling reactions were degassed (N_2 or Ar) prior to use. All other solvents were used as received. Where mixtures of solvents were used, ratios given refer to volumes used.

Chromatography

Flash chromatography was carried out using silica gel 40-60μ 60A. Analytical thin layer chromatography (TLC) was performed using aluminium plates precoated with silica gel (60 F_{254}), and materials were visualised by UV radiation at 254 nm, or by staining with potassium permanganate in aqueous sodium carbonate or phosphomolybdic acid in ethanol.

IR Spectroscopy

IR spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. Liquids were recorded as thin layers between NaCl plates, solids were recorded as compression formed discs made using KBr and resins were recorded by attenuated total reflection (ATR) using a golden gate accessory.

NMR Spectroscopy

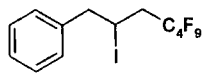
^{1}H NMR spectra were analysed in $CDCl_3$ or CD_3OD on Varian Oxford 200, Bruker AM250, Varian Unity 300, Varian VXR 400 or Varian Inova 500 spectrometers and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant ^{2}J (2 = number of bonds, Hz), assignment). The residual protic solvents $CHCl_3$ (δ_H = 7.26 ppm) or CD_3OD (δ_H = 3.31 ppm) were used as internal references. ^{13}C NMR spectra were recorded at 63 MHz on the Bruker AM250 spectrometer or 125 MHz on the Varian Inova 500 spectrometer and are reported, where appropriate, as chemical shift δ (ppm) (number of carbons, multiplicity, coupling constant $^{2}J_{C\text{-}F}$ (2 = number of bonds, C-F = coupling between ^{13}C and ^{19}F nuclei, Hz), assignment). The central resonance of $CDCl_3$ (δ_C = 77.00 ppm) was used as an internal reference. ^{19}F NMR spectra were analysed in $CDCl_3$ at 188 MHz on the Varian Oxford 200 spectrometer, 283 MHz on the Varian Unity 300 spectrometer or 375 MHz on the Varian Inova 500 spectrometer and are reported as δ (ppm) (number of fluorine atoms, multiplicity, assignment). ^{19}F spectroscopic data were referenced to $CFCl_3$ (δ_F = 0 ppm). Chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0 ppm) and coupling constants are quoted in Hertz.

Mass Spectrometry

Low resolution mass spectra were obtained on VG Analytical 7070E or VG Autospec Organic Mass spectrometers. High resolution mass spectra were obtained from the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea and acknowledgement is made to them for this service. Electrospray or electron ionisation methods were used to generate ions.

6.1 Experimental Procedures

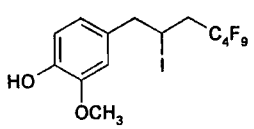
(4,4,5,5,6,6,7,7,7-Nonafluoro-2-iodoheptyl)benzene 294[150]



294

Allylbenzene (1.18 g, 1.32 cm^3, 10.0 mmol) was added dropwise over 5 min to a stirred solution of AIBN (0.16 g, 1.0 mmol) and 1-iodononafluorobutane (5.0 g, 2.49 cm^3, 14.4 mmol). The reaction was then heated to 70 °C and stirred for 48 h. After this time, the crude reaction mixture was cooled and distilled using a Kugelrohr bulb-to-bulb distillation apparatus (oven temperature 125 °C) to yield title compound 294 as a pale yellow oil (2.37 g, 51%); *m/z* (EI) 464 (M^+); ν_{max}(film) 1350, 1235, 737 and 699 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 2.85 - 3.04 (2H, m, C*H*$_2$$CF_2$), 3.30 (1H, dd, ^2J 11 Hz, ^3J 16 Hz, CH_ACH_B), 3.30 (1H, dd, ^3J 6 Hz, ^2J 11 Hz, CH_ACH_B), 4.49 – 4.55 (1H, m, C*H*I), 7.17 - 7.35 (5H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 19.2 (CHI), 40.6 (t, $^2J_{C\text{-}F}$ 20 Hz, CH_2CF_2) 46.9 (CH_2), 127.3, 128.6 (2C), 128.9 (2C), 138.5, ca. 100 - 130 (4 x v. weak m, 3 x CF_2 and CF_3); δ_F ($CDCl_3$; 188 MHz) -81.42 (3F, m, C*F*$_3$), -113.53 (2F, m, C*F*$_2$$CH_2$), -124.98 (2F, m, C*F*$_2$), -126.32 (2F, m, C*F*$_2$). All data agreed with that previously reported.[150]

2-Methoxy-4-(4',4',5',5',6',6',7',7',7'-nonafluoro-2'-iodoheptyl)phenol 296



296

Eugenol (1.64 g, 1.54 cm^3, 10.0 mmol) was added dropwise over 5 min to a stirred solution of AIBN (0.82 g, 5.0 mmol) and 1-iodononafluorobutane (3.46g, 1.72 cm^3, 10.0 mmol). After addition was complete, the reaction was heated to 70 °C and stirred for 48 h. Purification by flash chromatography (petroleum ether/ethyl acetate [8.5:1.5]) yielded the title compound 296 a pale yellow oil

(1.93 g, 38%); *m/z* (EI) 509 (M-H$^+$, 20%), 383 (M-I, 70%); HRMS (EI) 509.9727, $C_{14}H_{12}F_9O_2I$ requires 509.9733; ν_{max}(film) 3030 (br. OH), 1350, 1235, 737 and 699 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.80-2.91 (2H, m, C*H*$_2$CF$_2$), 3.14 (1H, dd, ^3J 8.5 Hz, ^2J 15 Hz, CH$_A$C*H*$_B$), 3.20 (1H, dd, ^3J 6 Hz, ^2J 15 Hz, C*H*$_A$CH$_B$), 3.90 (3H, s, OC*H*$_3$), 4.39-4.46 (1H, m, C*H*I), 5.64 (1H, s, O*H*), 6.68 - 6.71 (2H, m, Ar*H*), 6.87 - 6.89 (1H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 20.1 (CHI), 40.5 (t, $^2J_{C-F}$ 21 Hz, CH$_2$CF$_2$), 47.0 (CH$_2$CHI), 56.2 (OCH$_3$), 111.6, 114.7, 122.2, 130.6, 145.1, 146.7, ca. 100 - 130 (4 x v. weak m, 3 x CF$_2$ and CF$_3$); δ_F ($CDCl_3$; 188 MHz) -81.38 (3F, m, C*F*$_3$), -113.56 (2F, m, C*F*$_2$CH$_2$), -124.99 (2F, m, C*F*$_2$), -126.30 (2F, m, C*F*$_2$).

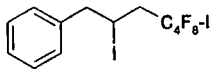
1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 302[158]

C_4F_9-SO_3H

302

Sodium dithionite (3.48 g, 29 mmol) and sodium hydrogen carbonate (2.02 g, 34.8 mmol) were added to a stirred suspension of 1-iodononafluorobutane (10.0 g, 28.9 mmol) in acetonitrile (7.5 cm^3) and water (5 cm^3) and stirred at room temperature for 20 h. After this time, the reaction mixture was filtered and evaporated under reduced pressure to yield sodium sulfite salt 301 as a white residue. This was redissolved in water (15 cm^3), cooled to 0 °C and hydrogen peroxide was added dropwise (3.10 cm^3, 37% *w/w* solution, 33 mmol). The reaction was stirred for 20 h at 0 °C and then water (20 cm^3) and diethyl ether (20 cm^3) were added. The layers were separated and the organic layer was extracted with water (3 x 20 cm^3). The combined aqueous layers were acidified (1M HCl) and extracted with diethyl ether (3 x 30 cm^3). The combined diethyl ether fractions were dried ($MgSO_4$) and evaporated to yield the title compound 302 as a yellow oil without further purification (4.12 g, 47%); *m/z* (ES$^-$) 299 (M-H$^+$, 25%), 283 ($C_4F_9SO_2$, 100%); ν_{max}(film) 3357 (OH), 1187, 1137, 1021, 657 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 7.92 (1H, br. s, SO$_3$*H*); δ_F ($CDCl_3$; 188 MHz) -83.07 (3F, m, C*F*$_3$), -125.46 (2F, s, C*F*$_2$), -128.36 (2F, s, C*F*$_2$S), -132.21 (2F, m, C*F*$_2$). All data agreed with that previously published.[158]

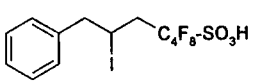
(4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptyl)benzene 304



304

Allylbenzene (1.29 g, 1.45 cm^3, 11.0 mmol) was added dropwise over 5 min to a stirred solution of AIBN (0.18 g, 1.10 mmol) and 1,4-diiodo octafluorobutane (5.0 g, 2.03 cm^3, 11.0 mmol). The reaction was then heated to 70 °C and stirred for 48 h. After this time, the crude reaction mixture was cooled and distilled using a Kugelrohr bulb-to-bulb distillation apparatus (oven temperature 100 °C) to yield title compound 304 a pale yellow oil (4.60 g, 73%); *m/z* (EI) 572 (M^+, 10%), 445 (M-I, 70%); HRMS (EI) 571.8735, $C_{13}H_{10}F_8I_2$ requires 571.8739; ν_{max}(film) 1181, 1127, 746 and 699 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.78-3.00 (2H, m, C*H*$_2$CF$_2$), 3.19 (1H, dd, ^3J 9 Hz, ^2J 14 Hz, CH$_A$C*H*$_B$), 3.31 (1H, dd, ^3J 6 Hz, ^2J 14 Hz, C*H*$_A$CH$_B$), 4.47 (1H, m, C*H*I), 7.20 - 7.38 (5H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 19.8 (CHI), 40.8 (t, $^2J_{C\text{-}F}$ 21 Hz, CH$_2$CF$_2$), 47.0 (CH$_2$), 127.3, 128.6 (2C), 129.0 (2C), 138.6, ca. 100 - 130 (4 x v. weak m, 4 x CF$_2$); δ_F ($CDCl_3$; 188 MHz) -59.00 (2F, m, C*F*$_2$I), -113.05 (2F, m, C*F*$_2$CH$_2$), -113.07 (2F, m, C*F*$_2$), -123.46 (2F, m, C*F*$_2$).

1,1,2,2,3,3,4,4-Octafluoro-6-iodo-7-phenylheptane-1-sulfonic Acid 305

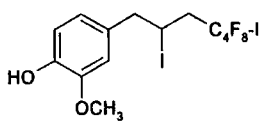


305

(4',4',5',5',6',6',7',7'-Octafluoro-2',7'-diiodoheptyl)benzene 304 (2.08 g, 3.5 mmol) was added to a stirred suspension of sodium dithionite (0.61 g, 3.5 mmol) and sodium hydrogen carbonate (0.35 g, 4.2 mmol) in acetonitrile (5 cm^3) and water (2.5 cm^3) and stirred at room temperature for 20 h. After this time, the reaction mixture was filtered and evaporated under reduced pressure. The residue was redissolved in water (3.5 cm^3), cooled to 0 °C and hydrogen peroxide (0.42 cm^3, 35% *w/w* solution, 4.2 mmol) was added dropwise. The reaction was stirred for 20 h at 0 °C and then water (20 cm^3) and diethyl ether (20 cm^3) were added. The

layers were separated and the organic layer was extracted with water (3 x 20 cm^3). The combined aqueous layers were acidified with 1M HCl and extracted with diethyl ether (3 x 30 cm^3). The combined diethyl ether fractions were dried ($MgSO_4$) and evaporated to yield the title compound **305** as a yellow oil without further purification (0.89 g, 44%); *m/z* (ES^-) 525 ($M\text{-}H^+$, 100%); HRMS (ES^-) 524.9260 ($M\text{-}H^+$), $C_{13}H_{10}F_8SO_3I$ requires 524.9268; ν_{max}(film) 3475 (OH), 1767, 1170, 1119, 1021, 909, 700 and 649 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.83 - 3.02 (2H, m, CH_2CF_2), 3.11 – 3.28 (2H, m, CH_2), 4.32 - 4.45 (1H, m, CHI), 7.10 - 7.26 (5H, m, ArH), 9.28 (1H, br. s, SO_3H); δ_C ($CDCl_3$; 100 MHz) 19.7 (CHI), 40.5 (t, $^2J_{C\text{-}F}$ 21 Hz, CH_2CF_2) 47.0 (CH_2), 127.3, 128.5 (2C), 129.1 (2C), 138.6, ca. 100 - 130 (4 x v. weak m, 4 x CF_2); δ_F ($CDCl_3$; 188 MHz) -113.23 (2F, m, CF_2CH_2), -122.21 (2F, m, CF_2), -124.13 (2F, m, CF_2S), -127.99 (2F, m, CF_2).

2-Methoxy-4-(4',4',5',5',6',6',7',7'-octafluoro-2',7'-diiodoheptyl)phenol **306**

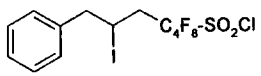


306

Eugenol (0.36 g, 0.34 cm^3, 2.20 mmol) was added dropwise to a stirred solution of AIBN (0.18 g, 1.10 mmol) and 1,4-diiodo octafluorobutane (1.00g, 0.40 cm^3, 2.20 mmol). The reaction was heated to 70 °C and stirred for 24 h. After this time, purification by flash chromatography (pet. ether/ethyl acetate [8:2]) yielded the title compound **306** as a pale yellow oil (0.63 g, 63% based upon eugenol); *m/z* (EI) 618 (M^+, 20%), 491 (M-I, 70%); HRMS (EI) 617.8793, $C_{14}H_{12}F_8I_2O_2$ requires 617.8786; ν_{max}(film) 3499 (br. OH), 2969, 2939, 1679, 1514 and 1182 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.78-2.92 (2H, m, CH_2CF_2), 3.13 (1H, dd, ^3J 8.5 Hz, ^2J 15 Hz, CH_ACH_B), 3.20 (1H, dd, ^3J 6 Hz, ^2J 15 Hz, CH_ACH_B), 3.90 (3H, s, OCH_3), 4.27 (1H, m, CHI), 5.64 (1H, br. s, OH), 6.67-6.71 (2H, m, ArH), 6.87-6.90 (1H, m, ArH); δ_C ($CDCl_3$; 100 MHz) 20.7 (CHI), 40.5 (t, $^2J_{C\text{-}F}$ 21 Hz, CH_2CF_2) 46.7 (CH_2CHI), 55.9 (OCH_3), 111.4 (ArCH), 114.4 (ArCH), 122.0 (ArCH), 130.4, 144.8,

146.5, 4 x CF_2 signals not observed; δ_F ($CDCl_3$; 188 MHz) -59.04 (2F, m, CF_2I), -113.08 (2F, m, CF_2), -113.37 (2F, m, CF_2), -123.11 (2F, m, CF_2).

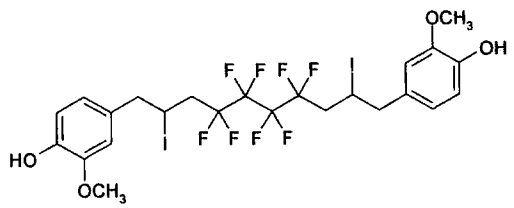
1,1,2,2,3,3,4,4-Octafluoro-6-iodo-7-phenylheptane-1-sulfonyl Chloride 310



310

(4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptyl)benzene 304 (2.06 g, 3.5 mmol) was added to a stirred suspension of sodium dithionite (0.61 g, 3.5 mmol) and sodium hydrogen carbonate (0.35 g, 4.2 mmol) in acetonitrile (12 cm^3) and water (6 cm^3). The reaction was stirred at room temperature for 20 h and after this time it was filtered and evaporated under reduced pressure. The residue was redissolved in water (10 cm^3), cooled to 0 °C and chlorine was bubbled through the solution for 20 min. The aqueous layer was then extracted with DCM (4 x 10 cm^3). The combined organic fractions were dried ($MgSO_4$) and evaporated to yield the crude product. Purification by distillation using a Kugelrohr bulb-to-bulb distillation apparatus (oven temperature 100 °C) gave title compound 310 as a yellow oil (0.81 g, 37%); *m/z* (ES^-) 567 : 569 (3 : 1, $M+Na^+$, 10%); ν_{max}(film) 1416 (SO_2Cl), 1217 (SO_2Cl), 1107, 752 and 700 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.92 - 3.14 (2H, m, CH_2CF_2), 3.51 - 3.77 (2H, m, CH_2), 4.37 - 4.45 (1H, m, CHI), 7.11 - 7.35 (5H, m, ArH); δ_C ($CDCl_3$; 100 MHz) 19.7 (CHI), 38.2 (t, $^2J_{C-F}$ 20 Hz, CH_2CF_2) 44.9 (CH_2), 127.4, 128.7 (2C), 128.8 (2C), 129.4, ca. 100 - 130 (4 x v. weak m, 4 x CF_2); δ_F ($CDCl_3$; 283 MHz) -104.33 (2F, m, CF_2SO_2Cl), -113.35 (2F, m, CF_2), -119.26 (2F, m, $CF_2CF_2SO_2Cl$), -123.41 (2F, m, CF_2).

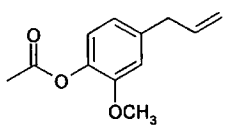
2-Methoxy-4-(4',4',5',5',6',6',7',7'-octafluoro-2',9'-diiodo-10'-(3"-methoxy-4"-hydroxy phenyl)-decyl)phenol 311



311

Further flash chromatography of the crude reaction mixture of phenol 306 (pet. ether/ ethyl acetate [7:3]) yielded bis-coupled by-product 311 as a pale yellow oil (0.32 g, 37% based upon eugenol); *m/z* (EI) 782 (M^+, 50%), 655 (M-I, 50%), 527 ($M-I_2$, 30%); HRMS (EI) 781.9623, $C_{24}H_{24}F_8I_2O_4$ requires 781.9631; ν_{max}(film) 3499 (br. OH), 2969, 2939, 1679, 1514 and 1182 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 2.79-2.90 (4H, m, 2 x C*H*$_2$CF$_2$), 3.12 (2H, dd, ^3J 8.5 Hz, ^2J 14.5 Hz, CH$_A$C*H*$_B$), 3.19 (2H, dd, ^3J 6 Hz, ^2J 14.5 Hz, C*H*$_A$CH$_B$), 3.89 (6H, s, 2 x OC*H*$_3$), 4.42 (2H, m, 2 x C*H*I), 5.68 (2H, br. s, 2 x O*H*), 6.68-6.70 (4H, m, 2 x Ar*H*), 6.86 - 6.88 (2H, m, 2 x Ar*H*); δ_C ($CDCl_3$; 125 MHz) 20.9 (CHI), 46.7 (t, $^2J_{C-F}$ 17 Hz, CH$_2$CF$_2$) 46.7 (CH$_2$CHI), 55.9 (OCH$_3$), 110.9 (2C, tt, $^2J_{C-F}$ 26 Hz, $^1J_{C-F}$ 212 Hz, 2 x CF$_2$), 111.4 (ArCH), 114.4 (ArCH), 117.7 (2C, tt, $^2J_{C-F}$ 24 Hz, $^1J_{C-F}$ 205 Hz, 2 x CF$_2$), 121.9 (ArCH), 130.4, 144.8, 146.4; δ_F ($CDCl_3$; 283 MHz) -113.40 (4F, m, 2 x C*F*$_2$), -123.90 (4F, m, C*F*$_2$).

4-Allyl-2-methoxyphenyl Acetate 316

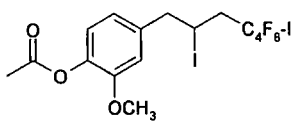


316

Eugenol (1.0 g, 0.94 cm^3, 6.1 mmol), acetic anhydride (2.5 g, 2.3 cm^3, 24.4 mmol) and lithium perchlorate (0.064 g, 0.6 mmol) were stirred at 40 °C for 18 h. After this time the reaction was quenched with water and the resulting mixture extracted with ethyl acetate (3 x 20 cm^3). The combined organic fractions were

dried ($MgSO_4$), filtered and evaporated to give the crude material. Purification by flash chromatography (pet. ether/ ethyl acetate [8:2]) yielded the title compound 316 as a clear oil (0.37 g, 30%); *m/z* (EI) 206 (M^+, 20%), 164 (M-OAc, 100%); HRMS (EI) 224.1282 (M+NH_4), $C_{12}H_{18}NO_3$ requires 224.1287; ν_{max}(film) 1765 (C=O), 1604, 1509 and 1034 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 2.31 (3H, s, C*H*$_3$), 3.40 (2H, d, ^3J 7 Hz, C*H*$_2$-CH), 3.81 (3H, s, OC*H*$_3$), 5.11 - 5.16 (2H, m, C*H*$_2$=CH), 5.96 - 6.04 (1H, m, CH_2=C*H*), 6.78 - 6.82 (2H, m, Ar*H*), 6.97 - 6.99 (1H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 20.3 (CH_3), 39.8 (CH_2), 53.4 (OCH_3), 112.4 (ArCH), 115.8 (CH_2=CH), 120.3 (ArCH), 122.2 (ArCH), 136.8 (CH_2=CH), 137.7, 138.7, 150.6, 168.8 (C=O).

2-Methoxy-4-(4',4',5',5',6',6',7',7'-octafluoro-2',7'-diiodoheptyl)phenyl Acetate 317

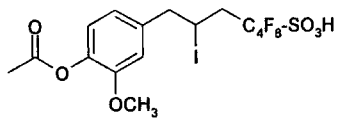


317

4-Allyl-2-methoxy-phenyl acetate 316 (0.30 g, 1.50 mmol) was added dropwise to a stirred solution of AIBN (0.12 g, 0.75 mmol) and 1,4-diiodooctafluorobutane (0.66 g, 0.27 cm^3, 1.50 mmol). The reaction was heated to 70 °C and stirred for 24 h. After this time, purification by flash chromatography (pet. ether/ethyl acetate [8.5:1.5]) yielded the title compound 317 as a pale yellow oil (0.39 g, 39%); *m/z* (EI) 660 (M^+, 10%), 618 (M-OAc, 90%), 491 (M-(I+OAc), 100%); HRMS (ES^+) 677.9256 (M+NH_4), $C_{16}H_{18}F_8I_2NO_3$ requires 677.9248; ν_{max}(film) 1766 (C=O), 1605, 1511, 1465, 1421 and 1370 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.31 (3H, s, C*H*$_3$), 2.78-2.97 (2H, m, C*H*$_2$$CF_2$), 3.16 (1H, dd, ^3J 9 Hz, ^2J 15 Hz, CH_AC*H*$_B$), 3.28 (1H, dd, ^3J 6 Hz, ^2J 15 Hz, C*H*$_A$$CH_B$), 3.84 (3H, s, OC*H*$_3$), 4.43 – 4.48 (1H, m, C*H*I), 6.77-6.80 (2H, m, Ar*H*), 6.99-7.00 (1H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 19.2 (CHI), 20.7 (CH_3C(O)), 40.8 (t, $^2J_{C-F}$ 21 Hz, CH_2CF_2) 46.6 (CH_2CHI), 55.9 (OCH_3), 94.0 (m, CF_2I), 113.1 (ArCH), 109.5 (m, CF_2), 110.7 (m,

$\mathbb{C}F_2$), 117.8 (m, $\mathbb{C}F_2$), 121.2 (Ar$\mathbb{C}$H), 122.8 (Ar$\mathbb{C}$H), 137.2, 138.9, 151.0, 169.0 ($\mathbb{C}$=O); δ_F ($CDCl_3$; 188 MHz) -59.03 (2F, m, C$\mathbb{F}_2$I), (-111.72) – (-114.62) (4F, m, 2 x C$\mathbb{F}_2$), -123.03 (2F, m, C$\mathbb{F}_2$).

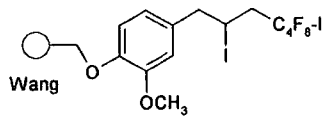
7-(4'-Acetoxy-3'-methoxyphenyl)-6-iodo-1,1,2,2,3,3,4,4–octafluoro heptane-sulfonic Acid 318



318

2-Methoxy-4-(4',4',5',5',6',6',7',7'-octafluoro-2',7'-diiodoheptyl)phenyl acetate 317 (0.18 g, 0.28 mmol) was added to a stirred suspension of sodium dithionite (0.048 g, 0.28 mmol) and sodium hydrogen carbonate (0.028 g, 0.33 mmol) in acetonitrile (1.5 cm^3) and water (1 cm^3) and stirred at room temperature for 20 h. After this time, the reaction mixture was filtered and evaporated under reduced pressure. The residue was redissolved in water (3.5 cm^3) and cooled to 0 °C. Hydrogen peroxide (0.03 cm^3, 35% *w/w* solution, 0.32 mmol) was added dropwise and the reaction was stirred for 24 h at 0 °C. Water (10 cm^3) and diethyl ether (10 cm^3) were then added. The layers were separated and the organic layer was extracted with water (3 x 10 cm^3). The combined aqueous layers were then acidified (1M HCl) and extracted with diethyl ether (5 x 5 cm^3). The combined diethyl ether fractions were dried ($MgSO_4$) and evaporated to yield the title compound 318 as a yellow oil without further purification (0.015 g, 16%); *m/z* (ES^-) 613 ($M\text{-}H^+$, 80%), 521 (100%); ν_{max}(film) 3357 (OH), 1767 (C=O), 1187, 1137, 1021 and 657 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.27 (3H, s, C$\mathbb{H}_3$), 2.80 - 3.02 (2H, m, C$\mathbb{H}_2CF_2$), 3.09 – 3.26 (2H, m, C$\mathbb{H}_2$), 4.32 - 4.44 (1H, m, C$\mathbb{H}$I), 6.73-6.76 (2H, m, Ar$\mathbb{H}$), 6.88-6.95 (1H, m, Ar$\mathbb{H}$); δ_C ($CDCl_3$; 100 MHz) 19.2 ($\mathbb{C}$HI), 20.7 ($\mathbb{C}H_3C(O)$), 40.8 (t, $^2J_{C\text{-}F}$ 21 Hz, $\mathbb{C}H_2CF_2$) 46.6 ($\mathbb{C}H_2CHI$), 55.9 (O$\mathbb{C}H_3$), 113.0 (Ar$\mathbb{C}$H), 121.2 (Ar$\mathbb{C}$H), 122.8 (Ar$\mathbb{C}$H), 137.4, 138.9, 150.9, 168.9 ($\mathbb{C}$=O), ca. 100 - 120 (4 x v. weak m, 4 x $\mathbb{C}F_2$); δ_F ($CDCl_3$; 188 MHz) -113.56 (2F, m, C$\mathbb{F}_2CH_2$), -122.22 (2F, m, C$\mathbb{F}_2$), -124.20 (2F, m, C$\mathbb{F}_2$S), -127.90 (2F, m, C$\mathbb{F}_2$).

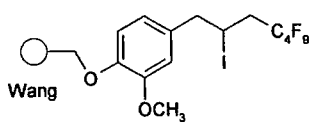
Wang-resin-bound 2-Methoxy-4-(4',4',5',5',6',6',7',7',7'-octafluoro-2',7'-diiodo heptyl) Phenol 319



319

Wang resin (0.26 g, 2.7 mmol/g, 0.71 mmol) was washed with DCM (5 cm^3) and anhydrous THF (3 x 5 cm^3). Triphenylphosphine (0.56 g, 2.14 mmol) and 2-methoxy-4-(4', 4', 5', 5', 6', 6', 7', 7'-octafluoro-2', 7'-diiodoheptyl)phenol **306** (1.32 g, 2.14 mmol) were added and the mixture suspended in anhydrous THF (4 cm^3). DIAD (0.43 g, 0.42 cm^3, 2.14 mmol) was added dropwise over 15 min and the reaction shaken at rt. After 16 h, the resin was filtered, washed with anhydrous THF, anhydrous DMF, MeOH, DCM, Et_2O, $CHCl_3$, DMF:water [1:1] and DMF (7.5 cm^3 each) and dried to yield the functionalised resin (0.47 g). A small portion of the functionalised resin (0.02 g) was shaken with 5% TFA/DCM (1.5 cm^3) for 30 min. After this time, the resin was filtered and washed with DCM (5 cm^3) and ether (5 cm^3). The combined filtrates were evaporated under reduced pressure to yield phenol **306** (5.7 mg, 0.009 mmol/0.02 g = 0.46 mmol/g, corresponding to 45% loading assuming quantitative cleavage and recovery), confirmed by ^1H and ^{19}F NMR spectroscopic data reported above.

Wang-resin-bound 2-Methoxy-4-(4',4',5',5',6',6',7',7',7'-nonafluoro-2'-diiodo heptyl)phenol 328

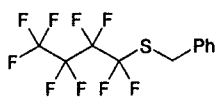


328

Wang resin (0.08 g, 2.7 mmol/g, 0.21 mmol) was washed with DCM (5 cm^3) and anhydrous THF (3 x 5 cm^3). To this was added triphenylphosphine (0.17 g, 0.64 mmol) and 2-methoxy-4-(4', 4', 5', 5', 6', 6', 7', 7', 7'-nonafluoro-2'-diiodoheptyl)phenol **296** (0.33 g, 0.64 mmol) and the mixture was suspended in

anhydrous THF (1 cm^3). DIAD (0.13 g, 0.13 cm^3, 2.14 mmol) was added dropwise over 15 min and the reaction was shaken at rt. After 24 h, the resin was filtered, washed with anhydrous THF, anhydrous DMF, MeOH, DCM and Et_2O (2 cm^3 of each) and dried to yield the functionalised resin **328**. A small portion of the functionalised resin (0.02 g) was shaken with 5% TFA/DCM (1.5 cm^3) for 30 min. After this time, the resin was filtered and washed with DCM (5 cm^3) and ether (5 cm^3). The combined filtrates were evaporated under reduced pressure to yield phenol **296** (6.8 mg, 0.013 mmol/0.02 g = 0.62 mmol/g, 54% loading assuming quantitative cleavage and recovery). ^1H and ^{19}F NMR spectroscopic data for phenol **296** agreed with solution phase data reported above.

1,1,2,2,3,3,4,4-Octafluoro-4-iodobutyl Benzyl Sulfide **348**

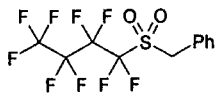


348

Benzyl mercaptan (1.24 g, 1.18 cm^3, 10 mmol) was added dropwise to a stirred suspension of potassium hydride (1.37 g, 35% suspension in oil, 12 mmol) in DMF (10 cm^3) at 0 °C. The reaction was allowed to warm to rt and then 1-iodononafluorobutane (4.15 g, 2.07 ml, 12 mmol) was added dropwise and the reaction stirred for 24 h. Diethyl ether (50 cm^3) was then added and the organic layer was washed with water (4 x 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product. Purification by flash chromatography (pet. ether) yielded the title compound **348** as a clear oil (0.80 g, 23%); *m/z* (EI) 342 (M^+ 60%), 121 (100%); 89 (100%); HRMS (EI) 342.0120, $C_{11}H_7F_9S$ requires 342.0125; ν_{max}(film) 1497, 1350, 1135, 1095, 992, and 864 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 4.18 (2H, s, CH_2), 7.31 – 7.37 (5H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz, ^{19}F de-coupled) 33.0 (CH_2), 109.1 (CF_2), 110.6 (CF_2), 117.7 (CF_2), 124.6 (SCF_2), 128.2 128.9 (2C), 129.2 (2C), 134.5; δ_F ($CDCl_3$; 280 MHz) -

81.38 (3F, m, C*F*$_3$), -88.20 (2F, m, SC*F*$_2$), -121.10 (2F, m, C*F*$_2$), -125.95 (2F, m, C*F*$_2$).

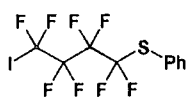
Nonafluorobutyl Benzyl Sulfone 350



350

1,1,2,2,3,3,4,4-Octafluoro-4-iodobutyl benzyl sulfide (0.40 g, 1.17 mmol) was dissolved in acetic acid (2 cm^3). Hydrogen peroxide (0.53 cm^3, 35% *w/w* solution, 6.0 mmol) in acetic acid (2 cm^3) was added dropwise and the reaction was heated to 100 °C and stirred for 4 h. After this time the reaction was cooled to rt and water (10 cm^3) was added, resulting in a white precipitate. Recrystallisation of the precipitate from petroleum ether yielded the title compound 350 as a white crystalline solid (0.15 g, 34%); mp 79-81 °C; *m/z* (ES-) 413 (M+K, 100%), 373 (M-H$^+$ 60%), 219 (C_4F_9, 100%); HRMS (ES$^-$) 372.9948 (M-H$^+$), $C_{11}H_6F_9SO_2$ requires 372.9939; ν_{max}(KBr Disk) 1421, 1224, 1144 (SO_2), 1059, 782 and 505 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 4.52 (2H, s, C*H*$_2$), 7.38 – 7.47 (5H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 58.0 (*C*H$_2$), 128.9 (2C), 130, 131, 132.0 (2C), ca. 100 - 130 (4 x v. weak m, 3 x *C*F$_2$ and *C*F$_3$); δ_F ($CDCl_3$; 283 MHz) -81.03 (3F, m, C*F*$_3$), - 112.48 (2F, m, C*F*$_2$SO$_2$), -121.50 (2F, m, C*F*$_2$), -126.27 (2F, m, C*F*$_2$).

1,1,2,2,3,3,4,4-Octafluoro-4-iodobutyl Phenyl Sulfide 352[137]

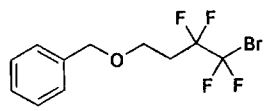


352

Thiophenol (0.55 g, 0.51 cm^3, 5 mmol) was added dropwise to a stirred suspension of sodium hydride powder (0.14 g, 6 mmol) in DMF (5 cm^3) at 0 °C. The reaction was allowed to warm to rt and then 1,4-diiodooctafluorobutane (2.72 g, 1.10 ml, 6 mmol) was added dropwise and the reaction stirred for 16 h. After

this time, diethyl ether (50 cm^3) was added and the organic layer was washed with water (4 x 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product. Purification by flash chromatography (pet. ether) yielded the title compound **352** as a clear oil (0.34 g, 16%); m/z (EI) 436 (M^+, 60%), 309 (20%), 159 (70%), 109 (90%), 77 (100%); HRMS (EI) 435.9032, $C_{10}H_5SF_8I$ requires 435.9029; ν_{max}(film) 3065, 1475, 1443, 1289, 1201, 1055, 1024, 928 and 898 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 7.37 – 7.55 (5H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 94.3 (tt, $^2J_{C\text{-}F}$ 42 Hz, $^1J_{C\text{-}F}$ 320 Hz, CF_2), 108.9 (tt, $^2J_{C\text{-}F}$ 62 Hz, $^1J_{C\text{-}F}$ 234 Hz, CF_2), 110.2 (tt, $^2J_{C\text{-}F}$ 33 Hz, $^1J_{C\text{-}F}$ 268 Hz, CF_2), 122.9 (t, S-CH), 123.0 (tt, $^2J_{C\text{-}F}$ 34 Hz, $^1J_{C\text{-}F}$ 300 Hz, CF_2), 129.4 (2C), 131.0, 137.4 (2C); δ_F ($CDCl_3$; 375 MHz) -58.84 (2F, m, ICF_2), -87.23 (2F, m, SCF_2), -112.76 (2F, m, CF_2), -118.63 (2F, m, CF_2). All data agreed with that previously published.[137]

(4-Bromo-3,3,4,4-tetrafluoro-butoxymethyl)benzene 355

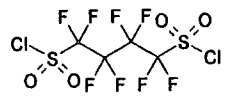


355

A solution of 4-bromo-3,3,4,4-tetrafluorobutan-1-ol (0.72 g, 2.61 mmol) in DMF (15 cm^3) was added dropwise to a suspension of sodium hydride (0.076 g, 3.20 mmol) in DMF (5 cm^3) at rt and the mixture stirred for 15 min. Benzyl bromide (0.55 g, 0.38 cm^3, 3.2 mmol) in DMF was then added dropwise and the reaction stirred at rt for 24 h. After this time, the reaction mixture was quenched with water (10 cm^3) and the layers were separated. The aqueous layer was extracted with DCM (3 x 30 cm^3) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude material. Purification by flash chromatography (petroleum ether) gave protected alcohol **355** as a clear oil (0.22 g, 27%); *m/z* (EI) 314:316 (M^+, 1:1, 40%), 207:209 (M-OBn, 1:1, 100%); HRMS (EI) 332.0272 (M+NH_4), $C_{11}H_{15}F_4NO^{79}Br$ requires 332.0273; ν_{max}(film) 1455, 1372, 1144 and 905 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 2.40 – 2.52 (2H, m, CH_2CF_2), 3.77 (2H, t, ^3J 7 Hz, CH_2-OBn), 4.55 (2H, s, OCH_2Ph),

7.30 – 7.37 (5H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 31.0 (t, $^2J_{C\text{-}F}$ 22 Hz, $\mathbb{C}H_2CF_2$), 62.4 (t, $^3J_{C\text{-}F}$ 4 Hz, $\mathbb{C}H_2CH_2CF_2$), 73.2 ($O\mathbb{C}H_2Ph$), 116.7 (tt, $^2J_{C\text{-}F}$ 32 Hz, $^1J_{C\text{-}F}$ 253 Hz, $\mathbb{C}F_2$), 117.5 (tt, $^2J_{C\text{-}F}$ 39 Hz, $^1J_{C\text{-}F}$ 310 Hz, $\mathbb{C}F_2$), 127.6 (2C), 127.8, 128.5 (2C), 137.6; δ_F ($CDCl_3$; 375 MHz) -66.46 (2F, m, $BrCF_2$), -111.41 (2F, m, CH_2CF_2).

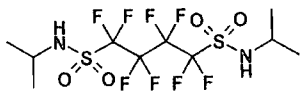
1,1,2,2,3,3,4,4-Octafluorobutane-1,4-disulfonyl Dichloride 368[119]



368

Sodium dithionite (15.33 g, 88 mmol) and sodium hydrogen carbonate (8.14 g, 96 mmol) were added to a stirred solution of 1,4-diiodooctafluorobutane (10.00 g, 4.02 cm^3, 22 mmol) in acetonitrile (15 cm^3) and water (10 cm^3) and stirred at room temperature for 20 h. After this time, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was washed with acetonitrile (100 cm^3) and then continuously extracted into methanol to remove inorganic materials. The methanol was evaporated and the purified residue was redissolved in water (50 cm^3), cooled to 0 °C and chlorine bubbled through the mixture for 20 min. The aqueous layer was extracted with dichloromethane (4 x 100 cm^3) and the combined organic fractions were dried ($MgSO_4$) and evaporated to give a crude white solid. Recrystallisation from petroleum ether yielded the title compound as a white solid (4.70 g, 53%); mp 38-40 °C, lit. mp 44-46 °C;[114] *m/z* (CI-) 363:365 (3:1, M^+-Cl); HRMS (ES^-) 362.8794, $C_4F_8S_2O_4{}^{35}Cl$ requires 362.8793; Anal. calcd. for $C_4F_8S_2O_4Cl_2$: C 12.03, F 38.10, Cl 17.79 %, found: C 12.06, F 36.59, Cl 17.85 %; ν_{max}(KBr Disc) 1417 (SO_2Cl), 1220 (SO_2Cl), 1147, 1078, 782 and 722 cm^{-1}; δ_C ($CDCl_3$; 125 MHz; ^{19}F de-coupled) 110.6, 115.0; δ_F ($CDCl_3$; 188 MHz) -104.52 (4F, m, 2 x $CF_2CF_2SO_2Cl$), -119.25 (4F, m, 2 x CF_2SO_2Cl). All data agreed with that previously published.[119]

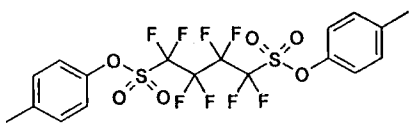
1,1,2,2,3,3,4,4-Octafluoro-butane-1,4-disulfonic Acid bis-Isopropylamide 370



370

A solution of 1,1,2,2,3,3,4,4-Octafluoro-butane-1,4-disulfonyl dichloride 368 (0.30 g, 0.75 mmol) in DCM (5 cm^3) was added dropwise to a stirred solution of isopropylamine (0.13 g, 0.19 cm^3, 2.25 mmol) and triethylamine (0.17 g, 0.23 cm^3, 1.65 mmol) in DCM (5 cm^3) and the mixture stirred at 0 °C for 4 min. After this time, a white solid had precipitated from the reaction mixture. This was filtered off and recrystallised from chloroform to yield the title compound 370 as a white solid (0.19 g, 57%); *m/z* (ES-) 329 (O_2S-C_4F_8-SO_2, 10%); Anal. Calcd for $C_{10}H_{14}S_2O_4N_2F_8$: C 26.97, H 3.60, N 6.29, F 34.16%, found: C 25.56, H 4.50, N 5.85, F 32.26%; ν_{max}(KBr Disc) 2966 (NH), 1644 (NH), 1615, 1505, 1384 (SO_2N), 1150 (SO_2N), 996, 885 and 666 cm^{-1}; δ_H (CD_3OD; 500 MHz) 1.30 (12H, d, ^3J 6.5 Hz, 4 x C*H*$_3$), 3.21 (2H, m, 2 x NH), 3.40 (2H, sept, ^3J 6.5 Hz, 2 x C*H*$(CH_3)_2$); δ_C (CD_3OD; 125 MHz) 19.7 (4 x CH_3), 43.9 (2 x $CH(CH_3)_2$), ca. 100 - 130 (2 x v. weak m, 2 x CF_2); δ_F (CD_3OD; 375 MHz) -124.03 (4F, m, 2 x C*F*$_2$), -132.31 (4F, m, 2 x C*F*$_2$).

1,1,2,2,3,3,4,4-Octafluoro-butane-1,4-disulfonic Acid di-*p*-Tolyl Ester 371

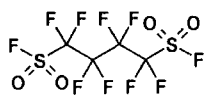


371

A solution of *p*-cresol (0.16 g, 1.5 mmol) in THF (5 cm^3) was added dropwise to a suspension of sodium hydride (0.054 g, 2.25 mmol) in THF (5 cm^3) at 0 °C and the mixture stirred for 15 min. To this was added a solution of 1,1,2,2,3,3,4,4-octafluorobutane-1,4-disulfonyl dichloride 368 (0.30 g, 0.75 mmol) in THF (5 cm^3) and the reaction stirred at 0 °C for 4 h. After this time, the reaction mixture was

diluted with diethyl ether (75 cm^3) and washed with water (2 x 10 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude material as an orange oil. Purification by flash chromatography [pet. ether] yielded the title compound 371 as a clear oil (0.18 g, 44%); *m/z* (ES+) 565 (100%, M+Na); HRMS (ES^+) 560.0441 ($M+NH_4^+$), $C_{18}H_{18}NS_2O_6F_8$ requires 560.0442; ν_{max}(KBr Disc) 1501, 1423 (SO_2-O), 1214, 1147, 891 and 822cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.40 (6H, s, C*H*$_3$), 7.17 – 7.26 (8H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 20.9 (CH_3), 115.6 (CF_2), 118.9 (CF_2), 121.0 (2C), 130.7 (2C), 138.5 (C-CH_3), 147.8 (C-O), ca. 100 - 130 (2 x v. weak m, 2 x CF_2); δ_F ($CDCl_3$; 188 MHz) -109.24 (4F, m, 2 x C*F*$_2$), -120.14 (4F, s, 2 x C*F*$_2$).

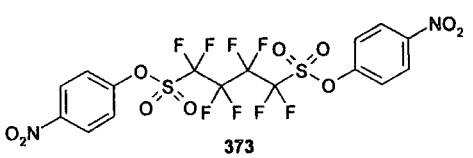
1,1,2,2,3,3,4,4-Octafluorobutane-1,4-disulfonyl Difluoride 372[119]



372

1,1,2,2,3,3,4,4-octafluoro-butane-1,4-disulfonyl dichloride 368 (1.0 g, 2.5 mmol) was dissolved in acetonitrile (2.5 cm^3) or DMF (2.5 cm^3) and 18-crown-6 (0.066g, 0.25 mmol) was added. Anhydrous potassium fluoride (0.63g, 10.8 mmol) was added and the reaction was stirred at rt for 6 h. After this time 100% conversion gave bis-sulfonyl fluoride 372 *in situ*, δ_F (DMF or MeCN; 188 MHz) +45.40 (1F, s, SO_2*F*), -107.28 (2F, m, 2 x C*F*$_2$$SO_2F$), -120.41 (4F, m, 2 x C*F*$_2$$CF_2SO_2F$).

1,1,2,2,3,3,4,4-Octafluoro-butane-1,4-disulfonic Acid di-*p*-Nitrophenyl Ester 373

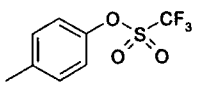


373

A solution of *p*-nitro phenol cresol (0.44 g, 3.1 mmol) in THF (2 cm^3) was added dropwise to a suspension of sodium hydride (0.09 g, 3.75 mmol) in THF (2 cm^3)

at 0 °C and the mixture stirred for 15 min. After this time, a solution of 1,1,2,2,3,3,4,4-octafluorobutane-1,4-disulfonyl dichloride 368 (0.50 g, 1.25 mmol) in THF (2 cm^3) was added dropwise and the reaction stirred at 0 °C for 4 h. After this time, the reaction mixture was diluted with DCM (100 cm^3) and washed with water (2 x 10 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude material as a white solid. Recrystallisation from chloroform yielded title compound 373 as a white solid (0.25 g, 33%); *m/z* (ES+) 627 (M+Na, 50%); 610 (100%); HRMS (ES^+) 603.9492 $(M)^+$, $C_{16}H_8O_{10}S_2N_2F_8$ requires 603.9487; ν_{max}(KBr Disc) 1537 (NO_2), 1485, 1422 (SO_2-O), 1350 (NO_2), 1211, 1139, 1012, 863 (Ar-N) and 751cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 7.47 – 7.51 (4, m, Ar*H*), 8.35 – 8.39 (4H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 122.5 (2C), 126.0 (2C), 147.1, 153.3, ca. 100 - 130 (2 x v. weak m, 2 x CF_2); δ_F ($CDCl_3$; 188 MHz) -108.49 (4F, m, 2 x C*F*$_2$), -119.86 (4F, m, 2 x C*F*$_2$).

p-Tolyl Trifluoromethanesulfonate Ester 374[145]

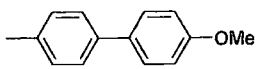


374

Trifluoromethanesulfonic anhydride (15.7 g, 9.13 cm^3, 55.6 mmol) was added dropwise to a solution of *p*-cresol (5.0 g, 46.3 mmol) and aqueous tripotassium phosphate (98 cm^3, 30% *w/v* solution, 138.9 mmol) in toluene (98 cm^3) at 0 °C. The reaction was stirred for 2 h at 0 °C and after this time the layers were separated and the aqueous layer was extracted with toluene (50 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude material. Purification by flash chromatography [pet. ether] yielded the title compound 374 as a colourless oil (2.65 g, 24%); *m/z* (EI) 240 (10%, M^+), 107 (100%, M-SO_2CF_3); ν_{max}(film) 1600, 1558 and 1500 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.40 (3H, s, C*H*$_3$), 7.05 – 7.15 (2 x 2H, m, Ar*H*); δ_C ($CDCl_3$; 100MHz) 20.8 (CH_3), 118.7 (q, $^1J_{C\text{-}F}$ = 321 Hz, CF_3), 121.0

(2C), 130.7 (2C), 138.5 (*C*-CH_3), 147.6 (*C*-O); δ_F ($CDCl_3$; 188 MHz) -73.36 (3F, s, CF_3). All data were identical with that previously reported.[145]

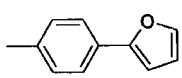
4'-Methoxy-4-methyl Biphenyl 376[146]



376

1,1,2,2,3,3,4,4-Octafluoro-butane-1,4-disulfonic Acid di-*p*-tolyl ester 371 (0.10 g, 0.18 mmol), 4-methoxyphenyl boronic acid (0.055g, 0.36 mmol), palladium acetate (0.002 g, 0.011 mmol), dppb (0.009 g, 0.022 mmol) and triethylamine (0.13 g, 0.16 cm^3, 1.26 mmol) were dissolved in anhydrous DMF (3 cm^3) and the resulting solution was thoroughly degassed (Ar). The reaction was heated the heated to 80 °C for 16h. After this time, DMF was removed *in vacuo* to yield the crude product. Purification by flash chromatography (pet. ether : ethyl acetate [9.5 : 0.5 - 8 : 2]) gave known biphenyl 376 as a clear oil (0.0068 g, 24%); *m/z* (EI) 198 (M+, 50%); δ_H ($CDCl_3$; 300 MHz) 2.40 (3H, s, Ar-CH_3), 3.84 (3H, S, OCH_3), 7.05 (2H, d, ^3J 9 Hz, Ar*H*), 7.20 (2H, d, ^3J 8 Hz, Ar*H*), 7.45 – 7.50 (4H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 21.3 (*C*H_3), 55.8 (O*C*H_3), 144.4 (2 C), 125.8 (2C), 128.2 (2C), 130.0 (2C), 134.4, 136.8, 139.0, 159.2. All data agreed with that previously reported.[146]

2-*p*-Tolyl-Furan 380[147]

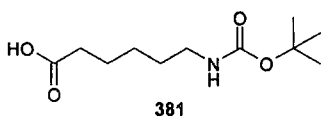


380

1,1,2,2,3,3,4,4-Octafluorobutane-1,4-disulfonic acid di-*p*-tolyl ester 371 (0.05 g, 0.092 mmol), 2-(tributylstannyl)furan (0.066g, 0.058 cm^3, 0.18 mmol) and lithium chloride (0.015 g, 0.37 mmol) were dissolved in THF (3 cm^3) and the resulting solution was thoroughly degassed (N_2). Tetrakis(triphenylphosphine)palladium (0.021 g, 0.018 mmol) was then added and the reaction was heated under reflux

for 16 h. After this time, THF was removed *in vacuo* and the crude product was taken up in ether (15 cm^3) and aqueous potassium fluoride solution (15 cm^3). The layers were separated and the aqueous layer was washed with more ether (15 cm^3). The combined ether fractions were dried ($MgSO_4$), filtered and evaporated to yield the crude product. Purification by flash chromatography (pet. ether : ethyl acetate [8 : 2]) gave known furan **380** as a clear oil (0.0098 g, 34%); *m/z* (EI) 158 (M+, 90%); ν_{max}(film) 1556, 1484, 819 and 730 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 2.36 (3H, s, Ar-C*H*$_3$), 6.41 (1H, dd, ^3J 1.5 and 3 Hz, furyl-*H*), 6.55 (1H, d, ^3J 3 Hz, furyl-*H*), 7.10 – 7.17 (2H, m, ArH), 7.45 (1H, d, ^3J 1.5 Hz, furyl-*H*), 7.59 – 7.65 (2H, m, Ar*H*); δ_C ($CDCl_3$; 100 MHz) 21.3 (*C*H$_3$), 104.4, 111.5, 123.8 (2C), 128.2 (2C), 136.8, 141.6, 154.2. All data were identical with that previously reported.[147]

6-*tert*-Butoxycarbonylamino-hexanoic Acid **381**[143]

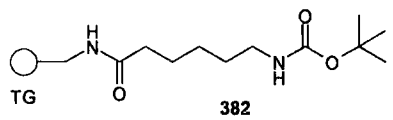


381

Di-*tert*-butyl dicarbonate (18.3 g, 83.9 mmol) was dissolved in dioxane (80 cm^3) and water (80 cm^3). This solution was added dropwise to a stirred solution of 6-aminocaproic acid (10.0 g, 76.2 mmol) in dioxane (80 cm^3) and water (40 cm^3) at 0 °C. The pH was adjusted to 9 – 10 with NaOH (1M) and the reaction was warmed to room temperature and stirred overnight. After this time, the solvent was removed under reduced pressure and the residual oil was redissolved in water (100 cm^3). The aqueous reaction mixture was extracted with ether (3 x 50 cm^3) and then acidified to pH 3 using citric acid. The acidified solution was then extracted with ethyl acetate (10 x 50 cm^3) and the combined organic fractions were dried ($MgSO_4$), filtered and evaporated to give a crude oil. Recrystallisation from petroleum ether yielded the title compound **381** as a white solid (13.32 g, 76%); mp 36-38 °C; lit. mp 48 °C;[141] *m/z* (ES+) 254 (100% M+Na), 198 (10%, [M-^{t}Bu]+Na); ν_{max}(KBr Disc) 3367 (OH), 1715 (C=O, CO_2H), 1683(C=O, CONH),

1520, 1253 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.36 (2H, m, CH_2-4), 1.43 (9H, s, C(CH_3)$_3$), 1.49 (2H, quint, ^3J 7.5 Hz, CH_2-3), 1.65 (2H, quint, ^3J 7.5 Hz, CH_2-5), 2.34 (2H, t, ^3J 7.5 Hz, CH_2-6), 3.11 (2H, m, CH_2-2), 4.56 (1H, br. s, CO_2H), 5.62 (1H, br. s, NH); δ_C ($CDCl_3$; 125 MHz) 24.3 (C-5), 26.2 (C-4), 28.4 (3C, C(CH_3)$_3$), 29.7 (C-3), 33.8 (C-6), 40.3 (C-2), 79.2 ($C(CH_3)_3$), 167.5 (NHC(O)O^{t}Bu), 178.9 (CO_2H).

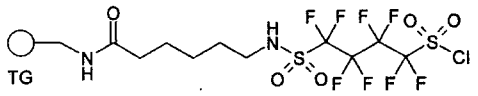
Resin-bound 6-*tert*-butoxycarbonylaminohexanoic Acid 382



382

Amino TentaGel (6.77 g, 0.26 mmol/g, 1.76 mmol) was washed with anhydrous DMF (3 x 5 cm^3). It was suspended in 20% piperidine in anhydrous DMF and shaken for 15 min after which time it was washed with DCM / methanol (alternately 5 x 5 cm^3 each) and DCM / diethyl ether (alternately 5 x 5 cm^3 each) and re-suspended in anhydrous DMF (10 cm^3). A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.01 g, 5.28 mmol), 1-hydroxybenzotriazole hydrate (0.71 g, 5.28 mmol) and 6-*tert*-butoxycarbonyl-aminohexanoic acid 381 (1.22 g, 5.28 mmol) in anhydrous DMF (15 cm^3) was added and the resin shaken at room temperature for 24 h. After this time, no amino groups remained (bromophenol blue indicator) and the resin was filtered, washed with DCM / diethyl ether (alternately 5 x 10 cm^3 each) and dried to yield the title resin 382; ν_{max}(ATR) 1648 cm^{-1} (amide C=O) and 1683 cm^{-1} (carbamate C=O).

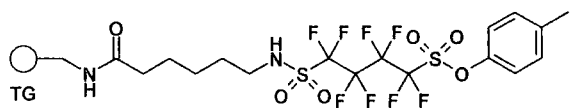
Resin-bound Perfluorosulfonyl Chloride 383



383

Resin-bound 6-*tert*-butoxycarbonylaminohexanoic acid 382 (6.77 g, 0.26 mmol/g, 1.76 mmol) was suspended in 50% TFA in DCM and shaken for 4 h. After this time, deprotection was confirmed to be complete (bromophenol blue indicator) and so the resin was filtered and washed with DCM (10 x 5 cm^3). The resin was then suspended in DCM (5 cm^3) and 1,1,2,2,3,3,4,4-octafluoro-butane-1,4-disulfonyl dichloride 368 (0.50 g, 1.25 mmol) was added. This suspension was then cooled to 0 °C, DIPEA (0.16 g, 0.22 cm^3, 1.25 mmol) was added dropwise and the reaction stirred at 0 °C for 16 h. After this time, the resin was filtered, washed with DCM, MeOH and Et_2O and dried to yield resin-bound sulfonyl chloride 383; ν_{max}(ATR) 1368 (SO_2Cl), 1354 (SO_2NH), 1174 (SO_2Cl) and 1152 (SO_2NH) cm^{-1}; δ_F ($CDCl_3$; 188 MHz) -104.02 (2F, m, CF_2SO_2Cl), -114.23 (2F, m, CF_2), -118.84 (2F, m, $CF_2CF_2SO_2Cl$), -120.29 (2F, m, CF_2).

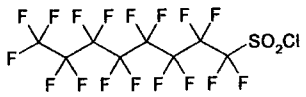
Resin-bound Perfluorosulfonate Ester 384



384

A solution of *p*-cresol (0.15 g, 1.4 mmol) in THF (2 cm^3) was added dropwise to a suspension of sodium hydride (0.039 g, 1.68 mmol) in THF (3 cm^3) at 0 °C and the mixture stirred for 15 min. This solution was then transferred *via* cannula to a suspension of resin bound sulfonyl chloride 383 (0.60 g, 0.24 mmol/g, 0.14 mol) and the reaction stirred at 0 °C overnight. After this time, the resin was filtered, washed with THF / water, DCM, MeOH and Et_2O and dried to yield resin-bound sulfonate ester 384; δ_F ($CDCl_3$; 188 MHz) -109.34 (2F, br. m, CF_2SO_3Ar), -113.86 (2F, br. m, CF_2), -120.18 (2F, br. m, $CF_2CF_2SO_3Ar$), -126.96 (2F, br. m, CF_2).

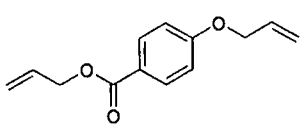
Perfluorooctane-1-sulfonyl Chloride 390



390

Sodium dithionite (3.19 g, 18.3 mmol) and sodium hydrogen carbonate (1.69 g, 20.15 mmol) were added to a stirred suspension of perfluorooctyl iodide (5.0 g, 2.45 cm^3, 9.16 mmol) in acetonitrile (10 cm^3) and water (10 cm^3) and stirred at room temperature for 6 h. After this time, inorganic materials were removed by filtration and evaporation of solvent under reduced pressure gave sodium sulfite salt 389 as a white residue. This was redissolved in water (10 cm^3), cooled to 0 °C and then chlorine was bubbled through the reaction mixture for 20 min. After chlorination, the aqueous reaction mixture was extracted with DCM (3 x 20 cm^3). The combined DCM fractions were dried ($MgSO_4$) and evaporated to yield the crude material. Recrystallisation from pet. ether gave title compound 390 as a white solid (2.81 g, 59%); mp 30 – 32 °C; *m/z* (ES^-) 483 ($M\text{-}Cl^+$, 100%), 419 (C_8F_{17}, 30%); ν_{max}(film) 1421 (SO_2Cl), 1370, 1233, 1203 (SO_2Cl), 1147 and 657 cm^{-1}; δ_C ($CDCl_3$; 125 MHz, ^{19}F de-coupled) 108.4, 110.2, 110.6, 110.7 (2C), 110.8, 115.3, 117.1; δ_F ($CDCl_3$; 188 MHz) -81.33 (3F, m, CF_3), -104.74 (2F, m,, CF_2SO_2Cl), -119.60 (2F, m, $CF_2CF_2SO_2Cl$), -121.85 - -122.34 (6F, s, 3 x CF_2), -123.19 (2F, s, CF_2), -126.63 (2F, s, CF_2).

Prop-2-enyl-4-propenyloxybenzoate 406[159]

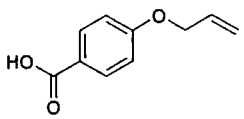


406

4-Hydroxybenzoic acid (10.0 g, 72.5 mmol) and potassium carbonate (30.0 g, 217.4 mmol) were suspended in DMF (150 cm^3). Allyl bromide (26.3 g, 18.8 cm^3, 217.4 mmol) was added dropwise and the reaction was heated to 50 °C overnight. After this time, ether (500 cm^3) and saturated sodium bicarbonate

solution (250 cm^3) were added. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to dryness using a Genevac evaporator to yield the known title compound 406 without further purification (14.5 g, 92%); m/z (EI) 218 (M^+, 20%), 161 (M-(O-All), 90%); ν_{max}(ATR) 1713, 1509, 1269, 1169 and 544 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 4.52 (2H, s, C*H*$_2$), 4.76 (2H, s, C*H*$_2$), 5.25 (2H, d, ^3J 10 Hz, CH=C*H*$_2$), 5.38 (2H, d, ^3J 16 Hz, CH=C*H*$_2$), 5.96 – 6.03 (2H, m, 2 x C*H*=CH_2), 6.89 (2H, m, Ar*H*), 7.97 (2H, m, Ar*H*); δ_C ($CDCl_3$; 125 MHz) 65.1 (*C*H_2), 68.6 (*C*H_2), 114.1 (2C), 115.1 (CH=*C*H_2), 117.7 (CH=*C*H_2), 122.3, 131.4 (2C), 131.7, 132.2 (*C*H=CH_2), 132.3 (*C*H=CH_2), 162.3 (*C*=O). All data agreed with that previously published.[159]

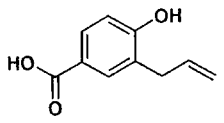
4-Allyloxybenzoic Acid 407[160]



407

Prop-2-enyl-4-propenyloxybenzoate (1.0 g, 4.6 mmol) was dissolved in water (15 cm^3) and THF (15 cm^3). Sodium hydroxide (0.90 g, 23 mmol) was added and the reaction was stirred overnight at rt. After this time the reaction mixture was extracted with ethyl acetate (2 x 10 cm^3) and the layers were separated. The aqueous layer was acidified to pH 3 with ice cold HCl (5M) and then extracted with ethyl acetate (3 x 100 cm^3). The combined ethyl acetate fractions from the extraction of the acidified mixture were dried ($MgSO_4$), filtered and evaporated to yield known acid 407 without further purification (0.34 g, 42%); m/z (EI) 178 (M^+, 30%); ν_{max}(ATR) 2934 (br. OH), 1667 (C=O), 1361, 1246, 948 and 768 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 4.60 (2H, d, ^3J 5 Hz, C*H*$_2$), 5.23 - 5.45 (2H, m, CH=C*H*$_2$), 5.96 - 6.15 (1H, m, C*H*=CH_2), 6.97 (2H, d, *J* 8.5 Hz, Ar*H*), 7.95 (2H, d, *J* 8.5 Hz, Ar*H*). All data agreed with that previously reported.[160]

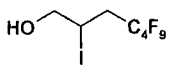
3-Allyl-4-hydroxybenzoic Acid 408[161]



408

4-Allyloxybenzoic acid (1.0 g, 5.6 mmol) was dissolved in DMF (5 cm^3). The solution was heated to 140 °C overnight and after this time DMF was removed using a Genevac Evaporator to yield phenol 408 which was not purified further (0.98 g, 98%); m/z = 178 (20%); ν_{max}(ATR) 3379 (br. phenol OH), 2957 (br. acid OH), 1699 (C=O), 1361, 1246, 948 and 768 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 3.40 (2H, d, ^3J 5 Hz, CH_2), 5.12 - 5.20 (2H, m, CH=CH_2), 5.70 (1H, br. s, O*H*), 5.86 - 5.95 (1H, m, C*H*=CH_2), 6.97 - 7.25 (3H, m, Ar*H*).

4,4,5,5,6,6,7,7,7-Nonafluoro-2-iodoheptan-1-ol 410[150]

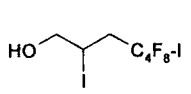


410

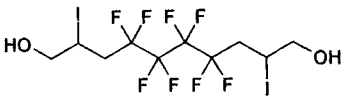
Allyl alcohol (1.18 g, 1.32 cm^3, 10.0 mmol) was added dropwise over 5 min to a stirred solution of AIBN (0.80 g, 5.0 mmol) and 1-iodononafluorobutane (5.0 g, 2.49 cm^3, 14.4 mmol). The reaction was then heated to 70 °C and stirred for 48 h. After this time, the crude reaction mixture was cooled and purification by distillation using a Kugelrohr bulb-to-bulb distillation apparatus (oven temperature 100 °C) gave the title compound 410 as a pale yellow oil (1.8 g, 65%); m/z (EI) 404 (M^+, 20%), 277 (M-I, 100%); ν_{max}(film) 3385 (br. OH), 1245, 1025, 880 and 738 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 2.04 (1H, t, ^3J 6 Hz, OH), 2.67 – 3.04 (2H, m, C$H_2$$CF_2$), 3.79 (2H, m, C$H_2$O*H*), 4.37 – 4.40 (1H, m, C*H*I); δ_C ($CDCl_3$; 125 MHz) 21.13 (CHI), 37.3 (t, $^2J_{C\text{-}F}$ 21 Hz, CH_2CF_2), 67.8 (CH_2OH), 110.0 (m, CF_3), 112.1 (m, CF_2), 117.6 (tt, $^2J_{C\text{-}F}$ 33 Hz, $^1J_{C\text{-}F}$ 287 Hz, CF_2), 118.4 (tt, $^2J_{C\text{-}F}$ 32 Hz, $^1J_{C\text{-}F}$ 256 Hz, CF_2); δ_F ($CDCl_3$; 188 MHz) -81.44 (3F, m, CF_3), -114.07 (2F, m, C$F_2$$CH_2$), -124.86 (2F, m, C$F_2$), -126.31 (2F, m, C$F_2$). All data agreed with that previously reported.[150]

4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptan-1-ol 412

4,4,5,5,6,6,7,7-Octafluoro-2,9-diiododecane-1,10-diol 413



412

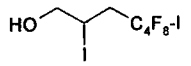


413

Allyl alcohol (0.13 g, 0.15 cm^3, 2.20 mmol) was added dropwise over 5 min to a stirred solution of AIBN (0.18 g, 1.10 mmol) and 1,4-diiodooctafluorobutane (1.0 g, 0.40 cm^3, 2.20 mmol). The reaction was then heated to 70 °C and stirred for 16 h. After this time, the crude reaction mixture was cooled and purification by flash chromatography (pet. ether, pet. ether/ethyl acetate [9:1], pet. ether/ethyl acetate [8:2]) yielded title compound 412 as a pale yellow oil (0.54 g, 48% based upon allyl alcohol); m/z (EI) 512 (M^+, 5%), 385 (M-I, 100%); HRMS (EI) 511.8375 (M^+), $C_7H_6F_8I_2O$ requires 511.8370; ν_{max}(film) 3447 (br. OH), 1170, 1069, and 674 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.44 (1H, br. s, O*H*), 2.65 – 2.80 (1H, m, C*H*$_A$H$_B$CF$_2$), 2.92 – 3.07 (1H, m, CH$_A$*H*$_B$CF$_2$), 3.78 (2H, m, C*H*$_2$OH), 4.36 – 4.41 (1H, m, C*H*I); δ_C ($CDCl_3$; 125 MHz) 23.3 (CHI), 37.3 (t, $^2J_{C-F}$ 21 Hz, CH_2CF_2), 67.8 (CH_2OH), 94.0 (tt, $^2J_{C-F}$ 42 Hz, $^1J_{C-F}$ 320 Hz, CF_2-I), 108.9 (tt, $^2J_{C-F}$ 32 Hz, $^1J_{C-F}$ 263 Hz, CF_2), 109.7 (tt, $^2J_{C-F}$ 34 Hz, $^3J_{C-F}$ 266 Hz, CF_2), 117.6 (tt, $^2J_{C-F}$ 31 Hz, $^1J_{C-F}$ 257 Hz, CF_2); δ_F ($CDCl_3$; 375 MHz) -59.32 (2F, m, IC*F*$_2$), -113.16 (2F, m, C*F*$_2$), -113.77 (2F, m, CH$_2$C*F*$_2$), -123.16 (2F, m, C*F*$_2$).

Further elution (pet. ether/ ethyl acetate [7:3]) yielded bis-coupled by-product 413 as a pale yellow oil (0.14 g, 23% based upon allyl alcohol); m/z (EI) 570 (M^+, 10%); HRMS (EI) 569.8792 (M^+), $C_{10}H_{12}F_8I_2O_2$ requires 569.8793; ν_{max}(film) 3373 (br. OH), 1431, 1168 and 726 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 2.28 (2 x 1H, br. s, 2 x O*H*), 2.67 – 2.82 (2H, m, 2 x C*H*$_A$H$_B$CF$_2$), 2.91 – 3.05 (2H, m, 2 x CH$_A$*H*$_B$CF$_2$), 3.75 – 3.84 (4H, m, C*H*$_2$OH), 4.40 – 4.45 (2H, m, C*H*I); δ_C ($CDCl_3$; 100 MHz) 22.2 (2 x CHI), 37.5 (t, $^2J_{C-F}$ 21 Hz, 2 x CH_2CF_2), 67.8 (2 x CH_2OH), 110.9 (tt, $^2J_{C-F}$ 42 Hz, $^1J_{C-F}$ 320 Hz, 2 x CF_2), 117.7 (tt, $^2J_{C-F}$ 31 Hz, $^1J_{C-F}$ 257 Hz, 2 x CF_2); δ_F ($CDCl_3$; 375 MHz) -113.96 (2F, m, 2 x CH$_2$C*F*$_2$), -123.95 (2F, m, 2 x C*F*$_2$).

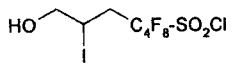
Optimised Synthesis of 4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptan-1-ol 412



412

Allyl alcohol (0.26 g, 0.30 cm^3, 4.40 mmol) was added dropwise to a stirred solution of AIBN (0.36 g, 2.20 mmol) and 1,4-diiodooctafluorobutane (10.0 g, 4.0 cm^3, 22.00 mmol). The reaction was then heated to 70 °C and stirred overnight. After this time, the crude reaction mixture was cooled and purification by flash chromatography (pet. ether, pet. ether/ethyl acetate [9:1], pet. ether/ethyl acetate [8:2]) yielded the title compound 412 as a pale yellow oil (1.88 g, 83%). All data agreed with that reported above.

1,1,2,2,3,3,4,4-Octafluoro-7-hydroxy-6-iodo-heptanesulfonyl Chloride 419

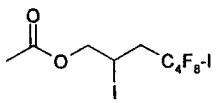


419

4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptan-1-ol 412 (0.5 g, 0.98 mmol) was dissolved in water (0.8 cm^3) and acetonitrile (2.4 cm^3). Sodium dithionite (0.34 g, 1.96 mmol) and sodium bicarbonate (0.18 g, 2.16 mmol) were added and the reaction stirred for 6 h at rt. After this time inorganic materials were removed by filtration and the solvent was evaporated under reduced pressure to give sodium sulfite 418 as a white residue. This was suspended in dry DCM (10 cm^3) and *N*-chlorosuccinimide (0.33 g, 2.45 mmol) was added. The reaction was stirred for 1 h at rt after which time DCM (50 cm^3) and water (10 cm^3) were added. The organic layer was separated and washed further with saturated sodium thiosulfate (50 cm^3). The layers were separated again and the organic layer was dried ($MgSO_4$), filtered and evaporated to give a crude white solid. Purification by flash chromatography (pet. ether, pet. ether/ethyl acetate [9:1], pet. ether/ethyl acetate [8:2]) yielded title compound 419 as a white solid (0.30 g, 63%); mp 50 - 52 °C; *m/z* (ES^-) 449 (M-Cl, 10%), 321 (M-(I+Cl), 30%); ν_{max}(golden gate) 3302

(br. OH), 1560, 1422 (SO_2Cl), 1212 (SO_2Cl) and 1050 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 2.48 (1H, br. s, O*H*), 2.63 – 2.83 (1H, m, C*H*$_A$H$_B$CF$_2$), 2.95 – 3.15 (1H, m, CH$_A$*H*$_B$CF$_2$), 3.80 (2H, m, C*H*$_2$OH), 4.34 – 4.42 (1H, m, C*H*I); δ_C ($CDCl_3$; 100 MHz) 21.2 (CHI), 37.3 (t, $^2J_{C-F}$ 21 Hz, CH_2CF_2), 67.8 (CH_2OH), 108.3 (m, CF_2), 111.0 (m, CF_2), 115.5 (tt, $^2J_{C-F}$ 35 Hz, $^1J_{C-F}$ 311 Hz, CF_2), 117.7 (tt, $^2J_{C-F}$ 31 Hz, $^1J_{C-F}$ 257 Hz, CF_2); δ_F ($CDCl_3$; 280 MHz) -104.50 (2F, m, C*F*$_2$SO$_2$Cl), -113.80 (2F, m, CH$_2$C*F*$_2$), -119.45 (2F, m, C*F*$_2$CF$_2$SO$_2$Cl), -123.61 (2F, m, C*F*$_2$).

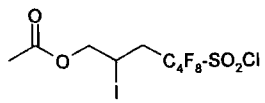
4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptyl Acetate 420



420

4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodo-heptan-1-ol 412 (0.47 g, 0.92 mmol), acetic anhydride (0.19 g, 0.17 cm^3, 1.84 mmol) and triethylamine (0.46 g, 0.64 cm^3, 4.6 mmol) were dissolved in dry DCM (10 cm^3). Dimethylaminopyridine (0.011 g, 0.092 mmol) was added and the reaction was stirred at rt for 24 h. After this time the reaction mixture was washed with HCl (1M, 10 cm^3), saturated sodium bicarbonate (10 cm^3) and brine (10 cm^3). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to yield the crude material. Purification by flash chromatography (pet. ether/ ethyl acetate [9:1]) yielded the title material 420 as a colourless oil (0.35 g, 69%); m/z (EI) 554 (M^+, weak ~1%), 494 (M-OAc, 10%), 427 (M-I, 50%), 43 (AcO, 100%); HRMS (EI) 553.8477 (M^+), $C_9H_8F_8I_2O_2$ requires 553.8488; ν_{max}(golden gate) 1745 (C=O), 1221, 1173, 1123, 1045, 713, and 671 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 2.12 (3H, s, C*H*$_3$), 2.65 – 3.05 (2H, m, C*H*$_2$CF$_2$), 4.26 – 4.45 (1H, m, C*H*I), 4.33 – 4.35 (2H, m, C*H*$_2$OAc); δ_C ($CDCl_3$; 125 MHz) 12.1 (CH_3), 20.6 (CHI), 38.1 (t, $^2J_{C-F}$ 21 Hz, CH_2CF_2), 68.4 (CH_2OAc), 94.0 (tt, $^2J_{C-F}$ 34 Hz, $^1J_{C-F}$ 256 Hz, CF_2-I), 108.9 (tt, $^2J_{C-F}$ 26 Hz, $^1J_{C-F}$ 213 Hz, CF_2), 109.8 (tt, $^2J_{C-F}$ 27 Hz, $^1J_{C-F}$ 213 Hz, CF_2), 117.4 (tt, $^2J_{C-F}$ 26 Hz, $^1J_{C-F}$ 206 Hz, CF_2), 170.0 (C=O); δ_F ($CDCl_3$; 375 MHz) -59.15 (2F, m, C*F*$_2$-I), -113.10 (2F, m, C*F*$_2$), -113.80 (2F, m, CH$_2$C*F*$_2$), -123.05 (2F, m, C*F*$_2$).

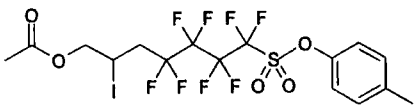
7-Chlorosulfonyl-4,4,5,5,6,6,7,7-octafluoro-2-iodoheptyl Acetate 422



422

4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptyl acetate 420 (0.16 g, 0.29 mmol) was dissolved in water (0.4 cm^3) and acetonitrile (1.2 cm^3). Sodium dithionite (0.1 g, 0.58 mmol) and sodium bicarbonate (0.054 g, 0.64 mmol) were added and the reaction mixture was stirred for at rt for 6 h. After this time inorganic materials were removed by filtration and the solvent was evaporated under reduced pressure to give sodium sulfite 421 as a white residue. This was suspended in dry DCM (10 cm^3) and *N*-chlorosuccinimide (0.086 g, 0.64 mmol) was added. The reaction was stirred for 1 h at rt after which time DCM (50 cm^3) and water (10 cm^3) were added. The organic layer was separated and washed with saturated sodium thiosulfate (50 cm^3). The layers were separated again and the organic layer was dried ($MgSO_4$), filtered and evaporated to give a crude white solid. Purification by flash chromatography (pet. ether, pet. ether:ethyl acetate [9:1], pet. ether: ethyl acetate [8:2]) yielded title compound 422 as a colourless oil (0.11 g, 73%); *m/z* (ES^-) 491 (M-Cl, 100%), 363 (M-(I+Cl), 30%); ν_{max}(ATR) 1745 (C=O), 1415 (SO_2Cl), 1210 (SO_2Cl), 1181, 1137, 1046, and 737 cm^{-1}; δ_H ($CDCl_3$; 300 MHz) 2.12 (3H, s, C*H*$_3$), 2.67 – 3.03 (2H, m, C*H*$_2$$CF_2$), 4.25 – 4.40 (3H, m, C*H*I and C*H*$_2$OAc); δ_C ($CDCl_3$; 100 MHz) 11.5 (*C*H_3), 20.7 (*C*HI), 38.0 (t, $^2J_{C\text{-}F}$ 21 Hz, *C*H_2CF_2), 68.4 (*C*H_2OAc), 170.1 (*C*=O), ca. 100 - 130 (4 x v. weak m, 4 x *C*F_2); δ_F ($CDCl_3$; 280 MHz) -104.53 (2F, m, C*F*$_2SO_2Cl$), -113.80 (2F, m, CH_2CF_2), -119.45 (2F, m, $CF_2CF_2SO_2Cl$), -123.60 (2F, m, C*F*$_2$).

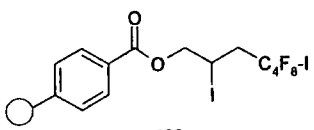
4,4,5,5,6,6,7,7-Octafluoro-2-iodo-7-*p*-tolyloxysulfonylheptyl Acetate 423



423

A solution of *p*-cresol (0.009 g, 0.083 mmol) in THF (2 cm^3) was added dropwise to a suspension of sodium hydride (0.0026 g, 0.11 mmol) in THF (3 cm^3) at 0 °C and the mixture stirred for 15 min. To this was added a solution of 7-chlorosulfonyl-4,4,5,5,6,6,7,7-octafluoro-2-iodoheptyl acetate 422 (0.04 g, 0.076 mmol) in THF (2 cm^3) and the reaction stirred at 0 °C for 16 h. After this time, the reaction mixture was diluted with diethyl ether (50 cm^3) and washed with water (2 x 10 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude material. Purification by flash chromatography [pet. ether] yielded the title compound 423 as a clear oil (0.029 g, 64%); *m/z* (EI) 598 (M^+, 5%), 471 (M-I, 15%); HRMS (ES^+) 615.9895 (M+NH_4), $C_{16}H_{19}O_5NF_8IS$ requires 615.9895; δ_H ($CDCl_3$; 300 MHz) 2.06 (3H, s, C*H*$_3$), 2.31 (3H, S, Ar-C*H*$_3$), 2.68 – 2.91 (2H, m, C*H*$_2$$CF_2$), 4.20 – 4.38 (3H, m, C*H*I and C*H*$_2$OAc); δ_C ($CDCl_3$; 100 MHz) 11.8 (CH_3), 20.7 (CHI), 20.9 (ArCH_3), 38.2 (t, $^2J_{C-F}$ 21 Hz, CH_2CF_2), 68.4 (CH_2OAc), 121.1 (2C), 130.6 (2C), 138.4 (C-CH_3), 147.8 (C-O), 170.0 (C=O), ca. 100 - 130 (4 x v. weak m, 4 x CF_2); δ_F ($CDCl_3$; 280 MHz) -109.23 (2F, m, C*F*$_2$$SO_3$Ar), -113.34 (2F, m, CH_2C*F*$_2$), -120.18 (2F, m, C*F*$_2$$CF_2SO_3$Ar), -123.80 (2F, m, C*F*$_2$).

Resin-bound 4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodo-heptan-1-ol 428

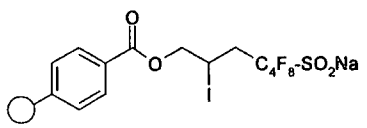


428

Carboxypolystyrene resin (0.25 g, 1.4 mmol/g, 0.35mmol), DMAP (0.065 g, 0.53 mmol) and 4,4,5,5,6,6,7,7-octafluoro-2,7-diiodoheptan-1-ol 412 were suspended in dry DCM (10 cm^3). DIC (0.13 g, 0.16 cm^3, 1.05 mmol) was added and the

reaction was shaken overnight at rt. After this time, the resin was filtered and washed with DCM, DCM/MeOH, MeOH, MeOH/Et_2O and Et_2O (2 x 5 cm^3 each) to give resin-bound iodide 428; ν_{max}(ATR) 1721 (C=O), 1492, 1176, 1121 and 697 cm^{-1}; δ_F ($CDCl_3$; 282 MHz) -58.22 (2F, br. s, CF_2-I), -111.44 (4F, br. s, 2 x CF_2), -121.30 (2F, br. s, CF_2).

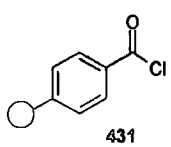
Resin-bound Sodium Sulfite 429



429

Resin bound iodide 428 (0.25mmol), sodium dithionite (0.44 g, 2.5 mmol) and sodium bicarbonate (0.23 g, 2.75 mmol) were suspended in DMSO (10 cm^3). The reaction mixture was heated to 40 °C and stirred overnight. After this time, the resin was filtered and washed with DMSO, DCM, DCM/MeOH, MeOH, MeOH/Et_2O and Et_2O (2 x 5 cm^3 each) to give resin-bound sodium sulfite 429; ν_{max} (ATR) 1722 (C=O), 1491, 1452, 1271, 1169 and 699 cm^{-1}; δ_F ($CDCl_3$; 282 MHz) -111.27 (2F, br. s, CF_2), -124.63 (2F, br. s, CF_2), -129.35 (2F, br. s, CF_2SO_2Na), -121.30 (2F, br. s, CF_2).

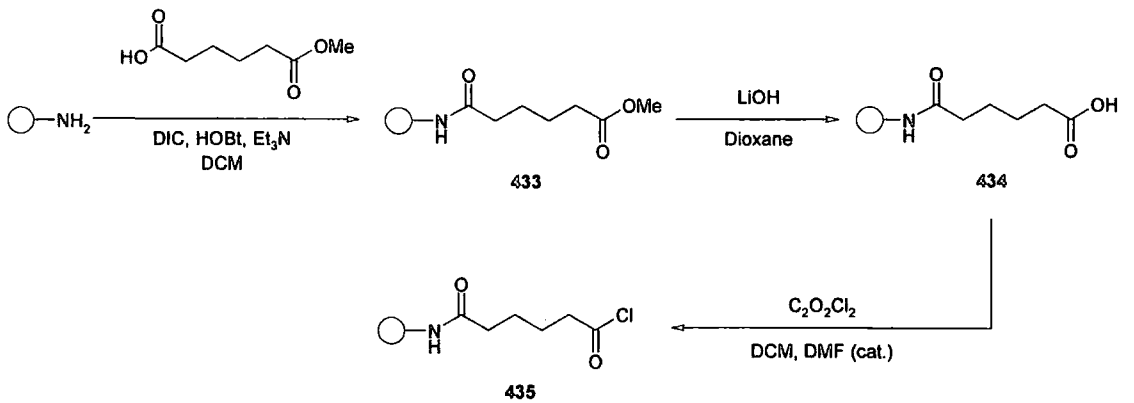
Resin-bound Benzoyl Chloride 431



431

Carboxypolystyrene (0.11 g, 1.4 mmol/g, 0.15 mmol) and oxalyl chloride (0.04 g, 0.026 cm^3, 0.30 mmol) were suspended in anhydrous DCM. DMF (1 drop) was added and the reaction stirred overnight at rt. After this time the resin was filtered and washed with anhydrous DCM (3 x 10 cm^3) to give resin-bound acid chloride 431; ν_{max}(ATR) 1770 (C=O), 1735 (fermi resonance) and 875 (C-Cl) cm^{-1}.

Resin-bound Acid Chloride 435[156]

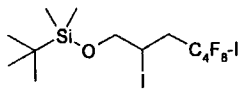


Amino TentaGel (0.9 g, 0.28 mmol/g, 0.25 mmol), adipic acid monomethyl ester (0.22 g, 0.20 cm^3, 1.4 mmol), DIC (0.18 g, 0.22 cm^3, 1.4 mmol), hydroxybenzotriazole hydrate (0.03 g, 0.25 mmol) and triethylamine (0.14 g, 0.19 cm^3, 1.4 mmol) were suspended in DCM (10 cm^3) and the reaction mixture was shaken overnight at rt. After this time bromophenol blue tested negative and so the resin was filtered and washed with DCM, DCM/MeOH, MeOH, MeOH/Et_2O and Et_2O (2 x 5 cm^3 each) to give resin-bound ester 433; ν_{max}(ATR) 1740 (ester C=O) and 1654 (amide C=O) cm^{-1}.

Resin-bound ester 433 was then suspended in 1,4-dioxane (10 cm^3) and lithium hydroxide (0.009 g, 0.38 mmol) was added. The reaction mixture was shaken overnight and after this time the resin was filtered and washed with 1,4-dioxane, DCM, DCM/MeOH, MeOH, MeOH/Et_2O and Et_2O (2 x 5 cm^3 each) to give resin-bound acid 434; ν_{max}(ATR) 2868 (OH), 1735 (acid C=O) and 1669 (amide C=O) cm^{-1}.

Acid 434 (0.25 mmol) was suspended in anhydrous DCM (10 cm^3). Oxalyl chloride (0.06 g, 0.04 cm^3, 0.5 mmol) and DMF (1 drop) were added and the reaction mixture was shaken overnight at rt. The resin was then filtered and washed with DCM, DCM/MeOH, MeOH, MeOH/Et_2O and Et_2O (2 x 5 cm^3 each) to yield acid chloride 435; ν_{max} (ATR) 1823 (acid chloride C=O) and 1654 (amide C=O) cm^{-1}.

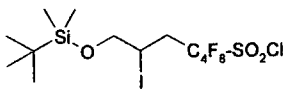
tert-Butyldimethyl-(4,4,5,5,6,6,7,7-octafluoro-2,7-diiodoheptyloxy)silane 438



438

4,4,5,5,6,6,7,7-Octafluoro-2,7-diiodoheptan-1-ol 412 (0.75 g, 1.47 mmol) and TBDMS triflate (0.58 g, 0.50 cm^3, 2.21 mmol) were dissolved in DCM (20 cm^3). 2,6-Lutidine (0.24 g, 0.26 cm^3, 2.21 mmol) was added dropwise and the reaction mixture was stirred at rt for 3 h. After this time, the reaction mixture was extracted with brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude material. Purification by flash chromatography (pet. ether/ ethyl acetate [9:1]) yielded the title compound 438 as a clear oil (0.58 g, 63%); m/z (EI) 625 (M^+, weak ~5%), 569 (M-*t*-Bu, 10%), 475 (50%), 201 (C_4F_8, 70%); ν_{max}(golden gate) 2955, 1256 (Si-Me), 1183 (Si-O), 1090, 837 and 779 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.08 (3H, s, Si-CH_3), 0.093 (3H, s, Si-CH_3), 0.91 (9H, s, C(CH_3)$_3$), 2.60 (1H, m, CH_AH$_B$CF$_2$), 3.12 (1H, m, CH$_A$$H_BCF_2$), 3.75 (1H, dd, ^3J 5 Hz, ^2J 11 Hz, CH_AH$_B$), 3.87 (1H, dd, ^3J 5 Hz, ^2J 11 Hz, CH_AH$_B$), 4.22 – 4.27 (1H, m, C*H*I); δ_C ($CDCl_3$; 125 MHz) –5.5 (Si-$\mathbb{C}$H$_3$), -5.4 (Si-$\mathbb{C}$H$_3$), 18.2, 18.7, 25.7 (C($\mathbb{C}$H$_3$)$_3$), 37.0 (t, $^2J_{C\text{-}F}$ 21 Hz, $\mathbb{C}$H$_2$CF$_2$), 68.2 ($\mathbb{C}$H$_2$), 94.2 (tt, $^2J_{C\text{-}F}$ 43 Hz, $^1J_{C\text{-}F}$ 320 Hz, $\mathbb{C}$F$_2$-I), 109.0 (tt, $^2J_{C\text{-}F}$ 32 Hz, $^1J_{C\text{-}F}$ 264 Hz, $\mathbb{C}$F$_2$), 109.9 (tt, $^2J_{C\text{-}F}$ 34 Hz, $^1J_{C\text{-}F}$ 268 Hz, $\mathbb{C}$F$_2$), 117.7 (tt, $^2J_{C\text{-}F}$ 31 Hz, $^1J_{C\text{-}F}$ 259 Hz, $\mathbb{C}$F$_2$); δ_F ($CDCl_3$; 188 MHz) –59.99 (2F, m, CF_2-I), -113.18 (2F, m, CF_2), -114.17 (2F, m, CF_2), -123.37 (2F, m, CF_2).

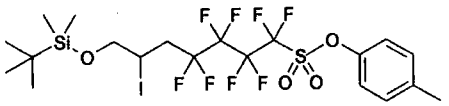
7-(*tert*-Butyldimethylsilyloxy)-1,1,2,2,3,3,4,4-octafluoro-6-iodoheptane sulfonyl Chloride 440



440

tert-Butyldimethyl-(4,4,5,5,6,6,7,7-octafluoro-2,7-diiodoheptyloxy)silane 438 (0.50 g, 0.80 mmol) was dissolved in water (2 cm^3) and acetonitrile (6 cm^3). Sodium dithionite (0.28 g, 1.60 mmol) and sodium bicarbonate (0.14 g, 1.76 mmol) were added and the reaction mixture was stirred at rt overnight. Inorganic materials were then removed by filtration and the solvent was evaporated under reduced pressure to give sodium sulfite 439 as a white residue. This was suspended in DCM (25 cm^3) and water (5 cm^3) and *N*-chlorosuccinimide (0.53 g, 4.0 mmol) was added. The reaction was stirred overnight at rt after which time DCM (50 cm^3) and saturated sodium thiosulfate (50 cm^3) were added. The layers were separated and the organic layer was dried ($MgSO_4$), filtered and evaporated to give the crude product. Purification by flash chromatography (pet. ether, pet. ether:ethyl acetate [9:1], pet. ether: ethyl acetate [8:2]) yielded title compound 440 as a clear oil (0.17 g, 36%); *m/z* (EI) 541 : 543 (3 : 1, M-*t*-Bu, 5%), 474 (5%), 383 (10%), 185 (40%); ν_{max}(golden gate) 1418 (SO_2Cl), 1213 (SO_2Cl), 1139 (Si-O), 836, and 540 cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.083 (3H, s, Si-CH_3), 0.096 (3H, s, Si-CH_3), 0.91 (9H, s, C(CH_3)$_3$), 2.62 (1H, m, CH_AH$_B$CF$_2$), 3.16 (1H, m, CH$_A$$H_BCF_2$), 3.75 (1H, dd, ^3J 4 Hz, ^2J 11 Hz, CH_AH$_B$), 3.88 (1H, dd, ^3J 4 Hz, ^2J 11 Hz, CH_AH$_B$), 4.23 – 4.27 (1H, m, CHI); δ_C ($CDCl_3$; 125 MHz) –5.5 (Si-$\mathbb{C}$H$_3$), -5.4 (Si-$\mathbb{C}$H$_3$), 17.9, 18.2, 25.7 (C($\mathbb{C}$H$_3$)$_3$), 36.9 (t, $^2J_{C\text{-}F}$ 24.5 Hz, $\mathbb{C}$H$_2$CF$_2$), 68.2 ($\mathbb{C}$H$_2$), 111.1 (tt, $^2J_{C\text{-}F}$ 32 Hz, $^1J_{C\text{-}F}$ 250 Hz, $\mathbb{C}$F$_2$), 115.6 (tt, $^2J_{C\text{-}F}$ 35 Hz, $^1J_{C\text{-}F}$ 290 Hz, $\mathbb{C}$F$_2$), 116.0 (tt, $^2J_{C\text{-}F}$ 37 Hz, $^1J_{C\text{-}F}$ 258 Hz, $\mathbb{C}$F$_2$), 117.8 (tt, $^2J_{C\text{-}F}$ 32 Hz, $^1J_{C\text{-}F}$ 259 Hz, $\mathbb{C}$F$_2$); δ_F ($CDCl_3$; 188 MHz) -104.45 (2F, m, CF_2SO$_2$Cl), -113.94 (2F, m, CF_2), -119.45 (2F, m, CF_2CF$_2$SO$_2$Cl), -123.83 (2F, m, CF_2).

7-(*tert*-Butyldimethyl-silyloxy)-1,1,2,2,3,3,4,4-octafluoro-6-iodoheptane-1-sulfonic Acid *p*-Tolyl Ester 441



441

A solution of *p*-cresol (0.016 g, 0.15 mmol) in THF (2 cm^3) was added dropwise to a suspension of sodium hydride (0.008 g, 0.33 mmol) in THF (3 cm^3) at 0 °C and the mixture stirred for 15 min. After this time, a solution of sulfonyl chloride 440 (0.13 g, 0.22 mmol) in THF (3 cm^3) was added and the reaction stirred at 0 °C overnight. The reaction mixture was then diluted with diethyl ether (50 cm^3) and washed with water (2 x 10 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography (pet. ether : ethyl acetate [9 : 1], pet. ether : ethyl acetate [8 : 2]) yielded the title compound 441 as a clear oil (0.04 g, 27%); *m/z* (EI) 613 (M-*t*-Bu, 5%), 392 (70%), 345 (30%), 313 (40%); ν_{max}(golden gate) 1509, 1421 (SO_2-O), 1139 (Si-O), 891, and 822 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 0.076 (3H, s, Si-CH_3), 0.089 (3H, s, Si-CH_3), 0.90 (9H, s, C(CH_3)$_3$), 2.37 (3H, s, CH_3), 2.62 (1H, m, CH_AH$_B$CF$_2$), 3.15 (1H, m, CH$_A$$H_BCF_2$), 3.74 (1H, dd, ^3J 6.5 Hz, ^2J 11 Hz, CH_AH$_B$), 3.75 (1H, dd, ^3J 6.5 Hz, ^2J 11 Hz, CH_AH$_B$), 4.23 – 4.28 (1H, m, CHI), 7.13 – 7.32 (4H, m, ArH); δ_C ($CDCl_3$; 100 MHz) –5.5 (Si-CH$_3$), -5.4 (Si-CH$_3$), 18.1, 18.3, 25.7 (C(CH$_3$)$_3$), 37.0 (t, $^2J_{C-F}$ 21 Hz, CH$_2$CF$_2$), 68.2 (CH$_2$), 121.1(2C), 130.6 (2C), 138.3, 147.9; ca. 100 - 130 (4 x v. weak m, 4 x CF$_2$); δ_F ($CDCl_3$; 188 MHz) -109.17 (2F, t, *J* 14 Hz, CF_2SO$_3$Ar), -114.01 (2F, t, *J* 16.5 Hz, CF_2), -120.19 (2F, m, CF_2CF$_2$SO$_3$Ar), -124.01 (2F, m, CF_2).

CHAPTER 7

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7 References

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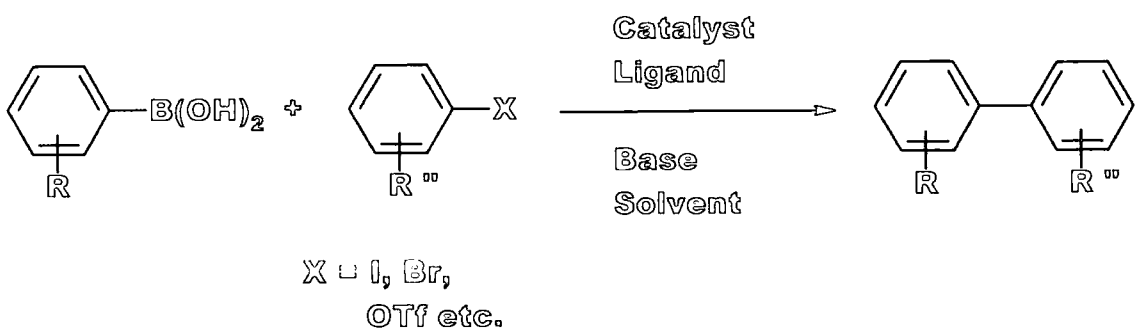
APPENDIX 1

SUZUKI ARRAY PROTOCOL



X = I, Br,
OTf etc.

A1 Protocol for Suzuki Arrays in Greenhouse

The protocol used to carry out arrays of 24 Suzuki reactions using a Radley Technologies Greenhouse Parallel Synthesizer is described in this Appendix. This procedure was adapted from one developed by Mr Ian B. Campbell of GlaxoSmithkline, Stevenage, UK and acknowledgement is made to him for the original protocol.

The conditions cover a range of catalysts, ligands, bases and solvents which have been employed regularly in Suzuki cross-coupling reactions. Arrays were carried out in a Radleys Discovery Technologies 24 array Greenhouse Parallel Synthesizer* and followed by GC and GCMS. The reactions were carried out on either 0.1 mmol scale or 0.05 mmol scale as described.

* Radleys Discovery Technologies, Shire Hall, Saffron Walden, Essex, CB11 3AZ, UK. www.radleys.com

A1.1 Reaction Conditions

GreenHouse Tube	Catalyst	Ligand	Base	Solvent
A1	$Pd(PPh_3)_4$		Cs_2CO_3	DMF
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF
A3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O
A6	$Pd(PPh_3)_4$		NaOH	DME / H_2O
B1	$Pd(OAc)_2$		K_2CO_3	DME / H_2O
B2	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Toluene
B3	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	DMF
B4	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	MeCN
B5	$Pd(OAc)_2$	(*o*-Tol)$_3$P	Et_3N	Dioxane / H_2O
B6	$Pd(OAc)_2$	Dppm	Et_3N	DMF
C1	$Pd(OAc)_2$	(2-furan)$_3$P	Et_3N	DMF
C2	$Pd(OAc)_2$	Dppe	Et_3N	DMF
C3	$Pd(OAc)_2$	Dppb	Et_3N	DMF
C4	$Pd(OAc)_2$	Dppf	Et_3N	DMF
C5	$Pd(OAc)_2$	$^tBu_2P$(BiPh)	K_3PO_4	EtOH / H_2O
C6	$Pd(OAc)_2$	$^tBu_2P$(BiPh)	K_3PO_4	Toluene
D1	$Pd_2(dba)_3$		KOAc	Toluene/EtOH
D2	$Pd_2(dba)_3$	Dppm	Cs_2CO_3	Dioxane
D3	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	DMF
D4	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O
D5	$PdCl_2$(Binap)		K_3PO_4	DMF
D6	$PdCl_2$(Binap)		CsF	THF / H_2O

Total: 4 catalysts, 7 ligands, 10 bases, 8 solvents, 1 boronic acid 1 aryl triflate [halide] require dispensing.

24 Reactions on 0.1 mmol scale. 3% catalysts, 6% ligands, 3 equivalents base.

A1.2 Dispense List

A1	Triflate [halide]	0.2 M in THF	
A2	Boronic Acid	0.2 M in THF	
A3	$Pd(PPh_3)_4$	0.01 M in THF	11.55 mg/ml
A4	Pd(OAc)2	0.01 M in THF	2.24 mg/ml
A5	$Pd_2(dba)_3$	0.01 M in THF	9.14 mg/ml
A6	$Pd(Binap)Cl_2$	0.01 M in THF	8.0 mg/ml
B1	P(*o*-Tol)$_3$	0.01 M in THF	2.02 mg/ml
B2	dppm	0.01 M in THF	3.85 mg/ml
B3	(2-furan)$_3$P	0.01 M in THF	2.32 mg/ml
B4	dppe	0.01 M in THF	3.98 mg/ml
B5	dppb	0.01 M in THF	4.26 mg/ml
B6	dppf	0.01 M in THF	5.54 mg/ml
B7	$^tBu_2P(BiPh)$	0.01 M in THF	2.98 mg/ml
C1	Na_2CO_3	1.0 M in H_2O	106 mg/ml
C2	$NaHCO_3$	1.0 M in H_2O	84 mg/ml
C3	NaOH	1.0 M in H_2O	40 mg/ml
C4	Et_3N		
C5	K_2CO_3	1.0 M in H_2O	138 mg/ml
C6	K_3PO_4	1.0 M in H_2O	203 mg/ml
C7	CsF	1.0 M in H_2O	151 mg/ml
D1	DMF		
D2	DME		
D3	PhMe		
D4	MeCN		
D5	Dioxane		
D6	H_2O		
D7	EtOH		
D8	THF		

A1.3 Solid Samples

Cs_2CO_3	3 x 97.5 mg
K_3PO_4	3 x 60.9 mg
$Ba(OH)_2$	1 x 51.3 mg
KOAc	1 x 29.4 mg

A1.4 Protocol

500 µl A1 to vessels A1 – D6	(24 dispenses)
500 µl A2 to vessels A1 – D6	(24 dispenses)
500 µl A3 to vessels A1 – A6	(3 dispenses)
500 µl A4 to vessels B1 – C6	(12 dispenses)
500 µl A5 to vessels D1 – D3	(3 dispenses)
500 µl A6 to vessels D4 – D6	(3 dispenses)
500 µl B1 to vessels B2 – B5	(4 dispenses)
500 µl B2 to vessels B6 and B2	(2 dispenses)
500 µl B3 to vessel C1	(1 dispense)
500 µl B4 to vessel C2	(1 dispense)
500 µl B5 to vessel C3	(1 dispense)
500 µl B6 to vessels C4 and D3	(2 dispenses)
500 µl B7 to vessels C5 and C6	(2 dispenses)

STOP

EVAPORATE THF (Genevac 12 minutes full power)

300 µl C1 to vessel A3	(1 dispense)
300 µl C2 to vessels A4 and D4	(2 dispenses)
300 µl C3 to vessel A1	(1 dispense)
50 µl C4 to vessels B2 – C4	(9 dispenses)
300 µl C5 to vessel B1	(1 dispense)

300 µl C6 to vessel C5	(1 dispense)
300 µl C7 to vessel D6	(1 dispense)
1000 µl D1 to vessels A1, A2, B3, B6 – C4, D3, D5	(10 dispenses)
700 µl D1 to vessel B1	(1 dispense)
700 µl D2 to vessels A3 – A6 and D4	(5 dispenses)
1000 µl D3 to vessels B2 and C6	(2 dispenses)
500 µl D3 to vessel D1	(1 dispense)
1000 µl D4 to vessel B4	(1 dispense)
500 µl D5 to vessel B5	(1 dispense)
1000 µl D5 to vessel D2	(1 dispense)
300 µl D6 to vessels A3 – A6, B1, B5, C5, D4, D6	(9 dispenses)
700 µl D7 to vessel C5	(1 dispense)
700 µl D8 to vessel D6	(1 dispense)

Add Cs_2CO_3 97.5 mg to vessels A1, D2 and D3

Add K_3PO_4 60.9 mg to vessels A2, C6 and D5

Add $Ba(OH)_2$ 51.3 mg to vessel A5

Add KOAc 29.4 mg to vessel D1

Reactions are heated at 80 °C for 16 h and analysed by GC and GCMS

APPENDIX 2

RESEARCH CONFERENCES

ATTENDED AND PAPERS PUBLISHED

A2.1 Research Conferences Attended

Sep 2004 5th International Symposium on Transition Metals in Organic Synthesis, *University of Strathclyde, UK* *

Sep 2004 The 4th Annual RSC Fluorine Subject Group Postgraduate Meeting, *University of Durham, UK* **

May 2004 3rd Year PhD Presentation, *University of Durham, UK* **

May 2004 Synthesis and Applications of Organoboronates, *University of Durham, UK*

May 2004 International Symposium on Advances in Synthetic, Combinatorial and Medicinal Chemistry 2004, *Mezhdunarodnaya Hotel, Moscow, Russia* *

Apr 2004 RSC Perkin North East Regional Meeting, *Leeds University, UK* *

Mar 2004 Avecia Poster Competition, *University of Durham, UK* *

Jan 2004 Organic Synthesis: It's Not Just Carbon, *University of Strathclyde, UK*

Dec 2003 2nd Postgraduate Symposium on Organic and Medicinal Chemistry, *Babraham Institute, Cambridge, UK* **

Aug 2003 UK GRAD School, *St. Hildas College, University of Oxford, UK*

Jul 2003 RSC Medicinal Chemistry Residential School, *University of Nottingham, UK*

Jul 2003 Combichem Comes of Age: Applications and Developments, *Churchill College, University of Cambridge, UK* ***

April 2003 14th Scottish Graduate Symposium on Novel Organic Chemistry, *University of Aberdeen, UK*

April 2003 Young Chemists in industry XII, *SCI International Headquarters, 14/15 Belgrave Square, London, UK*

Mar 2003 Perkin Division North East Regional Meeting, *University of Newcastle upon Tyne, UK*

Dec 2002 Modern Aspects of Stereochemistry, *Sheffield University, UK*

Apr 2002 13th Scottish Graduate Symposium on Novel Organic Chemistry, *University of St-Andrews, UK*

Apr 2002 RSC Perkin North East Regional Meeting, *University of York, UK*

Jan 2002 Mechanistic Aspects of the Design of Bioactive Materials, *University of Manchester, UK*

Dec 2001 Modern Aspects of Stereochemistry, *Sheffield University, UK*

* Poster presentation by the author

** Oral presentation by the author

*** Poster presentation awarded first prize

A2.2 Papers Published

New Linkers for Traceless Cleavage Strategies in Solid Phase Synthesis, J. Guo, P. J. H. Scott, P. G. Steel and I. B. Campbell, *Abstracts of Papers 226th ACS National Meeting, New York*, **2003**, 150.