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Investigation into the Reactivity of Pentafluorophenyl Vinylsulfonate in the Formation of Functionalized Sulfonamides of Biological Importance

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PhD Thesis

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Abstract

Sulfonamides constitute a vital and diverse class of therapeutic agents; hence the development of convenient and straightforward synthetic routes to such species is a valuable endeavour.

This thesis describes an exploration into the reactivity of the novel bifunctional acceptor pentafluorophenyl vinylsulfonate in the formation of biologically interesting sulfonamide species.

A variety of transformations were carried out effectively at the electron-deficient olefinic portion of pentafluorophenyl vinylsulfonate to provide functionalized pentafluorophenyl esters.

Subsequent displacement of the pentafluorophenyl moiety *via* an established aminolysis procedure then delivered the corresponding sulfonamide products.

During the course of this investigation, it was established that both radical and cycloaddition routes were successful in furnishing desirable compounds.

It was found that intermolecular radical addition of alkyl halides occurred readily and permitted the formation of a number of sulfonamide addition products.

In addition, Diels-Alder cycloaddition with carbocyclic dienes and furan formed stable *exo*-bicyclic sulfonamides.

Notably, 1,3-dipolar cycloaddition with a diverse library of *N*-methyl-nitrones gave the corresponding isoxazolidine species with unprecedented regio- and stereoselectivity. Subsequent aminolysis delivered functionalized heterocyclic sulfonamides with potential biological importance.

Contents

Abbreviations

AIBN 2,2-azobis(2-methylpropionitrile)

AMPA α–amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

ATP adenosine triphosphate

$BF_3.Et_2O$ boron trifluoride, ether complex

BSTFA N,O-bis(trimethylsilyl)-trifluoroactamide

$[(^tBu)_3PH]BF_4$ tri-*tert*-butylphosphonium tetrafluoroborate

Chloramine-T *N*-chloro-*p*-toluenesulfonamide, sodium salt

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

Grubbs II Grubbs second generation catalyst $C_{46}H_{65}Cl_2N_2PRu$

Hoveyda Hoveyda-Grubbs second generation catalyst $C_{31}H_{38}Cl_2N_2ORu$

KA kainic acid

LCMS liquid chromatography-mass spectrometry

$Mn(OAc)_3.2H_2O$ manganese (III) acetate dihydrate

MW microwave

nmr nuclear magnetic resonance

P petroleum ether 40-60 °C

$Pd_2(dba)_3$ tris(dibenzylideneacetone)dipalladium (0)

PFP pentafluorophenyl

PFPVS pentafluorophenyl vinylsulfonate

r.t. room temperature

SM starting material(s)

tlc thin layer chromatography

1.0 INTRODUCTION

This thesis describes the research undertaken on developing the sulfonamide motif as a modern and efficient element of current therapies. It builds on work originally developed in the Caddick laboratory and demonstrates the versatility of this methodology for the construction of biologically important sulfonamide libraries.

1.1 Sulfonamides as Potent Therapies for Disease

Sulfonamides are acknowledged as one of the most effective and diverse classes of therapeutic agents over the last fifty years. As management of disease has advanced and drug mode of action is better understood, sulfonamides have continued to be at the forefront of drug design through their ability to inhibit a wide range of therapeutic targets. The primary application of sulfonamides as valuable antibiotic agents has subsequently been extended to such targets as carbonic anhydrases (CAs); inhibition of which has been one route to successfully treating glaucoma, epilepsy and heart failure,[1] and the inhibition of CAs by sulfonamides is currently being recognised as a potential treatment for solid tumours;[2] and more recently cysteine proteases (CPs), which are currently thought to be key targets for the treatment of arthritis, Alzheimer's Disease and cancer.[3,4]

1.1.1 Sulfonamides as antibacterial agents

Sulfonamides were originally exploited as antibacterial drugs, the first being sulfanilamide (1), which was discovered to disrupt bacterial folic acid metabolism in 1935 (Figure 1).[5]

The revelation of sulfanilamide highlighted the sulfonamide motif as an important functionality in drug design, and instigated the development of sulfonamides from simple antibacterials to the potent treatments for an impressive variety of diseases presented today.

To emphasize the relevance of sulfonamides as potent antibacterial agents, it is noteworthy to underline the fact that some early sulfonamide antibacterials are still in clinical use. For example, sulfadiazine is currently incorporated in silver sulfadiazine (2) (Silvadene®), a topical treatment for severe burns, where its antimicrobial effects aid wound healing (Figure 1).[6] Sulfadiazine has also found clinical use as a treatment for toxoplasmic encephalitis in AIDS patients.[7]

Sulfamethoxazole (3) (Gantanol®, Figure 1) has been prescribed since 1961, and works by inhibiting the production of bacterial dihydrofolic acid. However, due to

the emergence of bacterial resistance, sulfamethoxazole is rarely administered alone today, and is more commonly prescribed in combination with another antibiotic, trimethoprim (Bactrim®), for the treatment of urinary tract infections.[8] Sulfamethoxazole can also be used in conjunction with a variety of other medication to treat conditions such as malaria, conjunctivitis and toxoplasmosis.[8] Finally, sulfathiazole (4) (Trysul®, Figure 1), is used to treat a number of vaginal bacterial infections.[9]

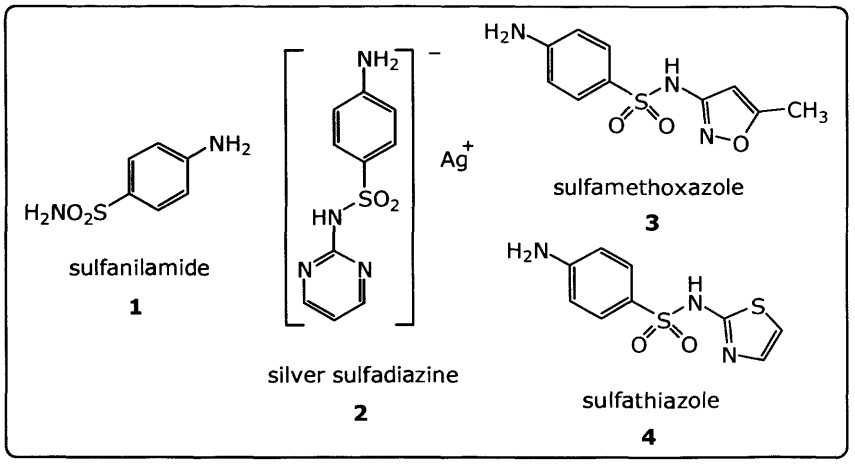


Figure 1

1.1.2 Sulfonamides as carbonic anhydrase inhibitors

Carbonic anhydrases are one of the most ubiquitous zinc-based enzymes in nature, found in bacterium and vertebrates alike. There are currently 14 known isoforms of carbonic anhydrase present in humans, namely cytosolic (CA I, CA II, CA III, CA VII), membrane bound (CA IV, CA IX, CA XII, CA XIV), one mitochondrial (CA V) and one secreted isoform (CA VI), with the sites of the remaining CA isoforms yet to be determined.[1]

CA enzymes are involved in numerous physiological functions within the body, but are primarily concerned with catalyzing the essential process of CO_2 conversion to bicarbonate in the cell. This feature is critical for respiration, CO_2 transportation, electrolyte excretion, pH regulation and homeostasis among others.[1]

Due to the wide distribution of carbonic anhydrase in its various isoforms throughout the body and its important physiological function, there are a vast number of possible targets for inhibitors, making it an attractive candidate for exploitation.

The classic systemic carbonic anhydrase inhibitors (CAIs) developed in the 1950s, which include acetazolamide (AZA), methazolamide (MZA), ethoxzolamide (EZA) and dichlorophenamide (DCP) have enjoyed longstanding clinical success as

antiglaucoma drugs (Figure 2), and instigated interest in the heterocyclic sulfonamide motif as a fruitful lead in developing therapies for other diseases. Notably, the topically acting antiglaucoma CAIs dorzolamide (DZA) and brinzolamide (BRZ) have been introduced clinically within the last 10 years.[1]

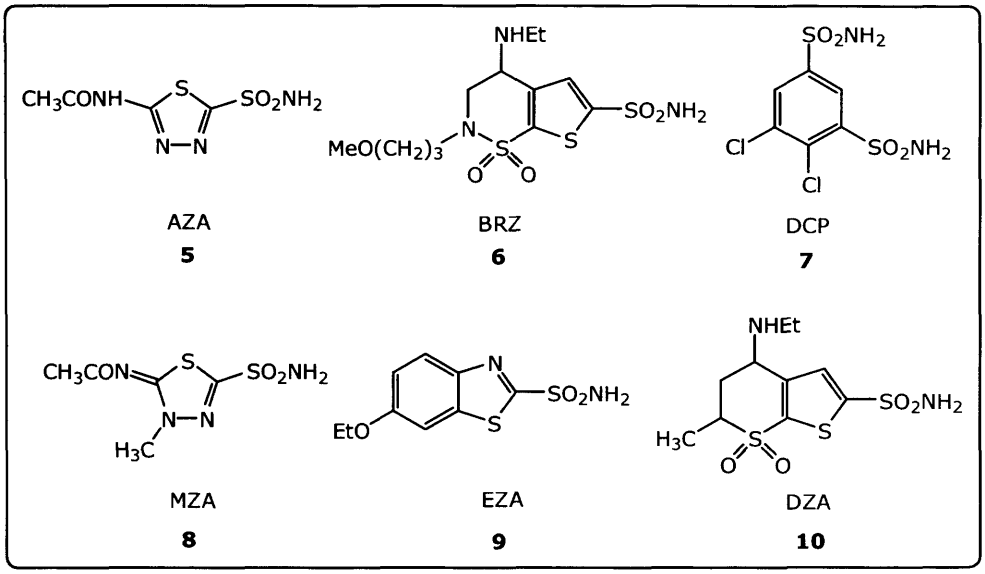


Figure 2

Research into the many isoforms of calcium anhydrase has shown that each specific isoform often has a distinct physiological role in the body. Subsequently, potential inhibitors are currently being designed to selectively act on the certain isoforms of interest, thereby avoiding any detrimental side effects arising from non-selective inhibitors.[10]

One of the most active areas of CAI research is concentrated on CA isoforms IX and XII, as the discovery that these isoforms are overexpressed in tumour cells makes them ideal targets for antitumour therapies. CA IX and XII are thought to be involved in the pH balance and intercellular communication of a wide variety of tumours, including cervix; kidney; lung; breast and colon carcinomas, yet are sparsely found in normal healthy cells. Thus specific inhibition of CA IX and/or XII could be of therapeutic benefit.[1]

Studies on the inhibition of CA IX have resulted in the discovery of a number of potent, sub-nanomolar sulfonamide-based inhibitors with improved activity compared to currently administered drugs (a selection are displayed in Figure 3). The most developed compound at this stage is indisulam (E7070), developed in Japan by Ozawa *et al.*, which is presently in advanced Phase II clinical trials for the treatment of solid tumours.[11]

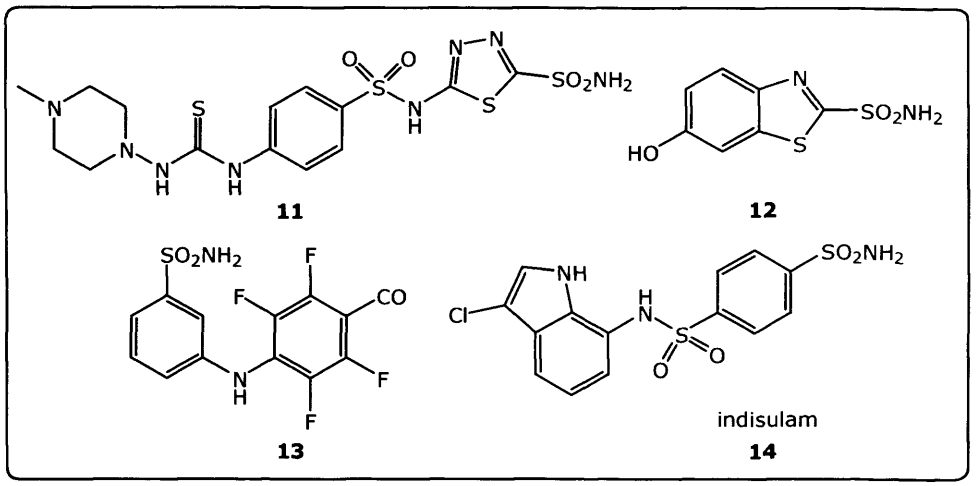


Figure 3

CA II is generally the most sensitive isoform to sulfonamide inhibition, and is the main isozyme involved in aqueous humour secretion in the eye, as well as the physiological processes of respiration and CO_2 transport common to all the carbonic anhydrases. The classic systemic antiglaucoma drugs (Figure 2) have exploited the sensitivity of CA II for over 50 years, with their mode of action resulting in lowering of the intraocular pressure in the eye.

New sulfonamide antiglaucoma drugs are currently being developed which are CA II specific and are reported to have greater bioavailability than BRZ and DZA, suggesting that superior therapies for the treatment of glaucoma could be forthcoming (Figure 4).[12]

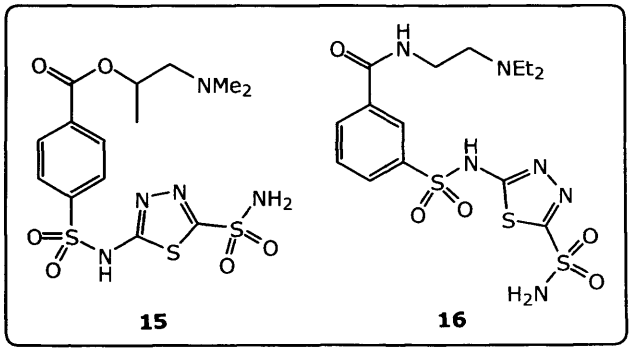
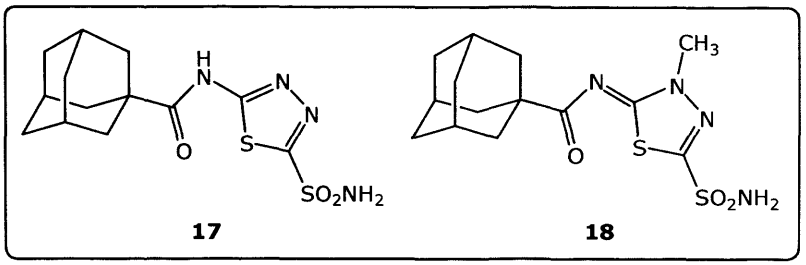


Figure 4

CA inhibitors are also thought to be potential anticonvulsants, for the treatment of epilepsy. This is due to the fact that CA is abundant in the brain neurones, primarily as the isoforms II, VII and XIV, which are associated with the secretion of cerebrospinal fluid. It has also been shown that the excitatory effect of bicarbonate anions in the brain, which contribute to the occurrence of seizures, is blocked by CAIs that can pass through the blood-brain barrier.[13]

A number of inhibitory sulfonamides have been designed for the treatment of epilepsy and depression *via* this mode of action (Figure 5). The most potent compounds in a study by Supuran *et al.* were found to be highly selective for isoform CA II and displayed superior potency in comparison with the classic anticonvulsants AZA and MZA.[13]

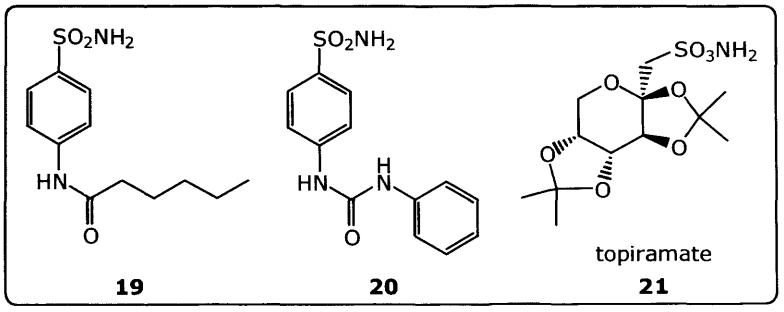


17 **18**

Figure 5

Obesity is also a condition that has the potential to be treated by sulfonamide CAIs. The mitochondrial isoform CA V is known to be associated with such physiological processes as ureagenesis, gluconeogenisis and lipogenesis.[14] Inhibition of lipogenesis is thought to be the mode of action for antiobesity drugs, since it was discovered that the antiepileptic sulfamate drug topiramate (21) (Figure 6), which is a potent CA II inhibitor, had the side effect of reducing body weight in administered patients. This is thought to be due to the drugs' efficient inhibition of both CA II and CA V, and topiramate has been patented as an antiobesity drug.[14]

Studies on sulfonamides in the quest for selective CA V or dual CA II/V inhibitors have been carried out recently, and a number of potent subnanomolar compounds have been identified for further investigation (Figure 6).[14]



19 **20** **21**

Figure 6

The regulation of bicarbonate anions by carbonic anhydrases is also prevalent in viral species, and CAIs have been suggested as novel treatments for diseases such as malaria. The mode of action in this case has been identified as the

interception of pyrimidine biosynthesis, where bicarbonate is utilized throughout the metabolic pathway.[15]

Plasmodium falciparum is the most widespread malarial parasite, and its CA has been isolated[16] and known to be distinct to that of the human host. It is postulated that sulfonamide mediated inhibition of CA I and/or II, which are highly concentrated in red blood cells, would represent a novel route towards alleviating malaria as a serious health issue, without the toxicity and parasite resistance that is associated with current antimalaria treatments.[15]

Initial research has isolated one compound in particular, an ureido-sulfonamide that is almost four times as effective as AZA, the clinically used systemic CAI (Figure 7).[15]

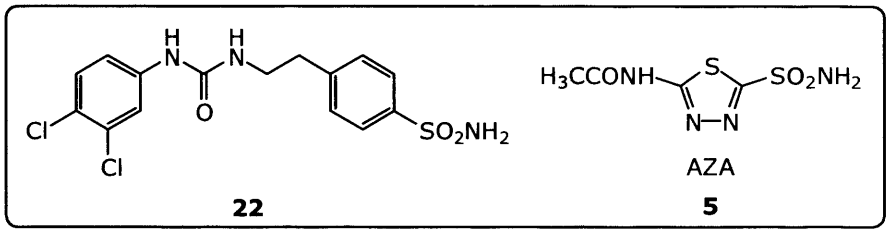


Figure 7

1.1.3 Sulfonamides as cysteine protease inhibitors

Cysteine proteases (CPs) constitute a varied and important class of enzymes, which are involved in myriad physiological events such as apoptosis, antigen processing and the degradation of proteins. Cysteine proteases have been implicated in the pathology of several diseases, including rheumatoid arthritis, inflammatory bowel disease, osteoporosis, stroke, Alzheimer's disease, cancer, and parasitic diseases such as malaria. Consequently, developing CP inhibitors to potentially address these disorders represents an attractive opportunity.[3,4]

Interleukin-1β is a cytokine concerned with both acute and chronic inflammation, and plays a role in septic shock, arthritis and Alzheimer's disease. This cytokine is regulated by the CP caspase-1 (also known as interleukin-1β converting enzyme, ICE); hence caspases have been investigated as potential targets for inhibitors.[3,4]

Harter *et al.* recently reported the synthesis of peptide-based sulfonamides that inhibited caspase-1 with nanomolar potency (Figure 8).[4]

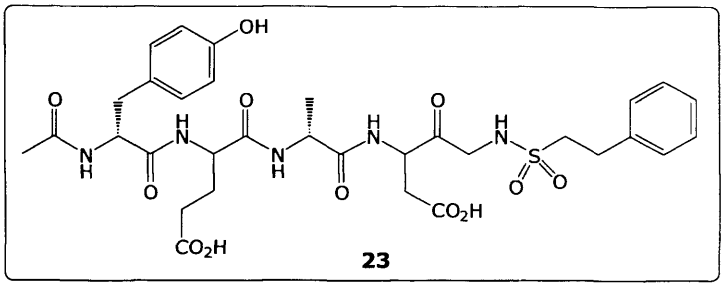


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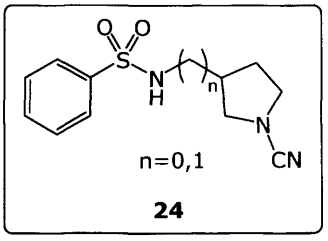
Figure 8

Cathepsins are a class of CPs that are mainly involved with intracellular proteolysis, but have also shown to have other functions, for example cathepsin K has an important role in bone physiology, thereby offering itself as a target for osteoporosis treatments, and cathepin L, which is present in healthy cell lysosomes, is known to be secreted outside the lysosome in disease states such as muscular dystrophy, cancer, multiple sclerosis and Alzheimer's disease, hence cathepsin L is also an interesting target for inhibitors.

Sulfonamides have been involved in the quest for cathepsin inhibitors. Falguyeret *et al* have reported sulfonamide compounds that were shown to effectively inhibit cathepsins K and L *in vitro* (Figure 9).[3,17]



24

Figure 9

Cysteine proteases are also important enzymes in nature, and are responsible for a variety of essential processes in protozoa. Hence, CPs represent novel targets for treating parasitic infections such as malaria and Chagas' disease (the leading cause of congestive heart failure and inflammation in South America, affecting over 18 million people and currently without adequate treatment).[18]

Potential inhibitors of cruzain, the major CP of the parasite *Trypanosoma cruzi* that causes Chagas' disease, have been developed by Roush *et al*. Vinyl sulfonamides (such as structure (25), Figure 10) were shown to be selective and potent inhibitors of cruzain, with their mode of action identified as being irreversible binding to a cysteine residue within the CP active site.[4]

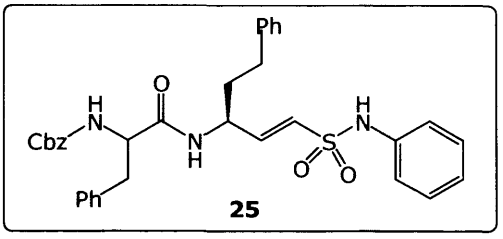


Figure 10

Analogous to the potential targets for calcium anhydrase inhibitors, malarial parasites are also of interest for CP inhibitors, especially since virulent strains such as *Plasmodium falciparum* are becoming resistant to current antimalarial drugs. One potentially fruitful target for inhibition is the papain family of cysteine proteases, specifically falcipain-2 and falcipain-3, which are required for the essential process of haemoglobin hydrolysis in the parasite.[19]

Shenai *et al.* have developed vinyl sulfonamides that display nanomolar inhibition of both falcipain-2 and falcipain-3, and consequently show potential as future antimalarial agents (Figure 11).[19]

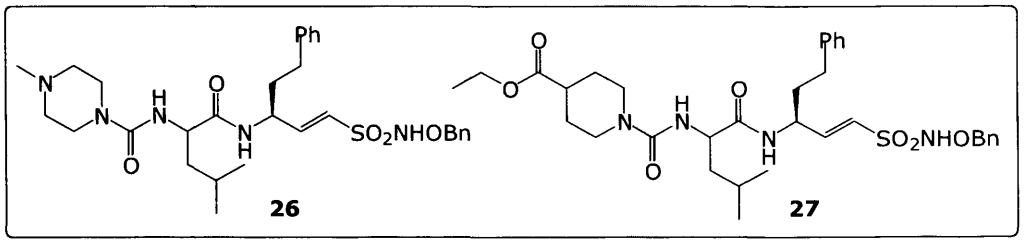


Figure 11

1.1.4 Sulfonamides as HIV protease inhibitors

Sulfonamides are widely established in the area of HIV protease inhibition, chiefly due to the successful antiviral drug amprenavir (28) (Figure 12), which boasts high oral bioavailability and a lengthy half-life. A number of compounds structurally related to amprenavir are currently in development, which display subnanomolar activity against previously resistant strains of mutant and wild type HIV proteases. For example, tipranavir (29) and DPC-681 (30) are in the process of Phase I clinical trials, and TMC-126 (31) and TMC-114 (32) (developed by Tibotec) are presently undergoing clinical human trials (Figure 12).[3]

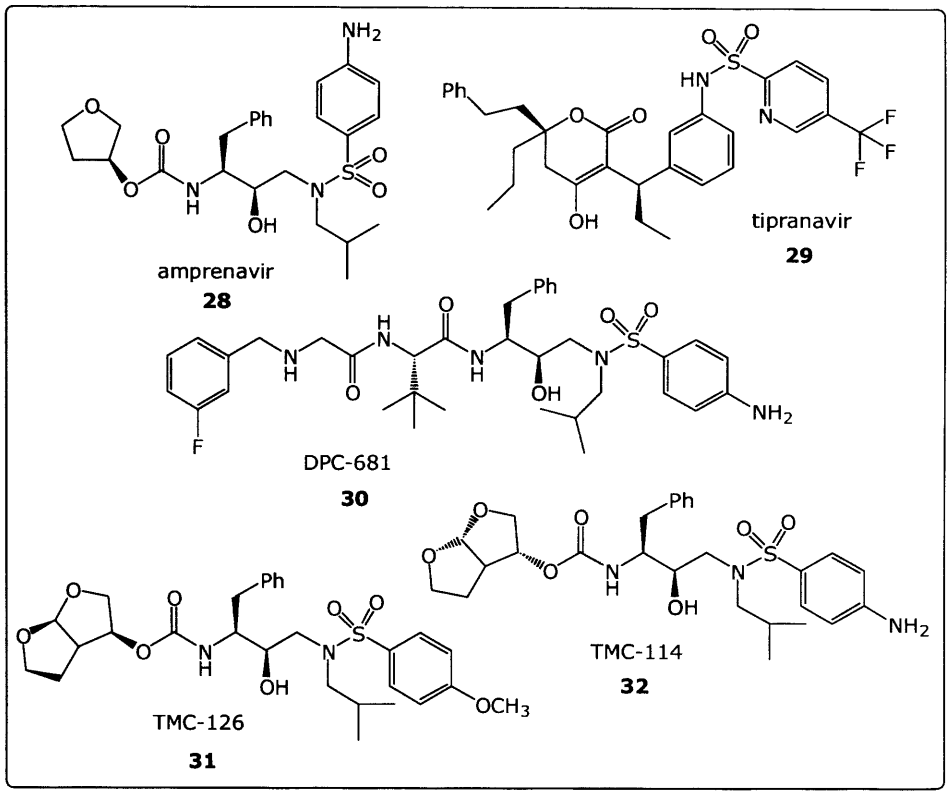


Figure 12

In addition, Stranix *et al.* have recently reported the formation of lysine sulfonamides which possess a high potency against wild type HIV proteases (Figure 13).[20]

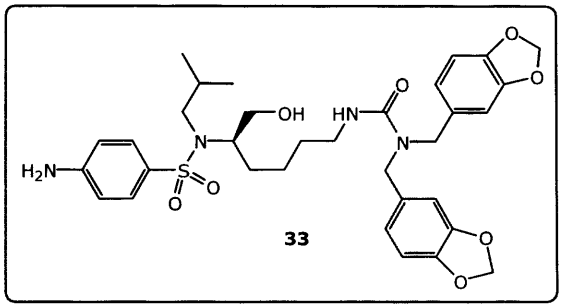


Figure 13

1.1.5 Sulfonamides as COX-II specific inhibitors

The development of sulfonamide-based COX-II specific inhibitors has been a major breakthrough in the administration of anti-inflammatories for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and post-surgical analgesia.

Cyclooxygenase (COX) enzymes are involved in the synthesis of prostaglandins (PGIs) and thromboxane (TX) from arachidonic acid, and are present as two

known isoforms in the body, namely COX-I, which is constitutive, and COX-II, which is induced in response to inflammation (although it is thought to be constitutively expressed in some tissues).
COX-I is involved in the synthesis of PGIs and TX in the gastric mucosa, platelets and kidneys. PGIs are important biological mediators and their roles include protecting the GI tract and maintaining renal homeostasis. TX promotes platelet aggregation in response to bleeding.
COX-II is generally induced when inflammation arises, and is thought to mainly affect those PGIs specifically involved in inflammation.[21]

Analgesia has traditionally been relieved with the use of non-selective NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen, but their lack of selectivity is renowned to cause side effects such as ulcers, bleeding (especially post-operative), and gastroduodenal erosion in susceptible patients.
These side effects are due to the suppression of the constitutive COX-I enzyme, which synthesizes platelets (which are involved in blood clotting) and the gastric-protecting PGIs. Consequently, COX-II specific inhibitors were designed to give pain relief without the adverse affects associated with conventional NSAIDs.[22]
The first COX-II inhibitors were launched in 1999; the sulfone rofecoxib (Vioxx®, Figure 14), and the sulfonamide celecoxib (Celebrex®, Figure 14). Valdecoxib (Bextra®, Figure 14) followed in 2002 and has been prescribed to 7 million patients worldwide for the treatment of OA, RA and post-surgical analgesia. The drugs display highly selective COX-II inhibitory properties, have fast acting and long lasting analgesic effect, and exhibit higher tolerance than NSAIDs.[23]

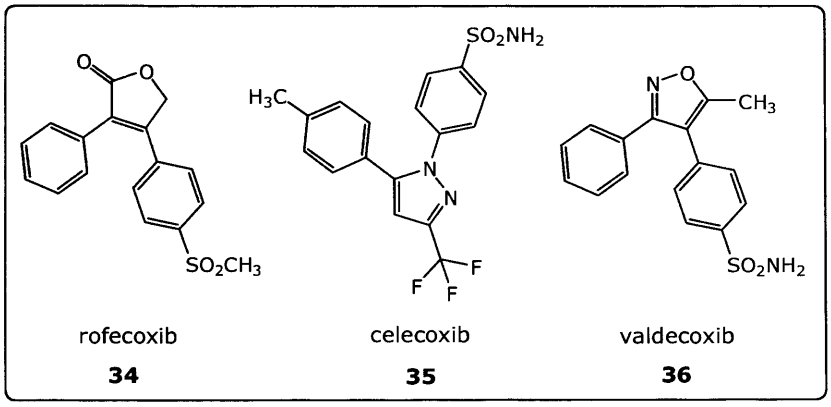


Figure 14

Despite these benefits, Merck withdrew rofecoxib (which had been prescribed to 80 million patients) in September 2004 following concerns of an increased risk of myocardial infarction and stroke. This is possibly due to the sole inhibition of

certain COX-II prostaglandins, whereas COX-I thromboxane is unaffected. Hence thromboxane effects are effectively exaggerated during administration, which is thought to potentially expose patients to cardiotoxicity.[21,23c)]
The chemistry of celecoxib and valdecoxib is thought to be distinct from that of rofecoxib so may not represent a similar hazard,[24] although fears of increased cardiovascular and gastrointestinal risk in patients administered valdecoxib[22,23,25] resulted in Pfizer withdrawing the drug in April 2005.

Nevertheless, coxibs are still considered valuable therapeutic agents, and there is evidence that their benefits reach further than just analgesia. For example, it has been observed that COX-II enzymes are often over expressed in tumour cells, particularly in colon carcinomas. Consequently, it has been postulated that COX-II specific inhibitors could produce a chemoprotective effect, and Maier *et al.* have shown that celecoxib induces apoptosis in both animal and human models.[26]
In addition, Supuran *et al.* have demonstrated that both valdecoxib and celecoxib strongly inhibit CA IX, which (as previously described) is the CA isoform associated with tumours. Both coxibs were found to have greater efficacy than the systemic CAIs AZA and MZA.[24]
Furthermore, celecoxib has been suggested as an add-on therapy in the treatment of neuropsychiatric disorders such as Alzheimer's disease, cerebral ischemia and schizophrenia. Reasoning for this is that the COX-II enzymes present in the brain tissue can be activated by cytokines, causing inflammation. Patients suffering from schizophrenia often display increased levels of cytokines in their spinal fluid, which possibly promotes incidences of inflammation-induced neuropsychiatric disorder. Celecoxib is thought to inhibit the COX-II activation by cytokines in the central nervous system, and consequently presents itself as a novel therapy for schizophrenia and other related diseases.[27]

1.1.6 Sulfonamides as diuretics

Sulfonamides display efficacy as potent loop diuretics, and are exemplified by furosemide (Lasix®, Figure 15), which was introduced clinically over 30 years ago. Diuretics work by initiating the loss of water, minerals and electrolytes from the body *via* urination, and are crucial drugs for the treatment of oedema (water retention), which arises in conditions such as chronic heart failure, renal failure, and cirrhosis.[28]
Furosemide is routinely prescribed for the long-term management of heart failure, and is often used in combination with other drugs to treat hypertension. Consequently, sulfonamides play a central role in this area, with more modern

diuretics such as torsemide (Demadex®, Figure 15) continuing the trend.[29]

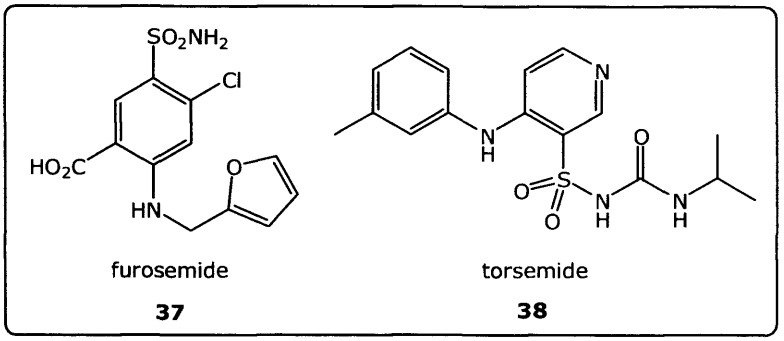


Figure 15

1.1.7 Sulfonamides as hypoglycaemic agents

Sulfonamides that act as hypoglycaemic drugs are of the sulfonylurea class, and include glibenclamide (Figure 16). These agents treat Type II (non-insulin dependent) diabetes mellitus, and work by initiating the release of insulin from islet β-cells in the pancreas, resulting in the lowering of blood sugar levels.[30]

Put explicitly, glibenclamide is a potent and selective inhibitor of the cellular ATP sensitive K^+ channel, and the subsequent depolarization of the cell membrane and influx of Ca^{2+} ultimately leads to insulin release. Its high affinity for this cellular binding site, deemed critical for ATP K^+ channel regulation, has allowed glibenclamide to be implicated in further therapeutic roles as the process of intercellular communication and signalling is better understood.[31]

For example, glibenclamide has been shown to give enhanced survival after haemorrhagic shock and endotoxemia by increasing arterial pressure upon administration. Improved renal function was also reported.[32] This is an illustration of the fact that as disease states are more thoroughly understood, the concept of employing sulfonamides is often proposed, which underlines the broad applicability of sulfonamides in general.

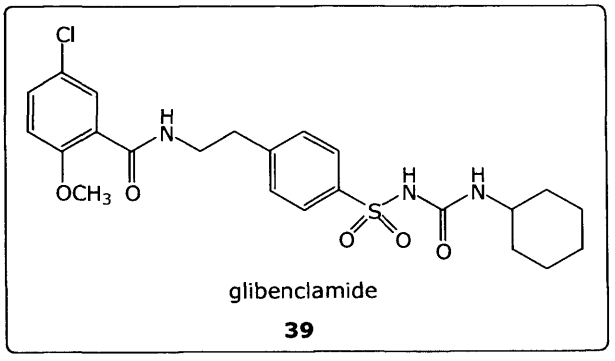


Figure 16

1.1.8 Other sulfonamide agents

There are further sulfonamide drugs that do not come under the above headings, but are worthy of a citation.

Sulfasalazine (Azulfidine®, Figure 17) has been approved for clinical use since 1950, and is an anti-inflammatory pro-drug. Once administered, sulfasalazine is metabolised in the colon to the active agent 5-aminosalicylic acid, and is used to treat disorders that are associated with inflammation of the colon, such as ulcerative colitis and Crohn's disease. Sulfasalazine is also prescribed for rheumatoid arthritis.[33]

Finally, perhaps the most illustrious sulfonamide drug at present is sildenafil (Viagra®, Figure 17), which is used to treat erectile dysfunction. In brief, sildenafil works by inhibiting the enzyme phosphodiesterase-5, whose role is the metabolism of cyclic guanosine monophosphate, a substance that is ultimately responsible for the regulation of blood within the penis. This inhibition results in the prolongation of penile erection.[34]

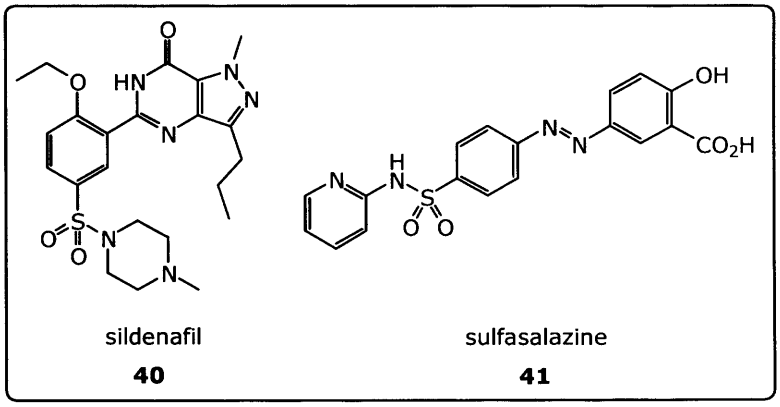


Figure 17

In conclusion, sulfonamides represent a diverse and relevant class of therapeutics. The sulfonamide motif commands recognition for its vital role in medicine over the last 50 years, and remains a potent tool for the delivery of modern and effective drugs to treat an increasing portfolio of diseases.

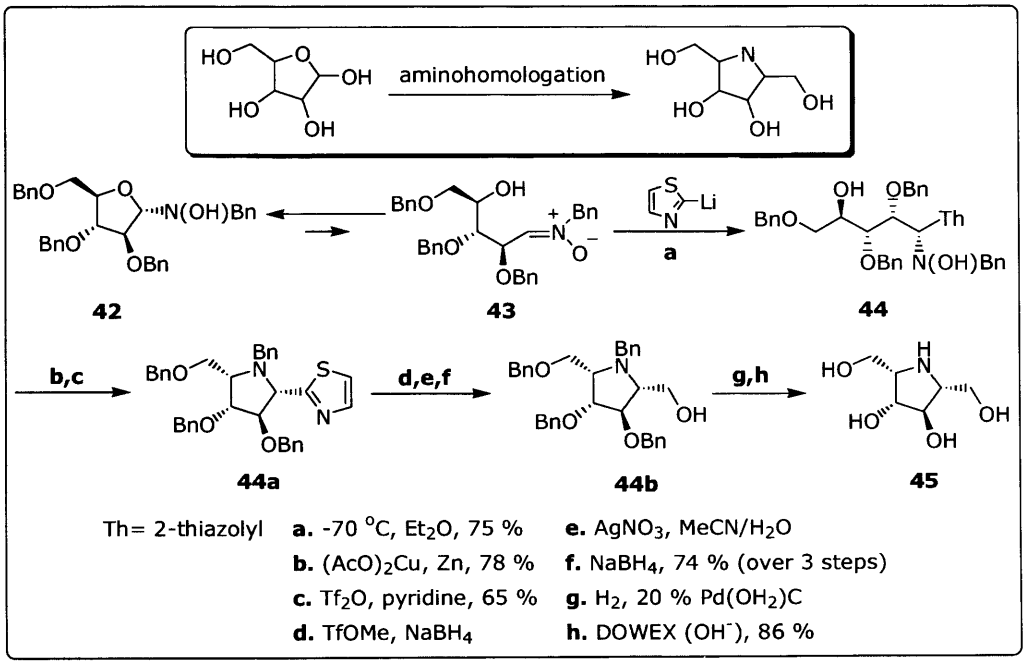
1.2 The Role of Nitrones in [3+2] Cycloaddition to Olefins

This thesis predominantly focuses upon the 1,3-dipolar cycloaddition of nitrones to an olefin (PFP vinylsulfonate), in efforts towards the formation of sulfonamides. Consequently, it is important to discuss the general utility of nitrones in organic synthesis, in addition to the often perplexing selectivity displayed in nitrone-olefin cycloaddition products.

1.2.1 Nitrones as valuable tools in natural product synthesis

Nitrones have been utilized as important intermediates in a number of natural product syntheses, often to enable the introduction of nitrogen into a molecule with high regio- and stereo-selectivity.

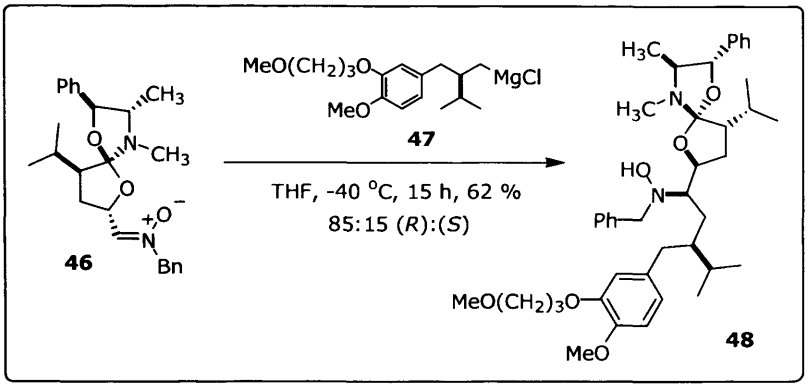
Dondoni and co-workers used nitrone chemistry to convert furanoses into pyrrolidine homoazasugars *via* aminohomologation (Scheme 1).[35] Pyrrolidines are recognised as potential drug candidates for conditions such as diabetes, viral infections and cancer metastasis, therefore an efficient route to their synthesis is evidently beneficial. The nitrone step in this synthesis concerned the stereoselective addition of 2-lithiothiazole to nitrone (43) generated *in situ* from the corresponding hydroxylamine (42), to give the open chain adduct (44). Further transformations furnished the target structures exemplified by (45).



Scheme 1

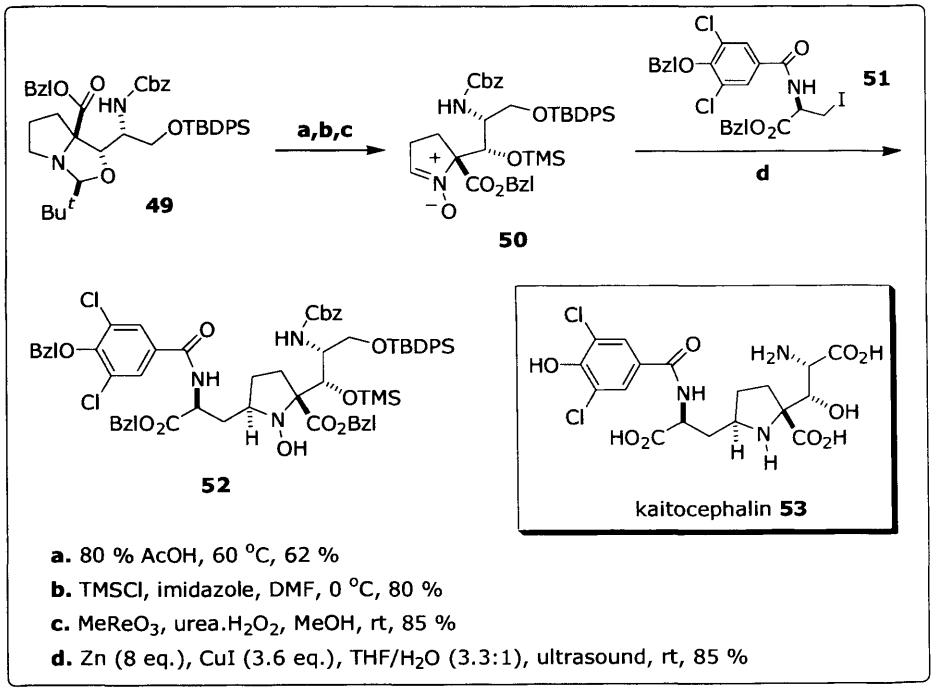
Dondoni also used nitrones as a key element in the total synthesis of SPP-100, a renin inhibitor that acts as an antihypertensive by reducing blood pressure long

term *in vivo*.[36] The addition of nucleophillic species to *N*-benzyl nitrones was discovered to be a convenient method for the introduction of amino functionality into the system. The central step involved coupling the functionalized nitrone (46) to the Grignard reagent (47) to furnish the (*R*)-hydroxylamine (48) as the major diastereoisomer (Scheme 2).



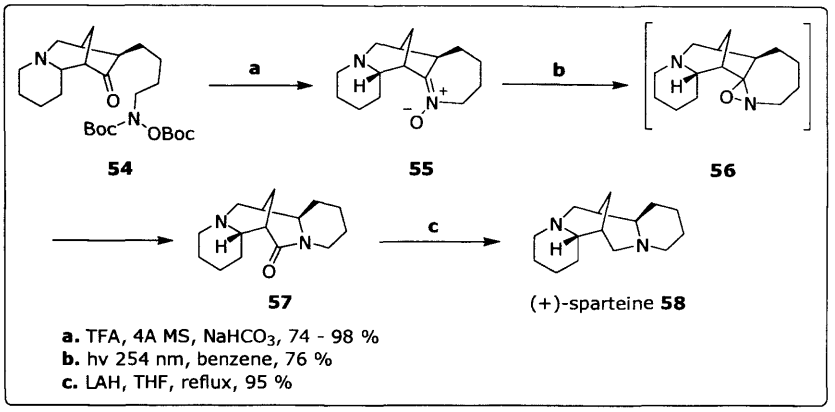
Scheme 2

The stereoselective coupling of a nitrone to a halide is the fundamental transformation in the total synthesis of kaitocephalin, a potent AMPA/KA receptor antagonist. Watanabe *et al.* found nitrone (50) underwent addition to the halide species (51) selectively, yielding hydroxylamine (52) as a single isomer in excellent yield (Scheme 3).[37]



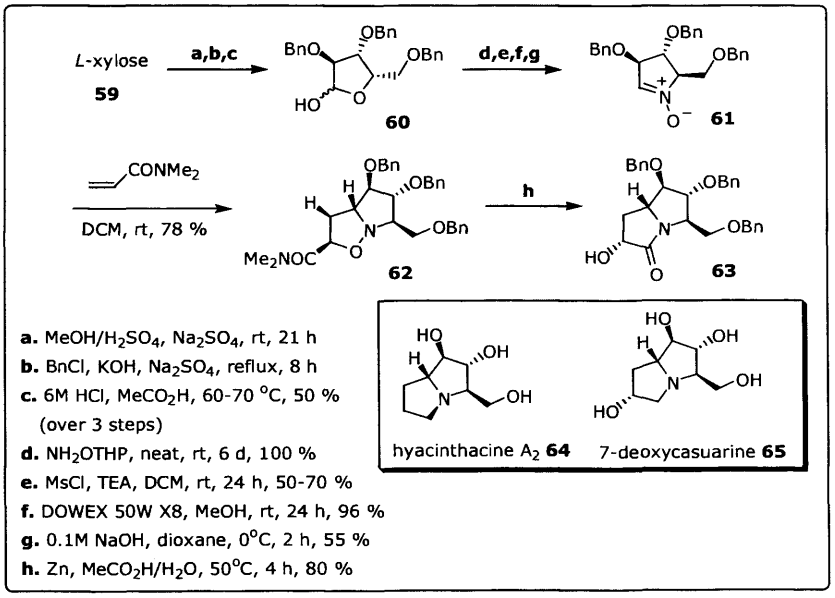
Scheme 3

The asymmetric total synthesis of (+)-sparteine was accomplished by Aubé and co-workers with the aid of nitrone intermediates (Scheme 4). Deprotection of the hydroxylamine (54) followed by intramolecular condensation gave the nitrone (55). Photolysis at 254 nm afforded rearrangement to lactam (57) in good yield, with further transformations furnishing the target molecule.[38]



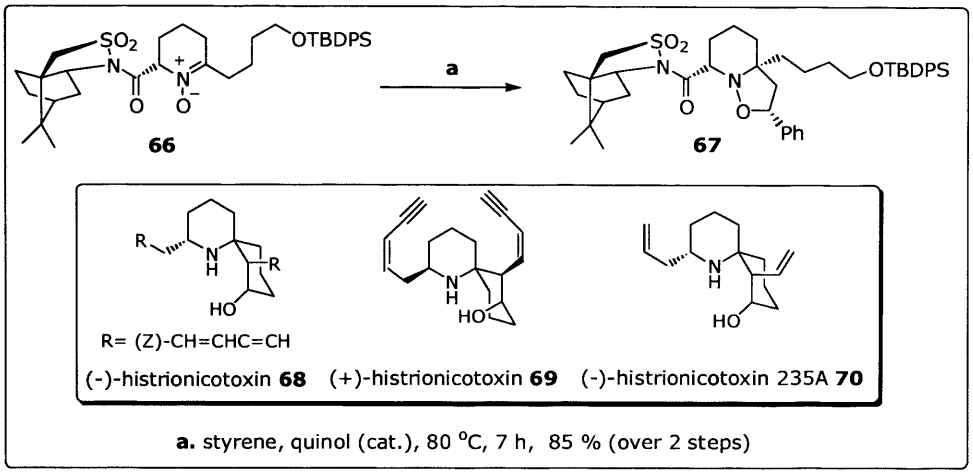
Scheme 4

Goti and co-workers determined the total syntheses of hyacinthacine A_2 and 7-deoxycasuarine with the use of trisubstituted chiral nitrones, formed from basic sugars (Scheme 5). Hyacinthacine A_2 (64) and 7-deoxycasuarine (65) are alkaloids that possess potent glycosidase inhibitory activity; therefore they present themselves as candidates for the treatment of conditions such as cancer, diabetes and viral infections. The synthesis represents a simple yet wholly stereoselective route to these polyhydroxypyrrolizidine species.[39]



Scheme 5

Holmes *et al.* reported the total syntheses of (-)-histrionicotoxin (68), (+)-histrionicotoxin (69) and (-)-histrionicotoxin 235A (70), with the cycloaddition of styrene to protect cyclic nitrone (66) as a key step in the synthesis of their spirocyclic core (Scheme 6). The histrionicotoxin alkaloids are naturally derived from the skin of the Colombian poison arrow frog *Dendrobates histrionicus*, and are known for their selective inhibition of the nicotinic acetylcholine receptors.[40]



Scheme 6

In conclusion, these examples illustrate the utility of nitrones in current organic synthesis, demonstrating that these species are important structures for the elucidation of interesting biologically active molecules.

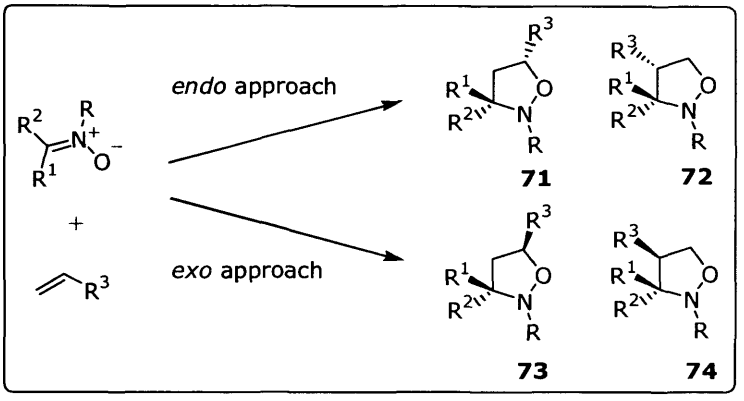
1.2.2 Selectivity in nitrone [3+2] cycloaddition to olefins

Considering the versatility of nitrones as synthetic tools, the desire to achieve selective nitrone cycloaddition is a priority, especially considering that the 1,3-dipolar cycloaddition reaction is perhaps one of the most versatile routes to five-membered heterocycles.[41]

Extensive mechanistic analysis by Huisgen and co-workers throughout the 1960's and 1970's introduced the concept of 1,3-dipolar cycloaddition, and established that the reaction takes place *via* a concerted (if slightly asynchronous) mechanism.[42] Despite initial objections,[43] Huisgen's findings continue to be the widely accepted view today.[44]

However, in spite of theoretical calculations, the regio- and stereochemical outcome of nitrone-olefin cycloaddition can be difficult to predict in practice, especially considering that it is possible for the cycloaddition to occur in two orientations to give a number of isomeric products (Scheme 7),[45] which are often dependent upon factors such as steric hindrance; solvent effects; substituents

and electron density of the olefin. Fortunately, the application of frontier orbital theory has bestowed a degree of clarity to this issue.



Scheme 7

The principles of perturbation theory were first applied to nitrone-olefin selectivity by Houk and co-workers in 1973.[47,48] This extensive theoretical and experimental study represented a turning point in the evaluation of 1,3-dipolar cycloaddition, as it could accurately predict the regio and stereochemical outcome in the majority of experimentally observed cycloadditions, many of which had previously been difficult to explain by other means. Today, it still remains the most reliable method to explain the generally complex mechanistic and selectivity issues presented in these reactions.[49]

Perturbation theory is based on the HOMO's (highest occupied molecular orbitals) and LUMO's (lowest unoccupied molecular orbitals) of both the dipolarophile and the 1,3-dipole. In brief, when the HOMO of the dipolarophile interacts with the LUMO of the dipole, and *vice versa*, a stabilisation of this transition state results. The magnitude of this stabilisation is a function of the energy difference between the interacting orbitals and so the closer these energies are, the higher the resulting stabilisation.

To take a simple [4+2] example, maleic anhydride undergoes cycloaddition with *cis*-butadiene *via* the low energy LUMO of the dienophile and the high energy HOMO of the diene, as this combination gives superior overlap in the transition state and therefore greater stabilisation (Figure 18).

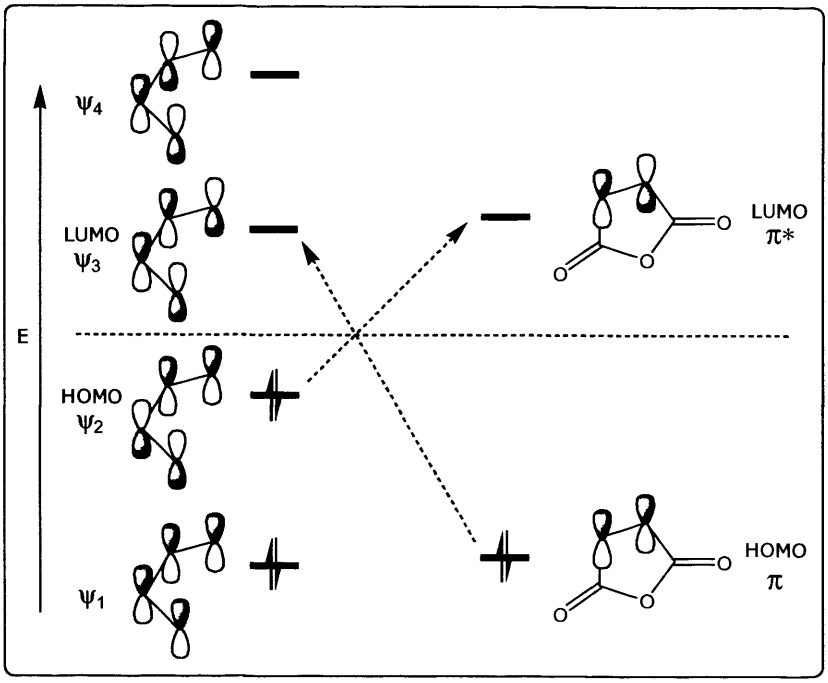


Figure 18

Prior to Houk's seminal study utilizing 1,3-dipoles, Fukui had developed and applied perturbation theory to cycloaddition mechanisms, with subsequent workers expanding various applications of the theory.[50,51]

A major step forward occurred when Houk recognised that perturbation theory could not only explain substituent effects, but also the reactivity and regioselectivity of 1,3-dipolar cycloaddition reactions.

Houk used the second order perturbation expression in his calculations, considering only the last term, relating to orbital mixing, and classified the reaction types in terms of orbital control, namely HO-controlled, HO/LU-controlled and LU-controlled.

Application of the frontier orbital model revealed that substituents that raised the dipole HO energy or lowered the dipolarophile LU energy accelerated HO-controlled reactions and decelerated LU-controlled reactions. Conversely, substituents that lowered the dipole LU energy or raised the dipolarophile HO energy accelerated HO-controlled reactions. HO/LU-controlled reactions could be accelerated by either frontier orbital interaction.[46]

Calculations of frontier orbital energies and coefficients for a number of dipolarophiles and 1,3-dipoles carried out by Houk *et al.* resulted in the conclusion that with unsubstituted dipoles, electron-deficient dipolarophiles have the smaller separation between the HOMO (dipole) and LUMO (dipolarophile) and

electron-rich dipolarophiles have the smaller separation between the LUMO (dipole) and HOMO (dipolarophile). Once coefficient effects were taken into account, regioselectivity could then be assessed.[47,52]

In terms of regioselectivity, Houk found that it was not necessary to include possible complications from closed-shell repulsions and electrostatic effects, as for most cases identification of the controlling frontier orbital interaction was sufficient in order to rationalise or predict the product regiochemistry. Theory suggested that all 1,3-dipoles would react with monosubstituted electron-rich dipolarophiles to form the product with the substituent adjacent to the 'anionic' atom (Figure 19). This was expected because perturbation theory predicted that all of these reactions were dipole LU-controlled (although for conjugated and electron-deficient dipolarophiles, the regiochemistry would depend on which frontier orbital interaction was dominant).[46]

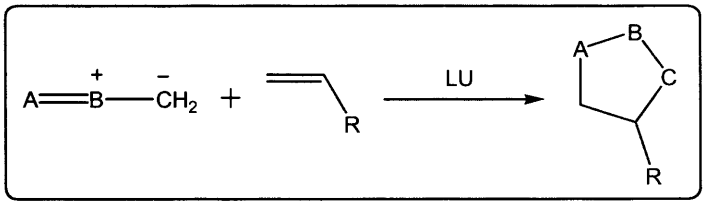


Figure 19

Houk's orbital energy calculations for the *nitrone* class of 1,3-dipoles are shown diagrammatically below (Figure 20). The data suggested, upon comparison with the corresponding frontier orbital coefficients, that for reaction of the parent species *N*-methyl nitrone (75) with electron-deficient dipolarophiles, the dipole HO interaction is the larger but does not contribute to regioselectivity. Consequently, the LU, which has a much larger coefficient on carbon, controls the regioselectivity with moderately electron-deficient and all other dipolarophiles, forming the 5-substituted cycloadduct. This conclusion has been verified experimentally, and indeed the majority of nitrone cycloaddition reactions result in production of the 5-substituted isoxazolidine.[46]

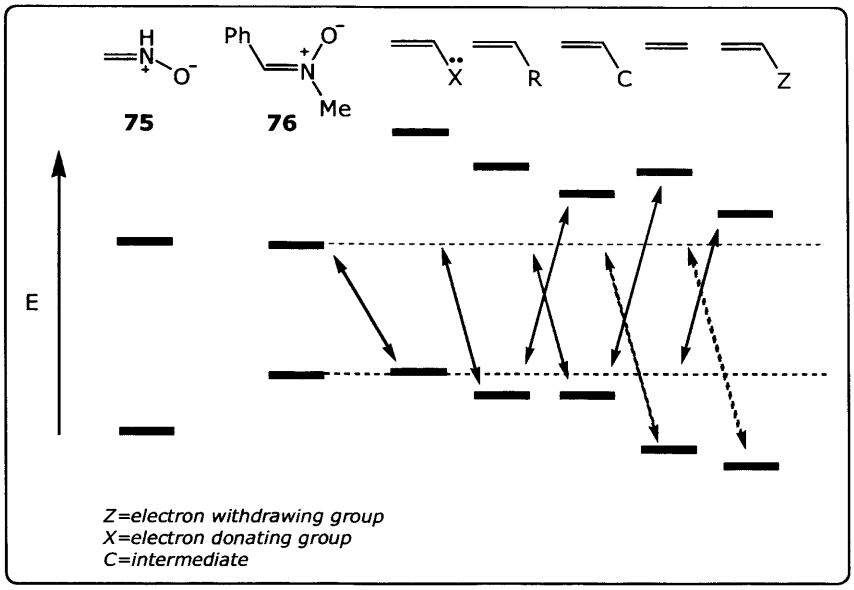


Figure 20

However, for the most widely studied species, *C*-phenyl-*N*-methyl nitrone, (76) frontier orbital energies indicate a *crossover* from LU control for electron-rich dipolarophiles to HO control with electron-deficient dipolarophiles (where the olefin substituent is Z; Figure 20 and Figure 21). Reasoning behind this is that the HO coefficient on carbon is decreased by the phenyl substituent on the nitrone, yet the methyl group increases the coefficient. Despite this disparity, the effect of the phenyl should predominate, leading to a larger coefficient on the oxygen than the carbon. Both substituents decrease the coefficient on carbon in the LU; hence the difference between the carbon and oxygen coefficients also decreases.

This led to the conclusion that with *very electron-deficient dipolarophiles*, dipole HO control ultimately predominates, so that 50:50 mixtures of cycloadducts would be expected with methylene nitrones (where terminal HO coefficients are similar), and *complete reversal* of regioselectivity would result with *C*-aryl-*N*-alkyl nitrones giving 4-substituted isoxazolidines.[46]

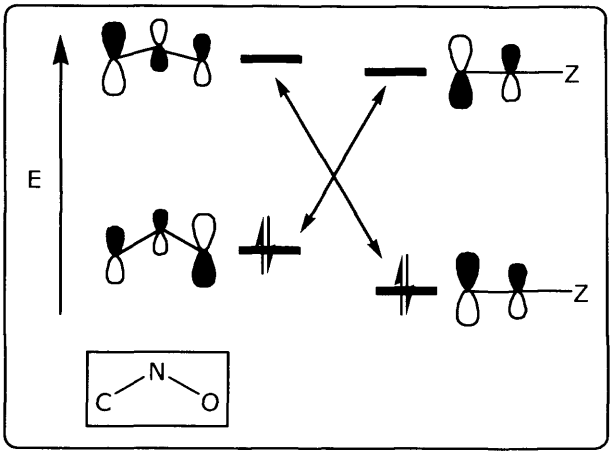
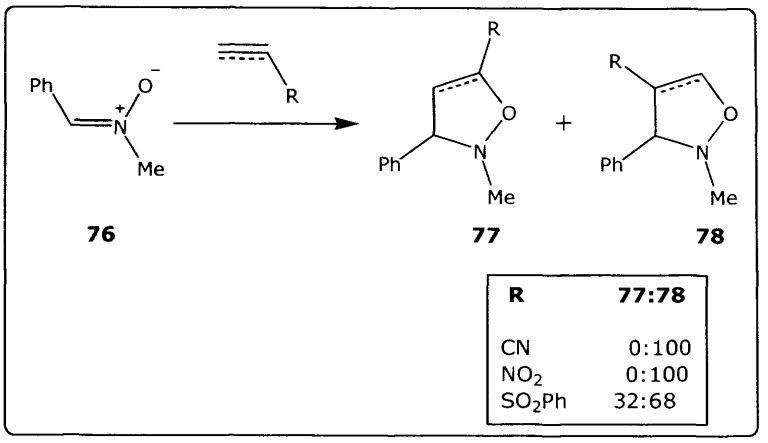


Figure 21

Although Coulombic effects and closed-shell repulsions are not considered in Houk's frontier orbital treatment, it was acknowledged that these terms from the second order perturbation expression did have some influence on the relative rates of cycloaddition for particular 1,3-dipoles. It was estimated that for conjugated and electron-deficient dipolarophiles, closed-shell repulsion effects between HO orbitals would strengthen the inclination for formation of adducts favoured by LU control. Furthermore, it was calculated that for dipolarophiles with strongly electron-withdrawing substituents, Coulombic forces favoured reversal in regioselectivity with such 1,3-dipoles as nitrones, nitrile oxides and diazoalkanes. Hypothetically, if the dipole LU interaction became sufficiently small, the Coulombic interactions could dominate, allowing formation of the 4-substituted adduct all the more favourable.[46]

Finally, Houk demonstrated that experimental observations vindicated his theoretical treatment. Regioselectivity could be predicted with confidence, whatever the electronic nature of the nitrone or dipolarophile. For example, it was shown experimentally that with mono-substituted electron-deficient dipolarophiles such as phenyl vinyl sulfone, nitroethylene and cyanoacetylene, reversal to give the 4-substituted cycloadduct as the major product occurred readily (Scheme 8). All these observations could be explained successfully using the frontier orbital hypothesis.[53] In addition, more recent experimental studies concerning electron-deficient dipolarophiles have justified the assertions of the frontier orbital model.[54,55]



Scheme 8

Moreover, Houk determined a general tendency in nitrone-dipolarophile cycloadditions for the amount of 4-substituted cycloadduct to increase as the ionisation potential (IP) of the nitrone decreased, or as the electron affinity of the dipolarophile increased. In terms of frontier orbital terminology, this would correspond to an increase in nitrone HO energy, or a decrease in dipolarophile LU energy respectively.[56]

The effect was illustrated in reactions with the electron-rich nitrone *C*-cyclopropyl-*N*-methylnitrone, which consequently has a significantly lower IP than *C*-phenyl nitrones. It was found that with electron-deficient dipolarophiles, the amount of 4-substituted cycloadduct increased as the electron deficiency of the dipolarophile increased. This observation was rationalised by frontier orbital theory, which proposed that since electron-rich nitrones have low-lying HO and LU orbitals, the HO (1,3-dipole)-LU (dipolarophile) interaction becomes wholly dominant, leading to formation of predominantly the 4-substituted adducts.[56]

These results also led to the conclusion that regioselectivity in the cycloaddition was electronically rather than sterically controlled, as steric effects did not prevent formation of the more hindered adducts. This finding is supported by the work contained within this thesis, as we observed the formation of 4-substituted adducts from the cycloaddition of sterically demanding nitrones to electron-deficient dipolarophiles. In addition, the 1,3-dipolar cycloadditions we performed were found to be wholly compatible with the frontier orbital hypothesis.[57]

Ever since 1969 when Huisgen first observed reversal of regioselectivity in nitrone cycloaddition with *N*-phenyl-*C*-methyl nitrone and methyl propiolate,[58] a rational explanation for this phenomenon had been sought. Houk's moulding of

perturbation theory towards the issue of 1,3-dipolar reactivity has been the most significant step in explaining experimental results. It has also bestowed much confidence in predicting the complex regiochemical outcomes prevalent in 1,3-dipolar cycloaddition.

Despite the dominance of the frontier orbital treatment since it's development for the rationalisation of 1,3-dipolar regioselectivity, there has been continued discussions on the issue. Development of modern computer modelling programmes has allowed many workers to explore other facets of the cycloaddition that could determine regioselectivity.
In general, most of this work has concentrated on systems where perturbation theory fails or gives ambiguous results, and various methods have been employed to generate an accurate theoretical result.[59-65]

In conclusion, the pioneering and extensive research by Huisgen and co-workers led to the proposal of the concerted mechanism for 1,3-dipolar cycloaddition. It is to their credit that the theory has withstood time and rigorous opposing conjecture to remain as the most widely accepted view today.
The application of frontier orbital theory to the complex issue of regioselectivity in 1,3-dipolar cycloadditions has proved to be so far the most successful and all encompassing of hypotheses in this field. The beauty is in its simplicity, and the numerous formerly perplexing cycloadditions it can explain with assurance. (This probably illustrates the dominance of frontier orbital stabilisation as the primary transition state factor in these reactions.)
Despite the supremacy displayed up to now by concerted mechanistic evidence coupled with frontier orbital theory in the rationalisation of selectivity, development of alternatives is a constant goal to explain exceptions to the rule. The evolution of modern computational techniques permits the vision that absolute resolution of selectivity in 1,3-dipolar cycloaddition will be forthcoming.

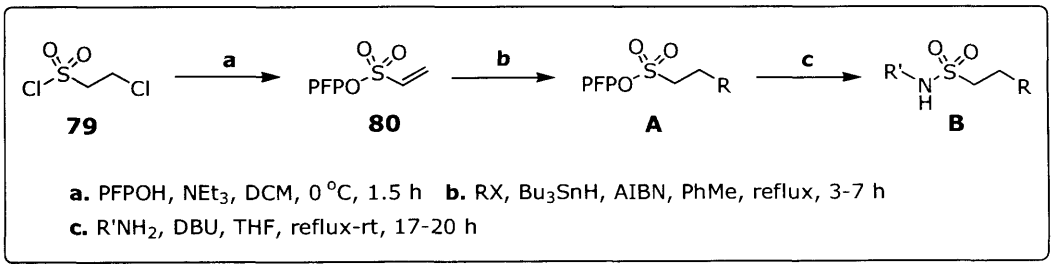
2.0 RESULTS AND DISCUSSION

2.1 Introduction

With the premise that sulfonamides continue to be at the forefront of drug development strategies, our remit was to widen the scope of previous work using pentafluorophenyl (PFP) vinylsulfonate within the Caddick group.[66] It was initially envisaged that the electron-deficient nature of the olefinic portion would make this species a suitable candidate for cycloaddition reactions with a variety of 1,3-dipoles and dienes. This would then result in interesting cyclic compounds open to further manipulation.

2.2 Radical Addition to PFP Vinylsulfonate

The investigation into PFP vinylsulfonate as a convenient building block for the synthesis of diverse sulfonamide products was originally developed using radical chemistry, whereby this bifunctional species (formed from the addition of a sulfonyl chloride to pentafluorophenol), readily underwent intermolecular tin-mediated radical addition to a number of alkyl halides, to give alkyl sulfonate esters. Subsequent displacement of the PFPO portion with a suitable amine was carried out smoothly in the presence of a strong base (DBU was favoured) to deliver the required sulfonamide in good yields (Scheme 9).[66]



Scheme 9

Examples of the species formed *via* this protocol are displayed below (Table 1). This illustrates the initial promise shown by PFP vinylsulfonate as a bifunctional, activated acceptor, and gave us the confidence to investigate further the potential of this species in other transformations.

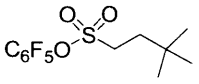
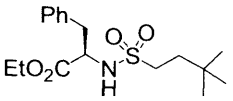
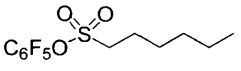
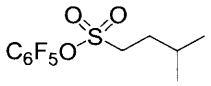
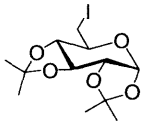
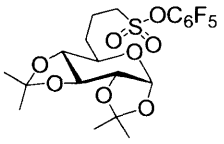
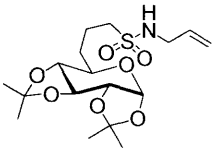
RX	Yield A %	Product A (81-84)	$R'NH_2$	Yield B %	Product B (85-86)
$(CH_3)_3CI$	89		Phe-OEt	77	
$CH_3CH_2CH_2CH_2I$	58		-	-	-
$(CH_3)_2CHBr$	29		-	-	-
	71		$CH_2CHCH_2NH_2$	69	

Table 1

2.3 1,3-Dipolar Cycloaddition to PFP Vinylsulfonate

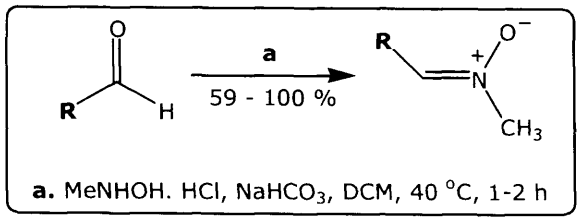
2.3.1 Nitrones as 1,3-dipoles

Investigation into the utility of PFP vinylsulfonate was then extended to focus on its ability to act as a dipolarophile in cycloaddition reactions.

The initial 1,3-dipoles to be examined were nitrones, primarily due to their ease of preparation, diversity and general stability. Nitrones are one of the most widely studied dipoles and undergo cycloaddition with a variety of olefins to form isoxazolidines.[67] They can be prepared in excellent yield *via* the condensation reaction of hydroxylamines with an appropriate aldehyde.[68]

During this investigation, a variety of nitrones were synthesised in this way, and incorporated aromatic and alkyl substituents with electron-withdrawing, electron-donating, polycyclic, heterocyclic, and halogen functionalities (Scheme 10, Table 2).

With these nitrone species in hand, the cycloaddition with pentafluorophenyl vinylsulfonate was attempted.



Scheme 10

R	Yield %	No.	R	Yield %	No.
Ph	92	76	Furyl	91	96
o-FPh	78	87	Naphthyl	86	97
m-ClPh	88	88	Cyclohexyl	99	98
p-ClPh	97	89	Cyclopropyl	100	99
p-BrPh	93	90	*D*-galactose	59	100
p-MeOPh	99	91	2,4,6-MeOPh	92	101
m-BrPh	100	92	2,4,6-MePh	98	102
p-NO_2Ph	93	93	C_5H_{11}	62	103
o-NO_2Ph	97	94	*p*-Allyloxy	100	104
2-Br-Furyl	97	95			

Table 2

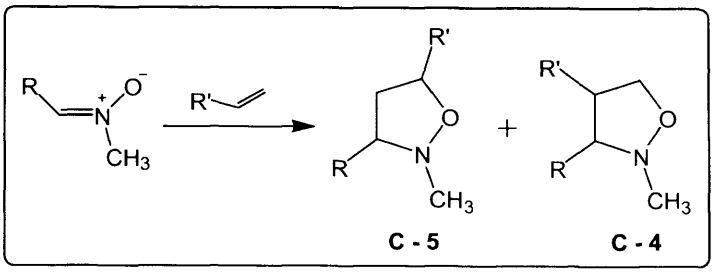
2.3.1.1 Nitrone cycloaddition with PFP vinylsulfonate

Cycloaddition of nitrones to sulfonate species has been seldom reported,[69] despite the use of the comparable dipolarophile phenyl vinyl sulfone in a variety of cycloaddition transformations.[70,71] It was therefore of considerable interest for us to see if nitrone cycloaddition to our sulfonate species would be successful.

Regarding literature precedent in this area, Houk *et al.* reported in 1973 that one of the most broadly used nitrones, *C*-phenyl-*N*-methyl nitrone, underwent cycloaddition with phenyl vinyl sulfone at 80 °C to furnish the isoxazolidine product in a 68:32 mixture of regioisomers, the major product being the C-4 substituted *trans* cycloadduct, and the minor a *cis*, *trans* mixture of the C-5 substituted isoxazolidine.[53]

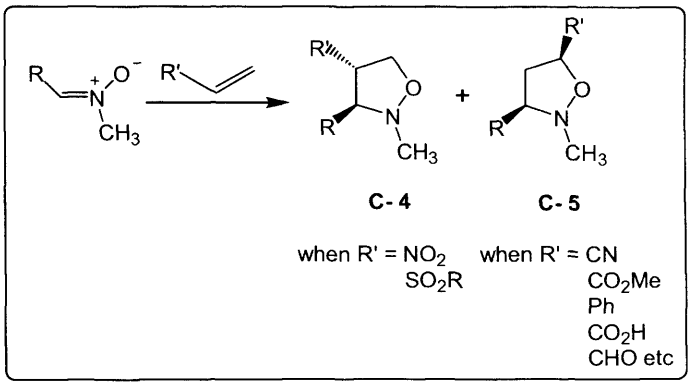
The interest here for us lay primarily in the regiochemical outcome of this reaction. An extensive literature study revealed it is widely acknowledged that for the cycloaddition of a nitrone to an olefin, the C-5 cycloadduct is usually the achieved product (Scheme 11). Previous experimental observations coupled with comprehensive theoretical analysis has shown that formation of the C-4 regioisomer is facilitated by the use of electron-deficient dipolarophiles, and in

some cases, the C-4 substituted isoxazolidine is the major product in the cycloaddition.[46-48,56,67]



Scheme 11

Whilst this behaviour has been observed, it is still very much an exception to the rule, with only a handful of electron-deficient dipolarophiles inducing this so-called 'reversal' in regiochemistry (Scheme 12). This select group includes methyl propiolate, nitroethylene, and phenyl vinyl sulfone, whereas acrylonitrile and ethyl acrylate produce C-5 substituted isoxazolidines, despite their electron-deficient nature.[67]



Scheme 12

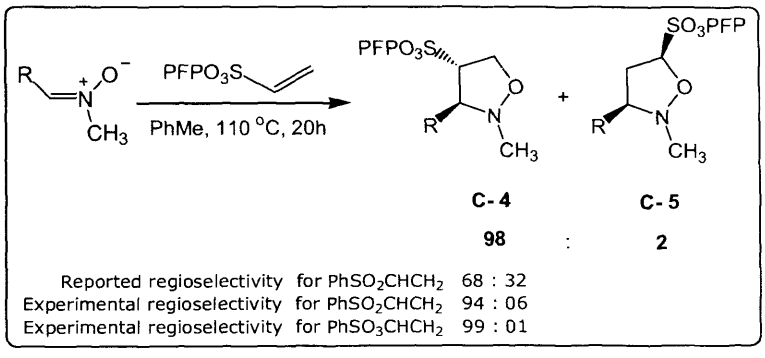
Considering that phenyl vinyl sulfone was known to induce this 'reversal', we postulated that PFP vinylsulfonate would also be likely to give the same outcome, furnishing C-4 substituted cycloadducts. To the best of our knowledge, the isoxazolidine product from an olefinic sulfonate has only been reported so far with sultones, which gave further impetus to test our theory.[69]

Whereas Houk carried out the analogous cycloaddition using phenyl vinyl sulfone at 80 °C, we undertook our cycloadditions in refluxing toluene (110 °C). This was initially attempted for the simple reason that nitrone cycloaddition is generally carried out in inert solvent, and usually requires thermal assistance in order for a successful transformation; thus a higher boiling solvent could produce more rapid

results. The significance of this action was not fully comprehended until later in our programme, and shall be discussed shortly.

The first cycloaddition reactions were carried out with *C*-phenyl-*N*-methyl nitrone and phenyl vinyl sulfone (as a control experiment to compare our results with that reported), phenyl vinylsulfonate, and PFP vinylsulfonate. Initial attempts to optimise the reaction conditions and identify the products by tlc (which tended to co-run with the starting materials) probably account for the longer than expected reaction times (up to 24 hours). Nevertheless, it was found that we could achieve cycloaddition with all the dipolarophiles in good yield, and x-ray crystallographic analysis of the major isomer from the phenyl vinylsulfonate cycloadduct revealed the regioselectivity to be C-4 *trans*, as we had envisaged.

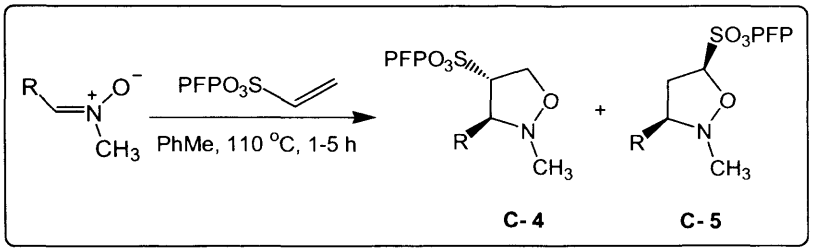
In addition to these very pleasing results, an unexpected bonus was the excellent stereoselectivity displayed in the cycloadducts. It was expected that, akin to previous findings, a mixture of stereoisomers would be produced, although the C-4 cycloadduct would probably dominate. However, we found that with all three of these cycloadditions, the major C-4 *trans* stereoisomer was virtually the only isomer achieved, with it comprising over 94 % of the total products gained (Scheme 13). This was a significant improvement on earlier work with phenyl vinyl sulfone,[71] and indeed only a handful of nitrone cycloadditions, whatever the dipolarophile, give one stereo- and regio-isomer exclusively.[67]



Scheme 13

As the only notable difference between our reaction conditions and previous efforts was the elevated temperature, we presumed that the improved selectivity was primarily due to a thermodynamically controlled process. This is reasonable; especially in view of the fact that isoxazolidines are prone to cycloreversion at high temperatures.[67] Further experimental proof of the correlation between temperature and stereoselectivity will be forthcoming in the following discussion.

Due to the success of cycloaddition with *C*-phenyl-*N*-methyl nitrone, other more functionalized nitrone species were employed to discover how broad the scope was for the reaction. As previously shown in Table 2, a variety of *C*-aryl-*N*-methyl and *C*-alkyl-*N*-methyl nitrones were synthesised and subsequently utilized in the attempted cycloaddition to PFP vinylsulfonate. The employment of more functionalized nitrones revealed that a reaction time of 1-5 hours was sufficient to yield the isoxazolidine cycloadducts in good yield and with continued excellent regio- and stereo-selectivity (Scheme 14; Table 3). In fact, the C-4 substituted *trans* isomer could be achieved exclusively in all of these transformations.



Scheme 14

R	Yield %	C-4 : C-5	No.
Ph	67	98 : 2	105
p-NO_2Ph	64	100 : 0	106
p-MeOPh	78	100 : 0	107
2-Furyl	75	100 : 0	108
m-ClPh	66	100 : 0	109
o-FPh	46	100 : 0	110
C_5H_{11}	66	100 : 0	111
Cyclohexyl	54	100 : 0	112
2-Naphthyl	65	100 : 0	113
Cyclopropyl	54	100 : 0	114
p-Allyloxy-Ph	88	100 : 0	115
2-Br-furyl	55	100 : 0	116
m-BrPh	60	100 : 0	117

Table 3

In support of our findings, n*O*e analysis of a typical example, 2-methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (113), indicated our anticipated regio- and stereo- chemistry to be accurate (Figure 22).

It was discovered that irradiation of H_b produced no enhancement of H_a. Equally, irradiation of H_a created no enhancement of H_b, but did produce enhancement of the *cis* proton H_c, which is indicative of the proposed *trans* stereochemistry.

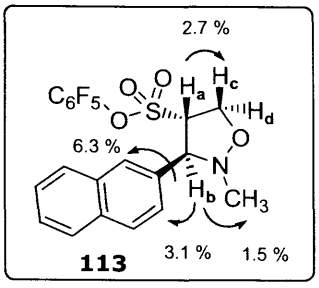
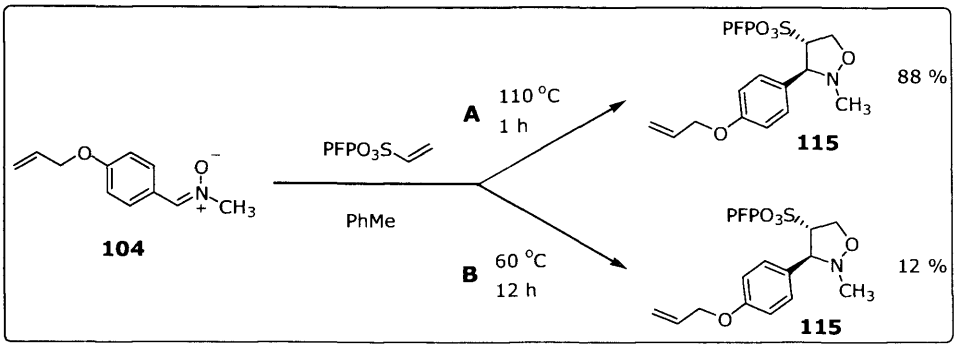


Figure 22

Cycloaddition could be achieved with the majority of the nitrones synthesised, the few exceptions being a nitrone incorporating a sugar substituent; 2,4,6-substituted aryl groups; and para-halogen substituted aryl nitrones. The reason for this lack of addition is not fully understood, especially considering that cycloaddition was successful with both ortho- and meta-halogen substituted aryl nitrones, and with other para-substituted deactivating groups.

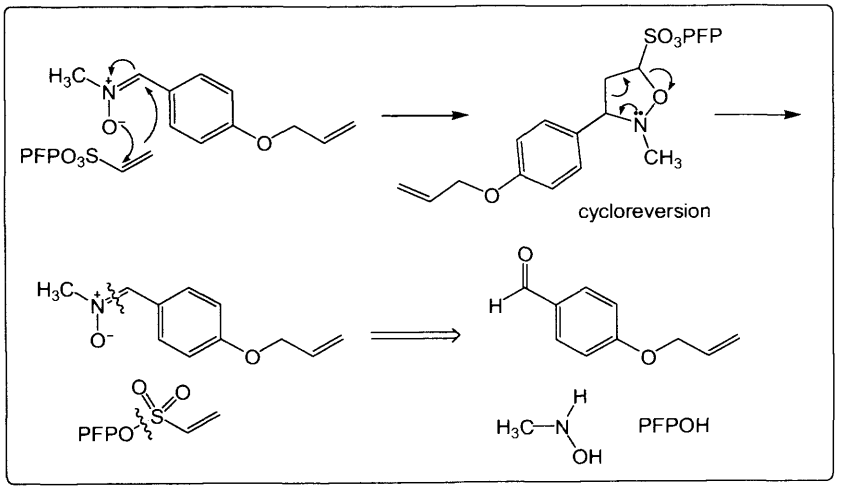
Whereas the cycloaddition products were achieved in respectable yields (Table 3), there is no obvious correlation between the yield and substituent type. All reactions were followed until completion (i.e. complete consumption of the dipolarophile, using a slight excess of the 1,3-dipole). However, the depleted yields for some of the cycloadducts could be due to thermal instability of the nitrone in question, or of any other products formed during the course of the reaction. Like isoxazolidines, nitrones are prone to undergo reverse reactions to reform their starting materials, and their thermal stability is not necessarily predictable. Finally, because these cycloadditions were carried out in refluxing toluene for up to 5 hours, the occurrence of decomposition products was perhaps inevitable.

It was previously stated that our increased reaction temperature improved the selectivity of the reaction; hence it was deemed that this hypothesis required qualification. A control reaction was carried out whereby the cycloaddition of *C*-(4-allyloxy-phenyl)-*N*-methylnitrone (104) to PFP vinylsulfonate was undertaken, first using our established conditions in refluxing toluene, and then at the lower temperature of 60 °C (also in toluene). The results are displayed in Scheme 15, which shows that conditions A gave the desired cycloadduct in 88 % yield after only 1 hour, whereas conditions B produced just 12 % of the same cycloadduct (plus decomposition products) after 12 hours.



Scheme 15

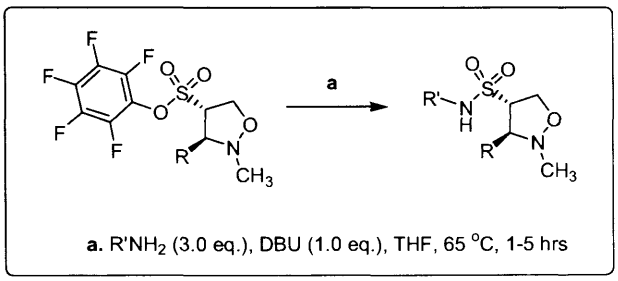
From this experiment, it is reasonable to suggest that the most thermodynamically stable cycloadduct is formed rapidly and exclusively at elevated temperatures, whereas at lower temperatures and over an extended period of time, there is modest formation of the most favourable C-4 isomer, and possibly also the less favourable C-5 isomer. During the 12 hour timescale of the reaction, it is likely that the remaining nitrone present would have decomposed down to its aldehyde and hydroxylamine starting reagents, as these were identified in the reaction mixture by tlc. In addition, as no 5-C product was isolated, it was presumed that this isomer also underwent cycloreversion followed by decomposition of the resulting nitrone and olefin. This was suspected because pentafluorophenol was also isolated from the reaction mixture (Scheme 16).
If this is the case, previously reported cycloaddition reactions of this type with inferior selectivity could possibly be improved by the use of higher reaction temperatures.



Scheme 16

2.3.1.2 Aminolysis of isoxazolidine cycloadducts

With a diverse variety of PFP-isoxazolidine cycloadducts in hand, aminolysis could then be attempted, whereby the PFPO portion is displaced by a suitable amine (Scheme 17). As this methodology is established within our laboratory,[66] it was thought wise to employ consistently reliable amines for this procedure.



Scheme 17

It was pleasing to discover that aminolysis proceeded smoothly with all the cycloadducts to furnish the corresponding sulfonamide products (118 - 135) in good yield within 5 hours in refluxing THF (Figure 23).

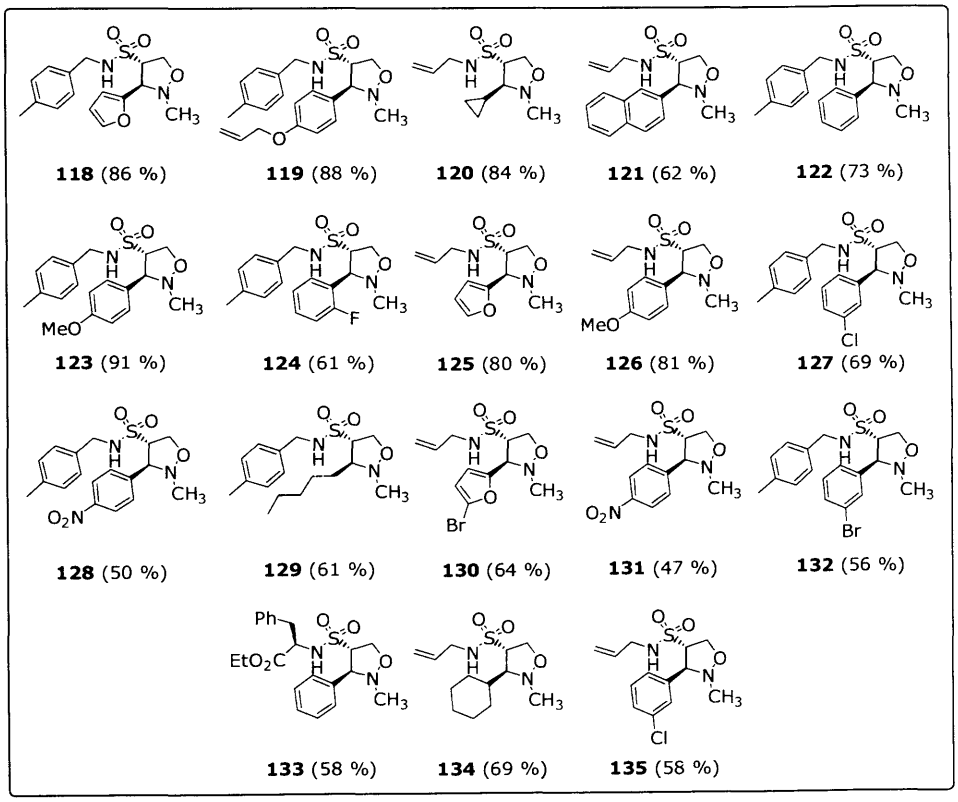


Figure 23

X-ray crystallographic analysis of an example sulfonamide structure, 2-methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide (128, Figure 24), confirmed the relative stereochemistry of the products.

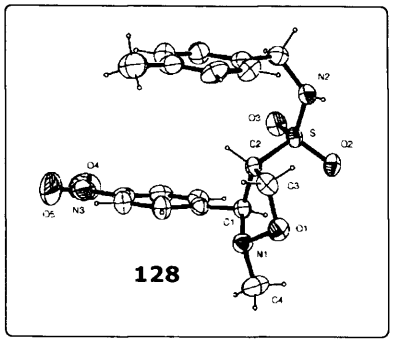
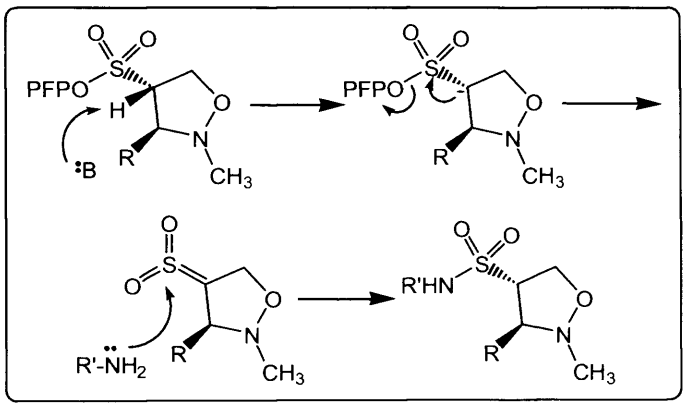


Figure 24

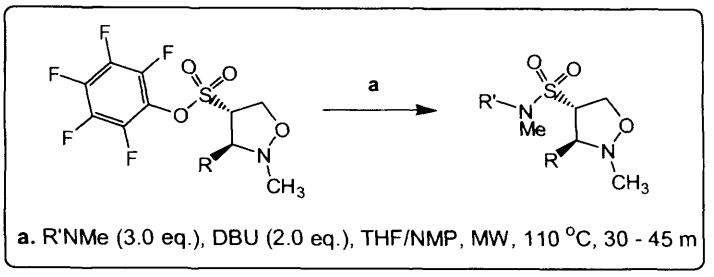
Notably, our previous work on the aminolysis procedure has raised interest regarding the mechanism. Because the displacement is only successful in the presence of a strong base, we have postulated that the sulfonamide is formed *via* a sulfene intermediate, rather than the conventional nucleophillic displacement of the leaving group with an amine (Scheme 18).[66]



Scheme 18

Due to the consistent and straightforward nature of the aminolysis method, it was postulated that this would be an ideal transformation to be employed in diversity orientated organic synthesis. Consequently, the procedure was carried out using an automated microwave instrument (the CEM Explorer^{TM})[72] with a number of stock PFP-sulfonate esters and a variety of *N*-methyl amines all previously unused in the aminolysis study (Scheme 19, Table 4). In this way, it was thought that the

rapid incorporation of diversity *via* this method would improve the practicality and appeal of the transformation.



Scheme 19

Entry	R	R'	Yield %	No.
1	*p*-MeOPh	$PhCH_2$	53	136
2	Cyclopropyl	C_6H_{11}	70	137
3	Naphthyl	$(CH_3)_3C$	25	138
4	*o*-FPh	CH_2CHCH_2	54	139

Table 4

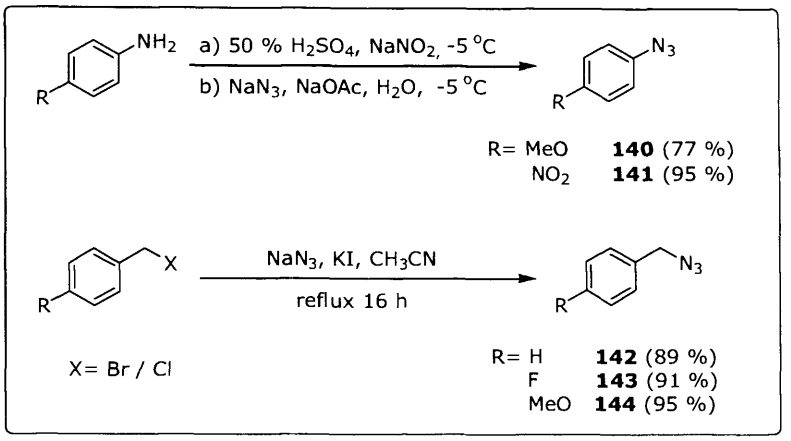
As the results show, an automated microwave procedure for the aminolysis step gives yields comparable to the thermal equivalent, but in half the reaction time. The lone exception is for the sterically demanding *tert*-butylmethylamine (entry 3), however, it would be unlikely for the yield to be improved under standard thermal conditions as this is a trend that occurs in other examples with sulfonate esters.[73]

2.3.2 Azides as 1,3-dipoles

Considering the opening success in the cycloaddition of PFP vinylsulfonate to nitrones, it was anticipated that cycloaddition to other 1,3-dipolar species could be achieved in a similar fashion.

The prospect of using azides in our cycloaddition study was of interest here, as the formation of sulfonamide triazolines was appealing from a biological perspective.

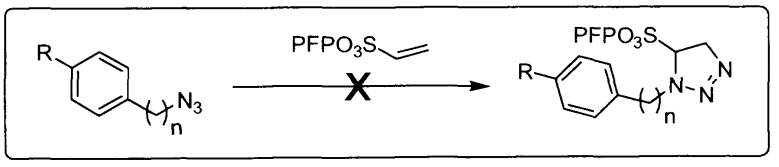
Azides are established 1,3-dipoles and have been shown to undergo cycloaddition with a variety of dipolarophiles (particularly alkynes).[74] In order to investigate the reactivity of PFP vinylsulfonate towards azides, a number of aryl-based species were synthesised in excellent yield (Scheme 20, structures 140 - 144).



Scheme 20

The cycloaddition of these azides to PFP vinylsulfonate was then attempted (Scheme 21). It was found that the required cycloaddition could not be achieved, despite tlc analysis indicating the consumption of PFP vinylsulfonate during the reaction, and the adjustment of reaction temperature and conditions (Table 5). Nmr analysis of the products attained revealed that pentafluorophenol was present in some instances, and that no heterocyclic ring protons were observed (i.e. the protons originating from the vinyl portion of the sulfonate).

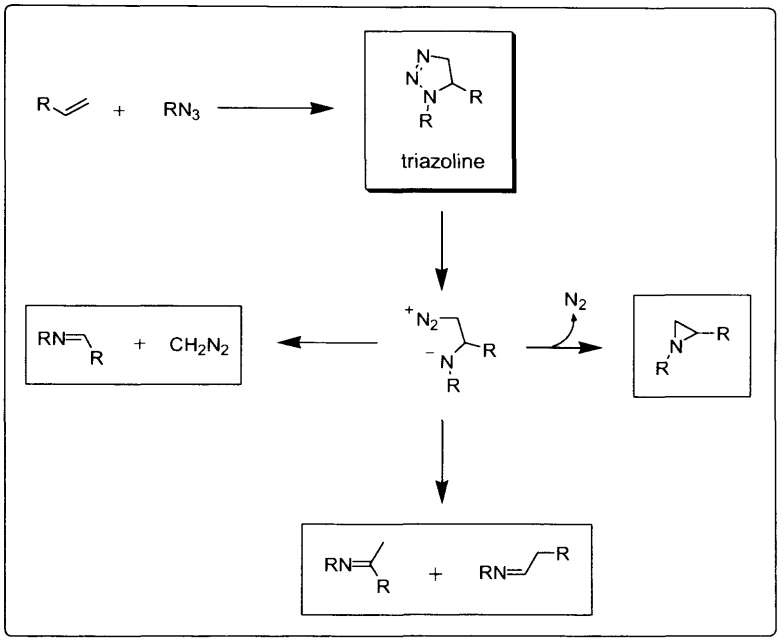
This led to the conclusion that cycloaddition had possibly taken place, but was immediately followed by rearrangement resulting in the expulsion of PFP, and maybe also N_2. In validation of this premise, it is well documented that triazolines are prone to react further under the reaction conditions, exhibiting decomposition patterns that involve the loss of nitrogen to give an aziridine or imine species (Scheme 22).[74]



Scheme 21

R	n	Reaction conditions	Result
MeO	0	PhMe, 80 ^{0}C, 2 h	Decomposition products obtained
MeO	0	THF, reflux 24 h	Decomposition products obtained
NO_2	0	THF, reflux 48 h, then rt 48 h	SM recovered
H	1	PhMe, reflux 20 h	Decomposition products obtained
F	1	CH_3CN, reflux 24 h	Decomposition products obtained
MeO	1	CH_3CN, reflux 4 d	Decomposition products obtained

Table 5



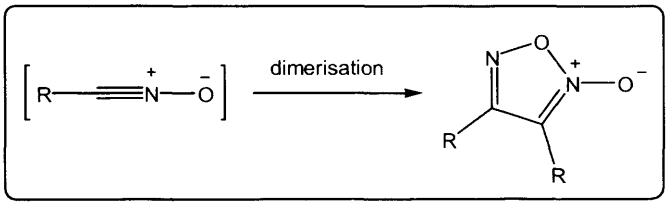
Scheme 22

In fact, azide cycloaddition with alkenes to form the primary triazoline product can be problematic, as the reaction is known to take over a week at ambient temperature. Increasing the temperature is perilous as most triazolines are thermally labile, and consequently decomposition products such as aziridines are achieved.[74-76] The stability of sulfur-based triazolines is unknown, although our study suggests that sulfonate species of this type are rather unstable. In addition, it has been reported that steric bulk of the olefin can contribute to lower yields and longer reaction times, which would also imply that PFP vinylsulfonate is not completely suited to the necessary reaction conditions.[75,76]

2.3.3 Nitrile oxides as 1,3-dipoles

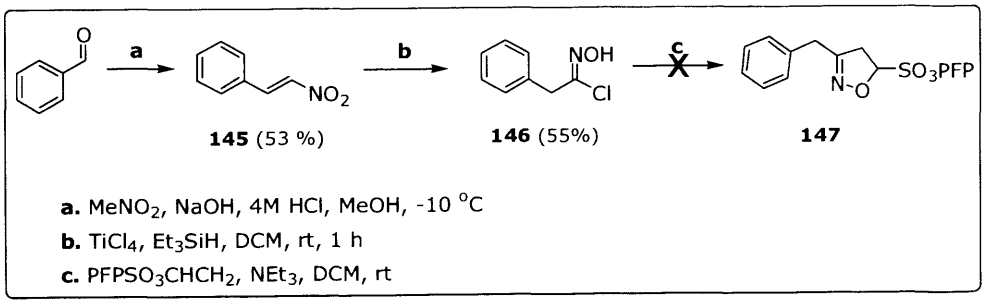
Following the difficulties encountered with azide cycloaddition, it was decided to attempt the cycloaddition with nitrile oxides, which are particularly reactive 1,3-dipoles and undergo cycloaddition to olefins to give isoxazolines. The precedent for alkene cycloaddition with nitrile oxides is much greater than for azides,[74,77] so it was hoped that the desired transformations could be achieved with similar success to that enjoyed with nitrones.

A drawback in the use of nitrile oxides is that the majority are very unstable (dimerisation to give a furoxan is rapid in the absence of a trapping agent, see Scheme 23) so the requisite species is generated slowly *in situ* using an amine base such as triethylamine.[78] In addition, a number of synthetic steps are required to form the dipole, and the preparatory methods are not always reliable.[79]



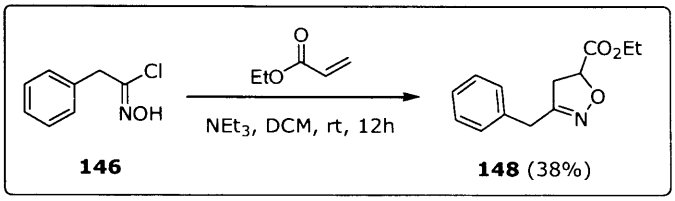
Scheme 23

There are three major routes to the synthesis of nitrile oxides, namely base treatment of hydroxamic acid chlorides;[80] oxidation of aldoximes;[81] or dehydrogenation of primary nitroalkanes.[82] In this investigation it was found that formation of the hydroximoyl chloride precursor was successful with conjugated nitro-olefins, using $TiCl_4$ as the source of Cl^+,[83] in a modification of the more usual NCS method first reported by Liu.[84] Unfortunately, *in situ* generation of the nitrile oxide was either ineffective or led to immediate dimerisation, as none of the dipolarophile was consumed during the course of the attempted cycloaddition (Scheme 24).



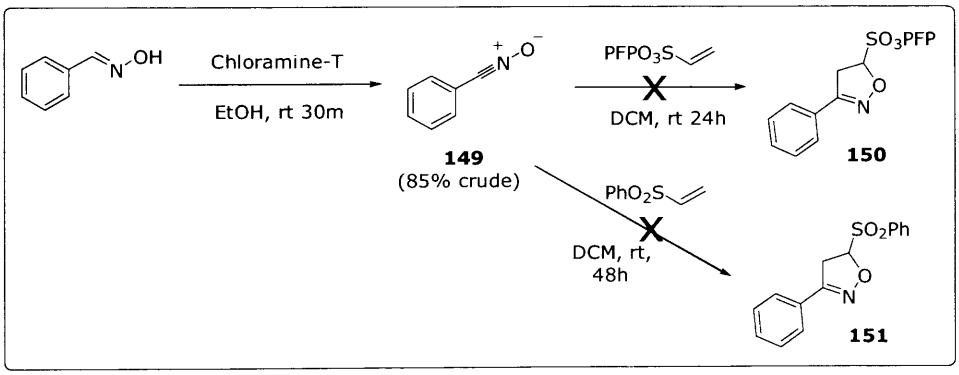
Scheme 24

At this time, it was thought prudent to perform a controlled experiment, in order to make sure the nitrile oxide species was being formed successfully. Thus, an analogous reaction was attempted using the electron-deficient and widely used dipolarophile ethyl acrylate. This gave the desired cycloadduct in reasonable yield (Scheme 25), which somewhat confirmed that the nitrile oxide was being generated *in situ* effectively, and the difficulty observed was in all probability due to PFP vinylsulfonate.



Scheme 25

At this point, it was noted that nitrile oxide cycloaddition to phenyl vinyl sulfone had been previously reported by Rai and co-workers.[85] The group found that generating the nitrile oxide from the initial aldoxime using Chloramine-T (*N*-chloro-*p*-toluenesulfonamide) allowed the species to be stable for up to 8 hours in solution, whereby it was added to the olefin. In this way, isoxazolines were produced in good yields.[85] Subsequently, this method was attempted with both phenyl vinylsulfone and PFP vinylsulfonate, but it was found that the cycloaddition results achieved by Rai *et al.* could not be repeated or applied to sulfonates (Scheme 26).



Scheme 26

Considering that the inherent instability of nitrile oxides *in situ* seemed to be problematic in this investigation, it was speculated as to whether stable, crystalline nitrile oxides could be generated. In this way, it would be certain that

the requisite reactive species was present in the reaction medium, and the possibility of dimerisation could be eliminated.

Subsequently, it was discovered that a small number of nitrile oxides are infinitely stable solids. These are generally sterically hindered aromatic species, due to substitution at both *ortho* positions, which greatly increases their stability (Figure 25) and are formed through oxidation of the corresponding aldoximes.[81] We utilized this route to produce a selection of nitrile oxides as stable crystalline white solids in excellent yield (Scheme 27).

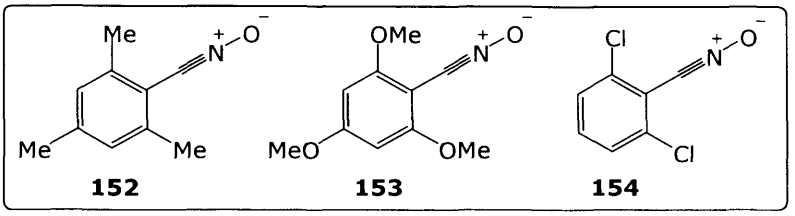
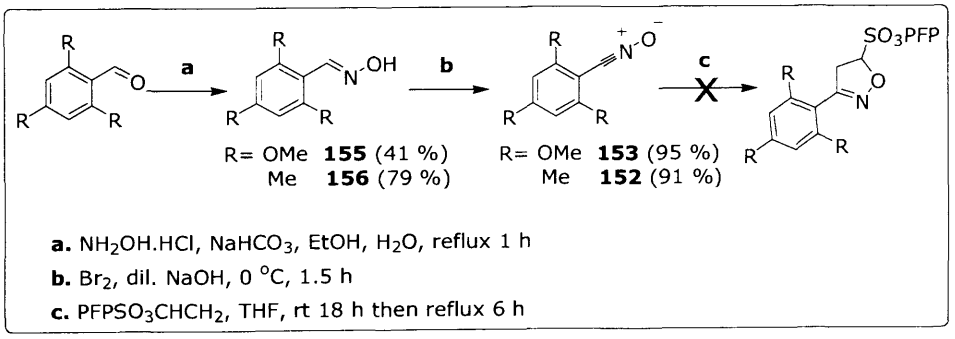


Figure 25

Cycloaddition was then attempted with PFP vinylsulfonate (Scheme 27). However, these endeavours were not successful, despite the apparent stability of the 1,3-dipole. Tlc analysis indicated no consumption of the dipolarophile, whereas the concentration of nitrile oxide almost immediately depleted, giving rise to other compounds. Nmr analysis signified these were likely to be decomposition products, and the reason for decomposition of these stable 1,3-dipoles in the presence of PFP vinylsulfonate is perplexing and not fully understood.

At this stage it is noteworthy to mention that 2,4,6-substituted aryl nitrones were also unsuccessful in cycloaddition with PFP vinylsulfonate, perhaps due to steric hindrance, although there are likely to be additional factors. This illustrates that highly substituted dipoles are unlikely to undergo cycloaddition with PFP vinylsulfonate, although does not explain the apparent decomposition of the nitrile oxides in this case.



Scheme 27

2.3.4 Azomethine ylids and nitro compounds as 1,3-dipoles

Azomethine ylids were thought to be potentially useful dipoles in our investigation into sulfonate cycloaddition. These are unstable species derived from imines, so are generated *in situ*. There are few examples of intermolecular cycloadditions of this type involving sulfur-based olefins, although they have been primarily used intramolecularly.[86] Harwood *et al.* reported that unlike other electron-deficient dipolarophiles employed in their study with cyclic azomethine ylids, phenyl vinyl sulfone *did not* trap the generated dipole and consequently no cycloadduct was obtained.[87] This result suggested that analogous attempts with PFP vinylsulfonate would also be unsuccessful, and provided grounds to defer endeavours in this area.

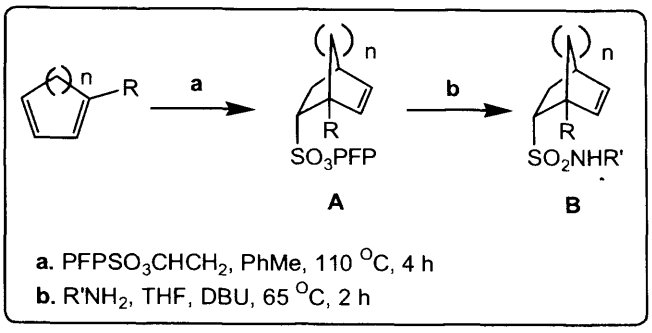
Nitro compounds were another type of 1,3-dipole considered during this investigation, as the potential cycloadducts could be of interest. Nitro species are isoelectronic with the 1,3-dipole ozone, and studies suggest that nitro functionalities will undergo a degree of cycloaddition to olefins.[88] To assess this the cycloaddition of nitromethane to PFP vinylsulfonate was attempted, but it was found that no discernable transformation took place upon stirring the reaction mixture at ambient temperature for several days. As a result, this 1,3-dipole was not investigated further.

2.4 Diels-Alder Cycloaddition to PFP Vinylsulfonate

Despite the lack of success in the cycloaddition of PFP vinylsulfonate to the majority of 1,3-dipoles, it was anticipated that the scope of the reaction could be extended to dienes that are known to readily undergo Diels-Alder type cycloaddition.

2.4.1 Formation of bicarbocyclic species *via* Diels-Alder cycloaddition

This section of the investigation was begun with the attempted cycloaddition of carbocyclic species to PFP vinylsulfonate. It was encouraging to find that the addition was undertaken readily with the dienes employed, with electron donating groups on the diene facilitating the reaction (Scheme 28; Table 6).



Scheme 28

However, it was evident that the addition was not as selective as previously experienced with nitrone cycloaddition. The reaction with cyclic dienes yielded both *endo* and *exo* isomers, with the *exo* isomer confirmed as the major product from nmr analysis.

R	n	Yield A % *exo*	No.	R'	Yield B %	No.
H	1	78	157a	CH_2CHCH_2	52	157b
H	1	--		H-Phe-OEt	44	158
H	1	--		CH_3PhCH_2	67	159
H	2	47	160a	CH_3PhCH_2	66	160b
OCH_3	2	87	161a	CH_2CHCH_2	56	161b
OCH_3	2	--		CH_3PhCH_2	53	162

Table 6

2.4.1.1 Aminolysis of bicarbocyclic cycloadducts

Aminolysis of the bicyclic cycloadducts was carried out as previously described. In all cases, the major *exo* product was employed in the displacement reaction. Table 6 illustrates that aminolysis could be achieved for all cycloadducts, although the moderate yields are due to some formation of the alternative isomer to B as a byproduct (Scheme 28). On the basis of previous theoretical considerations,[66] it was anticipated that the displacement reaction would proceed to yield the more thermodynamically favourable *exo* stereoisomer B as the major product, and this was confirmed by n*O*e studies (Figure 26). Irradiation at *endo* proton H_a results in enhancement of H_b; H_c and H_d, but no enhancement is observed in *exo* proton

H_g. Irradiation at H_d produces enhancement of H_a; H_e and H_f, which suggests the product is of *exo* conformation.

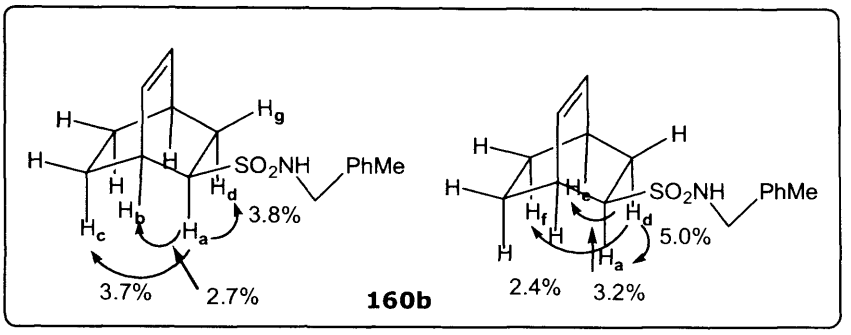
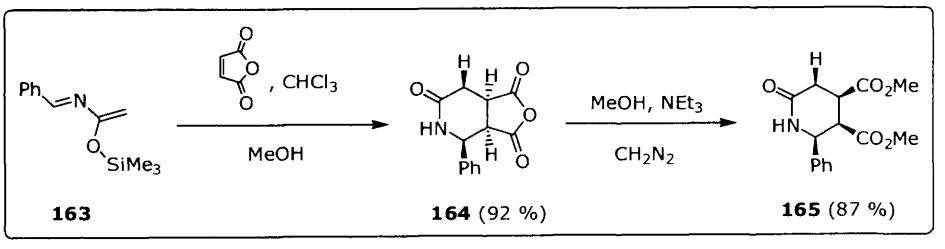


Figure 26

2.4.2 Heterodienes as 4π species

Considering that cycloaddition could be undertaken fruitfully with carbon dienes, it was postulated that an interesting twist on this reaction would be to attempt the cycloaddition with heterodienes, especially as it has been established that the Diels-Alder reactions of such species follow a similar pattern to their carbon equivalents.[49] The task here was to synthesise heterodienes sufficiently electron-rich to undergo cycloaddition to PFP vinylsulfonate.

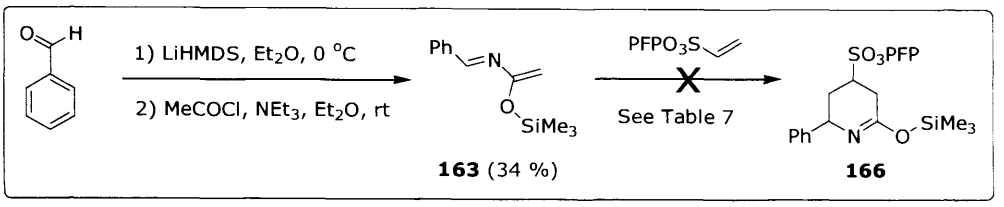
As a starting point, 2-azabutadienes were investigated as potential heterodienes for the required transformation; primarily due to their established reputation as willing participants in the Diels-Alder reaction.[49] The most common electron-rich 2-azadienes are oxazoles, and our cycloaddition attempts with these heterocycles is discussed in the following section. A number of acyclic 2-azadienes also act as electron-rich dienes and have been used successfully in cycloaddition reactions. Bayard *et al.* employed activated electron-rich 2-azadienes in their studies to form piperidones (Scheme 29).[89]



Scheme 29

Considering the highly activated nature of this diene, we hoped that it would also be a dynamic participant in an attempted cycloaddition with PFP vinylsulfonate.

Consequently, the azadiene was synthesised from benzaldehyde *via* a reported one-pot procedure,[90] and cycloaddition was undertaken (Scheme 30).



Scheme 30

Unfortunately this was unsuccessful, with tlc analysis indicating no consumption of the reagents after more than 48 hours (Table 7). An increase in the temperature and pressure with the aid of microwave irradiation led to the acquisition of decomposition products. As a result, this avenue of investigation was curtailed at this point.

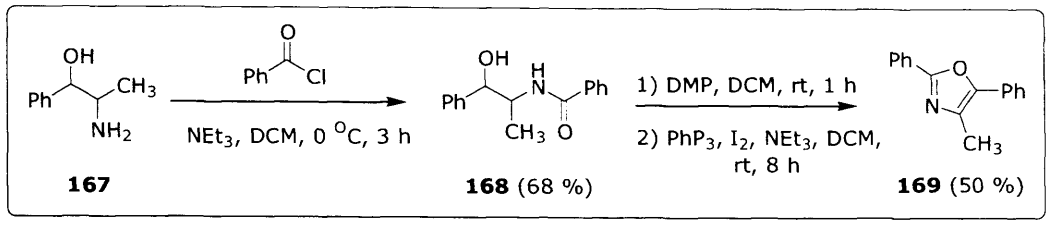
Eq. azadiene	Reaction conditions	Result
1.20	DCM, rt 12 h, then reflux 8 h, then rt 12 h	SM recovered
1.55	PhMe, MW (200 °C), 40 min	decomposition
1.50	THF, MW (150 °C), 30 min	decomposition

Table 7

2.4.3 Oxazoles as dienes

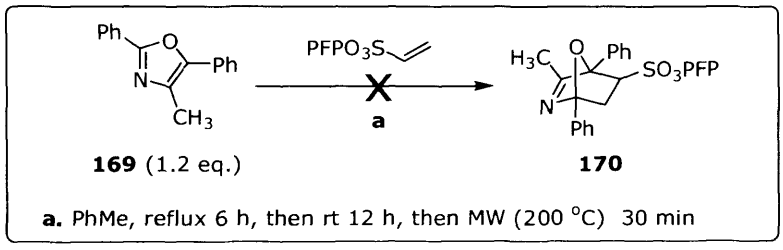
As has been previously highlighted, oxazoles are one of the most widely used electron-rich 2-azadienes.[49] Despite the unproductive results obtained with acyclic 2-azadienes, it was hoped that cycloaddition with activated oxazoles would be more successful, especially as they have been shown to undergo cycloaddition with electron-deficient dienophiles.[49]

A typical method for synthesising oxazoles is *via* cyclodehydration of α-acylamino ketones (the Robinson-Gabriel synthesis). Wipf has recently developed a more efficient route through this method, and it was this procedure that we used in our investigation for the formation of substituted oxazoles (Scheme 31).[91]



Scheme 31

Norephedrine was first acylated in good yield following a procedure by Contreras *et al.*[92] This species was then oxidised with Dess-Martin periodinane and cyclodehydrated in the one-pot procedure outlined by Wipf. This furnished the substituted oxazole in moderate yield, which was then subjected to cycloaddition conditions with PFP vinylsulfonate (Scheme 32). It was found that the addition could not be achieved, with complete recovery of the starting reagents. This negative result provided ground to suspend activity in this area.

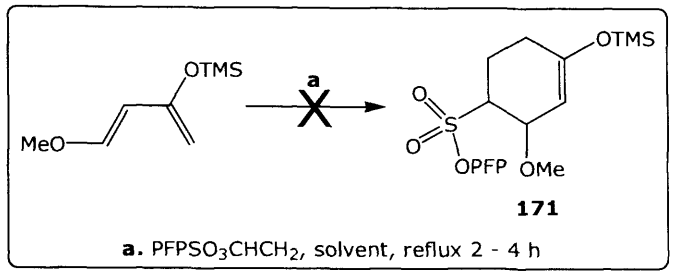


Scheme 32

2.4.4 Danishefsky's diene

Due to the lack of success with heterocyclic dienes, it was thought prudent to attempt the cycloaddition with a carbon-based diene. Danishefsky's diene (*trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene) was considered a suitable diene to employ at this stage, as the species is very electron rich, commercially available[93] and is known to be a willing partner is a variety of cycloaddition reactions.[94]

Subsequently, cycloaddition was attempted with PFP vinylsulfonate (Scheme 33), but under reflux conditions of 2 to 4 hours, it was discovered that no identifiable products could be obtained (Table 8).



Scheme 33

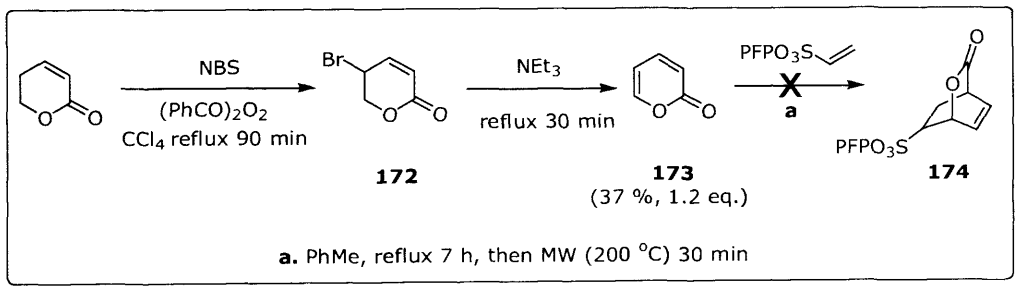
Entry	Conditions	Result
1	PhMe, reflux 4 h	decomposition products isolated
2	THF, reflux 2 h	decomposition products isolated
3	THF, reflux 4 h	decomposition products isolated

Table 8

2.4.5 2*H*-Pyrones as dienes

2*H*-pyran-2-ones have been shown from their reactivity to be considerably non-aromatic, and the parent unsaturated lactone α–pyrone is known to be a good diene in Diels-Alder reactions with both electron-deficient and electron-rich dienophiles.[49,95] This prompted us to investigate the diene for possible cycloaddition with PFP vinylsulfonate.

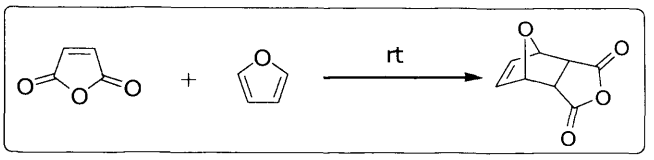
α-pyrone was prepared according to literature procedures[96] to give the diene (173) in reasonable yield over two steps (Scheme 34). Cycloaddition was then attempted, but unfortunately no reaction was observed and only starting materials were recovered (Scheme 34).



Scheme 34

2.4.6 Furans as dienes

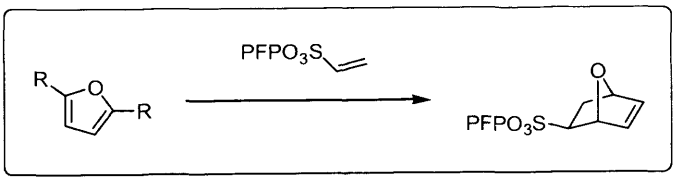
Furan has low aromaticity compared to both pyrrole and thiophene, consequently it was postulated that furan would be the most likely of these five membered species to undergo cycloaddition to PFP vinylsulfonate. Indeed, furan will actively participate in cycloaddition reactions with dienophiles of high reactivity,[49] perhaps the most famous example being maleic anhydride (Scheme 35).



Scheme 35

However, cycloaddition reactions involving furan are prone to retroaddition, especially at higher temperatures, so low yielding transformations cannot usually be improved through thermal assistance. Nevertheless, attempts to circumnavigate this problem have included the exploitation of high pressures, which favours the formation of cycloadducts (although pressures in the region of 8000-20,000 atm are required to improve the yield), and Lewis acid catalysis.[49] Notably, zinc iodide has been shown to considerably reduce reaction times in cycloaddition with acrylonitrile even at atmospheric pressure.[97]

Consequently, cycloaddition of furans to PFP vinylsulfonate was attempted under a variety of conditions (Scheme 36, Table 9). Microwave radiation was employed as this allowed reactions to be carried out at increased pressure, hence making the conditions more favourable to addition. Unfortunately, it was found that the microwave-mediated conditions did not aid the cycloaddition, with the greatest yield of the cycloadduct obtained being only 15 % (when the reaction was carried out in neat furan). Lewis acids such as $BF_3.Et_2O$ were also found not to assist the transformation.



Scheme 36

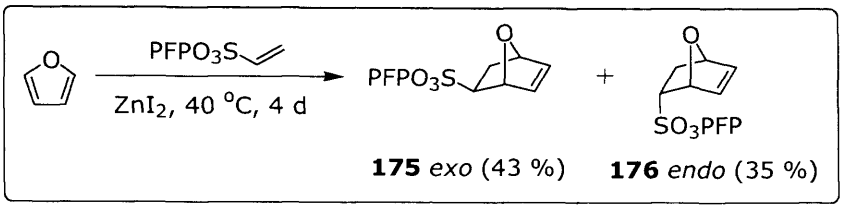
R	Eq. diene	Reaction conditions	Result
H	2.0	PhMe, reflux 24 h	SM recovered
H	1.5	PhMe, MW (200 °C) 2.5 h	15 % product, 60 % SM recovered
CH_3	5.0	$BF_3.Et_2O$, PhMe, MW (180 °C) 35 m	SM recovered
CH_3	5.0	$BF_3.Et_2O$, THF, -78 °C→rt 2 h, then reflux 24 h	SM recovered
H	5.0	PhMe, MW (200 °C) 1 h	SM recovered
H	3.0	1,4-dioxane, MW (200 °C) 20 m	SM recovered

Table 9

It was postulated that the relatively high temperatures employed in these attempts were possibly causing substantial retroaddition of any cycloadduct formed, which could explain the low yields achieved. Subsequently, the prospect of carrying out the addition at ambient temperature and pressure was a possibility. In related work from 1985, Klein and Deeb successfully used phenyl vinylsulfonate in cycloaddition with furans to give the cycloadduct quantitatively after 20 days at room temperature, and in 50 % yield after 4 days at 70 °C.[98] We anticipated that the reduced yield in the latter case was probably due to retroaddition complications, which had evidently not been a problem at ambient temperatures. This led to the conclusion that cycloaddition of furan to PFP vinylsulfonate could indeed be improved if carried out at lower temperatures, although the prospect of 3 week-long reactions did not give us the desired impetus to attempt the cycloaddition without catalysis, due to its impracticability.
The value of using a Lewis acid catalyst once again came into play at this juncture. Despite the limited success that had been achieved so far with the species tried, we hoped that this could be improved with the modification in reaction conditions.

As previously stated, zinc iodide has been used successfully in furan cycloaddition to olefins. Brion found that heating the neat addition components with catalytic ZnI_2 (0.3 eq.) at 40 °C for 48 hours, yielded mixtures of *endo* and *exo* cycloadducts in excellent yields with a variety of olefinic species.[97]
In accordance with this result, we attempted to repeat the procedure with PFP vinylsulfonate. It was very pleasing to discover that Brion's conditions were also compatible with our olefin, hence cycloaddition was complete after 4 days at 40

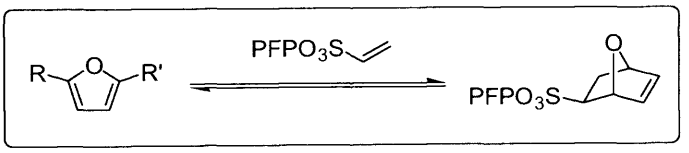
°C with ZnI_2, giving a 1.2:1 mixture of *exo*:*endo* cycloadducts in excellent yield. The isomers could be separated by column chromatography and were isolated as white solids (Scheme 37).



Scheme 37

It was anticipated that this procedure could be applied to substituted furans, in order to produce more functionalized cycloadducts. Consequently, addition was attempted with a number of commercially available 2,5-substituted furans (Scheme 38, Table 10). It was discovered that reaction conditions required a degree of optimisation depending on the furan in question, although despite this cycloaddition could not be achieved in some cases, even after prolonged reaction times. A notable exception was with 2-methoxyfuran, where the *endo* isomer was formed exclusively after 3 days, but in only 25 % yield (the remaining material being decomposition products). This result suggested (as would be expected with a very electron-deficient dipolarophile) that activated, electron-rich furans react most successfully, whereas less activated or electron-deficient furans give depleted yields or don't participate in the cycloaddition.

It has been postulated that the equilibrium in these reactions lies predominantly to the left, consequently adjustments have to be made to drive the equilibrium to cycloadduct formation.[99] This makes the scope of furyl cycloaddition difficult to assess, as favourable conditions for cycloaddition don't seem to be predictable, especially considering the typical reaction time of these reactions, and the specific conditions likely to be required for each species.



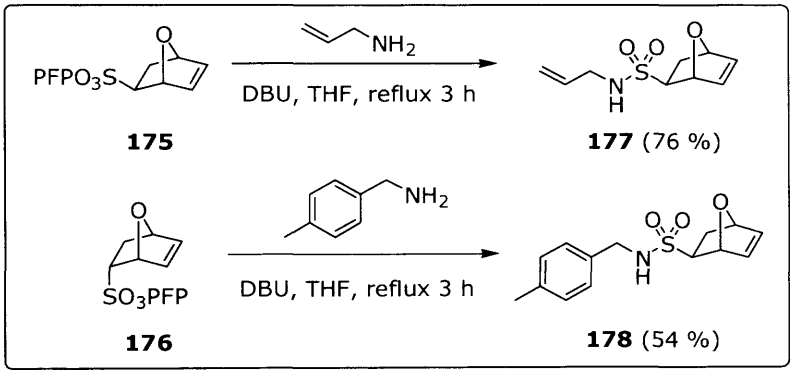
Scheme 38

R	R'	Eq. ZnI_2	Reaction conditions	Result
Me	Me	0.3	40 °C 5 d	decomposition
Me	COMe	0.3	40 °C 5 d	SM recovered
$CH_2OC(O)Me$	CHO	0.3	Et_2O, rt 3 d	SM recovered
H	OMe	0.3	40 °C 12 h	decomposition
H	OMe	0.3	Et_2O, rt 3 d	decomposition
H	OMe	0.3	Et_2O, rt 3 d	25 % product

Table 10

2.4.6.1 Aminolysis of furanyl cycloadducts

Our protocol for amine displacement of the PFP portion was then carried out on the successfully produced furanyl cycloadducts to give the corresponding sulfonamide products (Scheme 39). It was encouraging to find that the bridging oxygen structure survived the reaction process, and the resulting sulfonamides were formed in excellent yield and good selectivity.



Scheme 39

Notably, n*O*e studies confirmed that both the *endo*- and *exo*- PFP sulfonates yielded the more thermodynamically stable *exo* sulfonamide species upon aminolysis (Figure 27). Irradiation at *endo* proton H_a produced enhancement of H_b; H_c and H_d, but no enhancement of the *exo* proton H_e. Irradiation at H_b generated enhancement of H_a and H_c Hence this is indicative of an *exo* sulfonamide product.

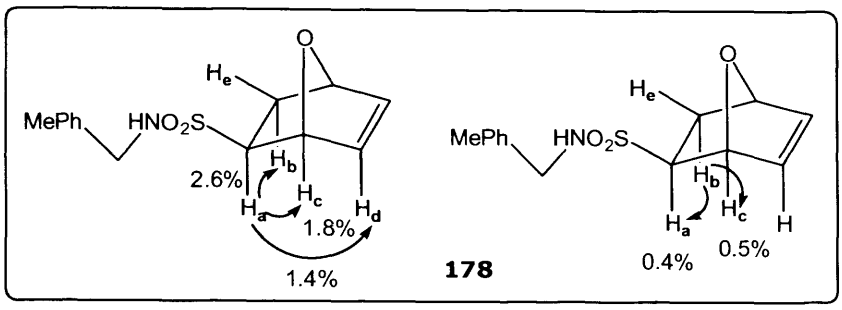
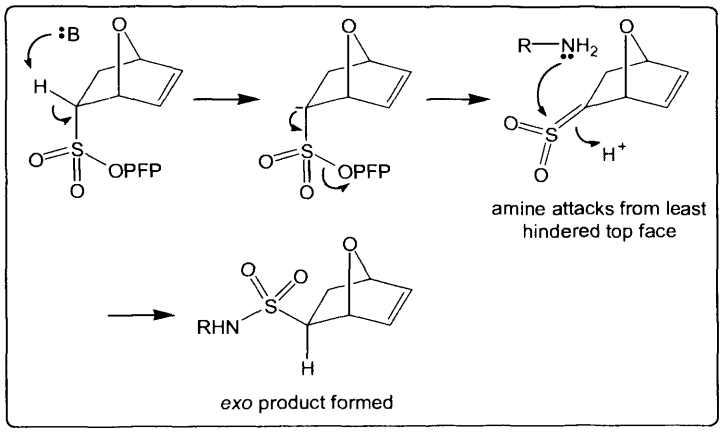


Figure 27

The sulfene mechanism for sulfonamide formation highlighted earlier (Scheme 18) [66] is also thought to apply with these structures. Consequently, the selectivity for *exo* products is considered to be due to the conformation of the sulfene intermediate being more favourable towards amine attack from the least hindered top face, which generates the *exo* sulfonamide (Scheme 40).



Scheme 40

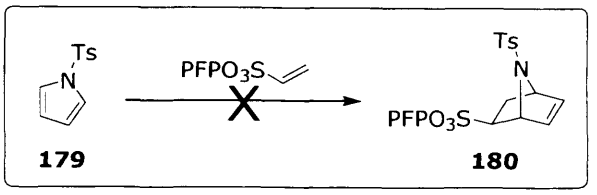
2.4.7 Pyrrole and thiophene as dienes

Pyrrole and thiophene are much more aromatic species than furan, so do not undergo cycloaddition readily. They are generally poor dienes so require forcing conditions to undergo cycloaddition even with highly activated dienophiles.[49]

Therefore, it was anticipated that cycloaddition of these species to PFP vinylsulfonate would not be successful. However, for the purposes of completion, addition was attempted with both thiophene and pyrrole, and as expected no cycloadducts were obtained after prolonged heating.

Subsequently it was hypothesised that substitution of the pyrrole ring with electron-withdrawing groups would make the system less aromatic, and hence

more receptive to cycloaddition. Consequently, we synthesised a tosyl-substituted pyrrole and attempted cycloaddition to PFP vinylsulfonate (Scheme 41), initially in toluene at reflux for 6 hours, which resulted in no consumption of any starting materials. This mixture was then stirred at ambient temperature for a further 12 hours, but no progression in the reaction occurred.



Scheme 41

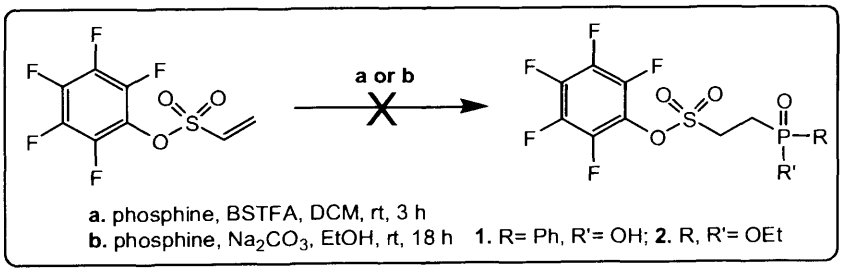
In a further attempt, we modified the reaction conditions and performed the transformation with reagents successful in previous work using furan, namely catalytic (0.3 eq.) ZnI_2, heated at 40 °C in THF. Unfortunately, product formation could not be achieved even after 3 days, and so any further exploration was suspended here.

2.5 Michael Addition to PFP Vinylsulfonate

The previous work with PFP vinylsulfonate has shown that the olefinic portion is activated towards both cycloaddition and radical addition. In order to uncover further potentially useful transformations, it was thought that investigation into Michael addition would be fruitful, as this could lead to a considerable number of varied and interesting species.

2.5.1 Phosphine addition to PFP vinylsulfonate

The Michael addition of phosphines to PFP vinylsulfonate (Scheme 42) was of interest as this could lead to potentially valuable products, and the addition has previously been successful with electron-deficient olefins.[100]



Scheme 42

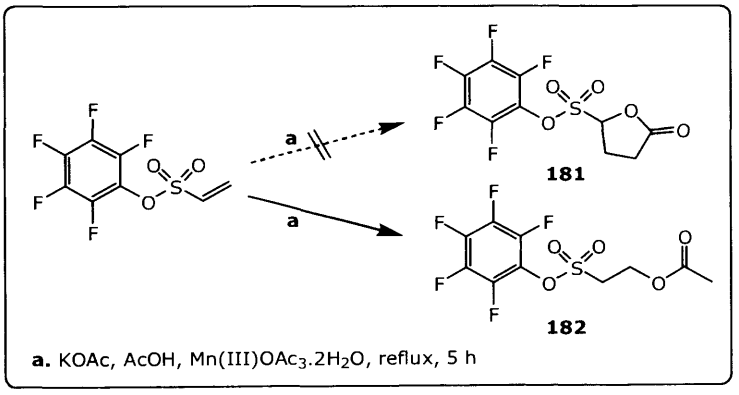
The reaction was initially attempted with phenyl phosphinic acid (1) and diethyl phosphite (2), using BSTFA as the base in DCM at ambient temperature. It was found that after 3 hours the starting materials were consumed, but analysis of the crude mixture indicated that only decomposition products were present (Table 11, entries 1 and 2). The reaction was then repeated under the modified conditions of sodium carbonate as the base with a polar solvent (EtOH), in the anticipation that decomposition could be prevented, but the result after 18 hours at ambient temperature was ultimately negative (Table 11, entry 3).

Entry	Phosphine	Conditions	Result
1	**1**	**a**	decomposition
2	**2**	**a**	decomposition
3	**1**	**b**	decomposition

Table 11

2.5.2 Lactone formation *via* ROH Michael addition

An investigation within the literature revealed that electron deficient olefins can form γ-lactones in reaction with carboxylic acids in the presence of $Mn(OAc)_3$,[101] and it was thought worthwhile to attempt this reaction with PFP vinylsulfonate using the easily obtainable acetic acid (Scheme 43).



Scheme 43

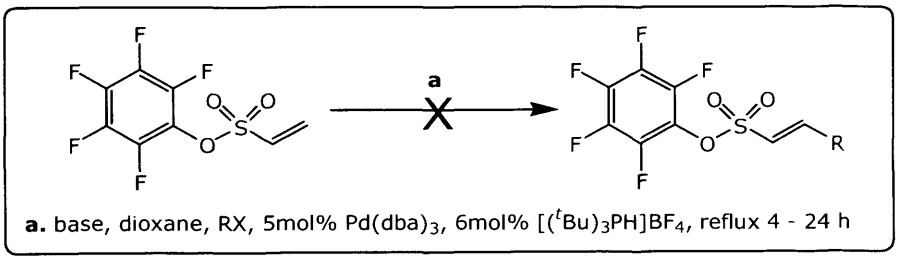
It was found that complete consumption of PFP vinylsulfonate occurred over 5 hours in refluxing acetic acid in the presence of an excess of $Mn(OAc).2H_2O$ and catalytic KOAc, to give a product isolated in 46 % yield. However, nmr analysis revealed that the Michael addition product (182) was solely obtained rather than the expected γ-lactone (181). Despite this unforeseen result, the transformation has shown that PFP vinylsulfonate is a willing participant in the Michael addition

to oxygen nucleophiles, an ability that could be exploited in further research.

2.6 Heck Coupling to PFP Vinylsulfonate

The coupling of aryl halides to PFP vinylsulfonate was an attractive prospect, as the Heck reaction has significant value in organic synthesis, and the resulting species could represent useful intermediates for further transformations.

The Heck reaction coupling PFP vinylsulfonate and the simple aryl halides iodobenzene and 1-bromo-4-nitrobenzene (Scheme 44, Table 12, entries 1-4) was attempted under argon using the established combinations of cesium carbonate or dicyclohexylmethylamine as the base; Fu's air-stable phosphonium salt $[(^tBu)_3PH]BF_4$ as the ligand;[102] and $Pd_2(dba)_3$ as the palladium (0) source, in refluxing dioxane for up to 24 hours, but it was found that under these conditions no product could be isolated and only PFPOH as a decomposition product was obtained. This was also the result when the reaction was carried out at room temperature (Table 12, entry 7) and in neat solvent (Table 12, entry 8).



a. base, dioxane, RX, 5mol% $Pd(dba)_3$, 6mol% $[(^tBu)_3PH]BF_4$, reflux 4 - 24 h

Scheme 44

Entry	RX	Pd	Solvent	Ligand	Base	T	Result
1	PhI	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	reflux	decomposition
2	*p*NO_2PhBr	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	reflux	decomposition
3	PhI	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	$CyNMe_2$	reflux	decomposition
4	*p*NO_2PhBr	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	$CyNMe_2$	reflux	decomposition
5	ROTf	$Pd(OAc)_2$	DMF	--	NEt_3	rt-reflux	SM recovered
6	RONf	$Pd(OAc)_2$	DMF	--	NEt_3	rt-reflux	SM recovered
7	PhI	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	rt-65 °C	decomposition
8	PhI	$Pd_2(dba)_3$	neat	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	rt	decomposition

Table 12

Consequently, it was thought prudent to attempt the coupling using other leaving groups such as triflates and nonaflates. The commercially available ethyl-2-(trifluoromethane sulfonyloxy)-1-cyclohexene-1-carboxylate was employed as a model triflate species with which to test the coupling procedure (Table 12, entry 5; R = $C_6H_8C(O)OEt$). Standard triflate coupling conditions were used (Pd $(OAc)_2$; DMF; NEt_3),[103] and the reaction was stirred first at ambient temperature for 6 hours, then at 60 °C for 18 hours, but no reaction was observed.

Lastly, a nonaflate was utilized in this coupling protocol (Table 12, entry 6; R = C_6H_9). In this case, the species was prepared *in situ* from the reaction of 1-cyclohexenyloxytrimethylsilane with perfluoro-1-butanesulfonyl fluoride (NfF) in the presence of catalytic TBAF.[104] The nonaflate intermediate was prepared successfully within 18 hours at ambient temperature, but following the addition of PFP vinylsulfonate and the Heck reagents described above, no coupling was observed.

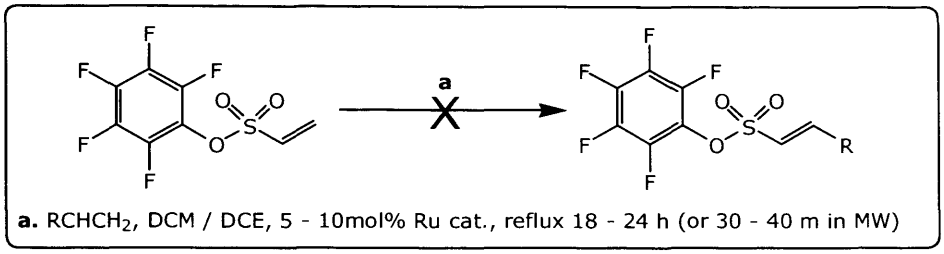
At this stage, it was perceived that PFP vinylsulfonate was not inclined to undergo Heck coupling under any kind of conditions, and subsequently this area of study was curtailed.

2.7 Cross Metathesis with PFP Vinylsulfonate

The next facet to be investigated was cross metathesis (CM). Success in this reaction would also be of interest, as products resulting from a CM transformation with PFP vinylsulfonate were likely to be varied and open to further manipulation. The olefins employed in this study have been reported to undergo CM with phenyl vinyl sulfone, so were thought to be suitable substrates in this case.[105,106]

Consequently the metathesis was attempted (Scheme 45), whereby PFP vinylsulfonate was added to 1.5 equivalents of the selected olefin in a non-polar solvent (usually DCM, or DCE if a higher reflux temperature was desired) followed by addition of a ruthenium catalyst (either Grubbs second generation catalyst, or the Hoveyda-Grubbs second generation catalyst, which have both been shown to be effective with sulfones[105,106]). The reaction was then stirred at reflux for up to 24 hours, but in each case it was found that only starting materials could be recovered, with no desired product in evidence (Table 13, entries 1-4). The reaction was then repeated in refluxing DCE, but this made no difference to the outcome (Table 13, entry 5). Finally, it was reasoned that a constructive way to force the reagents towards product formation was by performing the reaction at high temperature and pressure in a microwave. Consequently, the transformation

was attempted at 130 °C in DCM for 40 minutes under microwave radiation (Table 13, entry 6), but no product could be identified and only starting materials were isolated.



a. $RCHCH_2$, DCM / DCE, 5 - 10mol% Ru cat., reflux 18 - 24 h (or 30 - 40 m in MW)

Scheme 45

Due to the unsuccessful results in this study, it was decided to attempt a control experiment in order to ensure the reaction protocol was valid. Hence the metathesis was undertaken with phenyl vinyl sulfone using the literature procedure followed for some previous attempts with PFP vinylsulfonate, namely 1-octene and 5mol% Grubbs second generation catalyst in refluxing DCM for 18 hours (Table 13, entry 7).[106] This resulted in quantitative yield of the metathesis product, which vindicated the procedure, thereby isolating PFP vinylsulfonate as the troublesome reagent in this case. As a result, this area of research was suspended at this point.

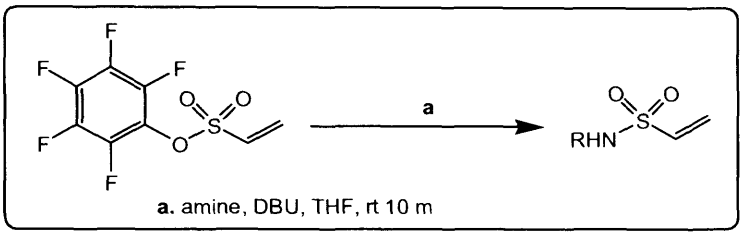
Entry	Olefin	Ru catalyst	Solvent	T	Result
1	styrene	Grubbs II	DCM	reflux	SM recovered
2	5-hexen-1-ol	Grubbs II	DCM	reflux	SM recovered
3	styrene	Hoveyda	DCM	reflux	SM recovered
4	5-hexen-1-ol	Hoveyda	DCM	reflux	SM recovered
5	1-octene	Grubbs II	DCE	reflux	SM recovered
6	1-octene	Grubbs II	DCM	130 °C in MW	SM recovered
--	--	--	--	--	--
7	1-octene	Grubbs II	DCM	reflux	100 % yield

Table 13

2.8 Heck Coupling and Cross Metathesis with Vinyl Sulfonamides

2.8.1 Formation of vinyl sulfonamides *via* the direct aminolysis of PFP vinylsulfonate

Due to the lack of success in the Heck and cross metathesis reactions when using PFP vinylsulfonate, it was postulated that the acceptor could be adapted in a way that could facilitate the desired transformations. It was suggested that converting PFP vinylsulfonate into its more stable sulfonamide form, (*via* the established aminolysis procedure)[66] before attempting any derivatization, could be a simple way to circumnavigate the problems encountered with the PFP ester (Scheme 46).



Scheme 46

Consequently, aminolysis was carried out with a variety of amines and *N*-methyl amines, and it was discovered that PFP vinylsulfonate underwent the reaction very rapidly at room temperature (within 10 minutes), to furnish the corresponding sulfonamides in moderate to good yields (Table 14, entries 1-4).

An intriguing feature in this procedure was the formation of disubstituted product during aminolysis with benzylmethylamine (Table 14, entry 2 & Figure 28), which accounted for the modest yield of monosubstituted product achieved, the remainder being isolated as the disubstituted product. Notably, it was discovered that benzylmethylamine was the only species in this study with a propensity to undergo disubstitution; the moderate yield isolated from *L*-proline (Table 14, entry 3) was not due to disubstitution reactions, but decomposition and solubility issues.

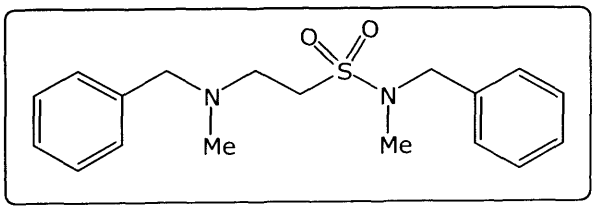


Figure 28

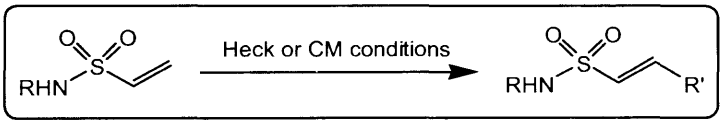
In addition, the reaction was attempted with *N*-methylaniline (Table 13, entry 5), but it was found that no desired product could be isolated. Conceivably, this result was expected as our studies have shown that alternative procedures are often required for PFPO displacement with anilines.[66,107]

Entry	Amine	Yield %	Comments	No.
1	4-methylbenzylamine	58	--	183
2	benzylmethylamine	55	45 % disubstituted product also isolated	184
3	*L*-proline	27	PFPOH also isolated	185
4	*N*-methylpropylamine	79	--	186
5	*N*-methylaniline	0	possibly expected	187

Table 14

2.8.2 Heck and cross metathesis reactions with vinyl sulfonamides

Once a number of vinyl sulfonamides had been synthesised, both Heck and CM procedures were attempted using the previous conditions and reagents (Scheme 47).



Scheme 47

Unfortunately, it was found that neither Heck coupling (Table 15, entries 1 and 2) nor cross metathesis (Table 15, entries 3-5) could be carried out with much success. In the Heck reactions it was found that, unlike in the analogous reaction with PFP vinylsulfonate whereby decomposition occurred, the sulfonamide starting materials were not consumed, with no indication of reaction taking place.

In the cross metathesis, it was discovered that as previously, the reaction was difficult to drive toward product formation. The only (minor) success (Table 15, entry 5) occurred when the sulfonamide was subjected to microwave irradiation at 130 °C for 40 minutes with 1-octene, which delivered an 8 % yield of isolated product (188) (Scheme 48). However, further microwave heating combined with an excess of reagents failed to increase the yield.

As a consequence of these results, it was decided that this area of study would be suspended at this stage.

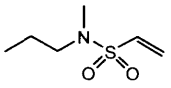
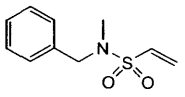
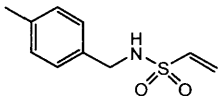
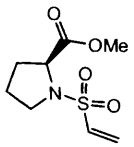
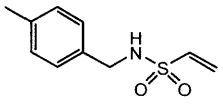
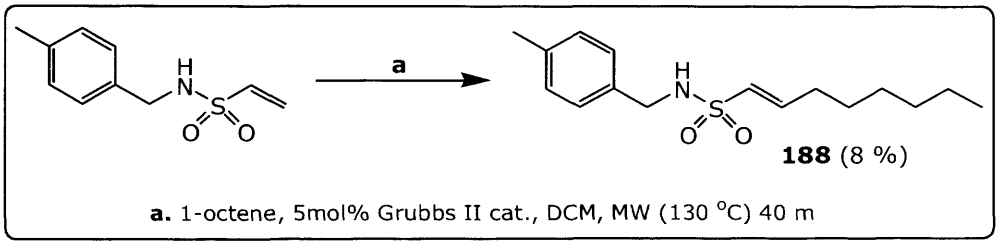
Entry	Substrate	Reagent	Catalyst	Solvent	Ligand	Base	T °C	Yield %
1		PhI	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	70	0
2		PhI	$Pd_2(dba)_3$	dioxane	$[(^tBu)_3PH]BF_4$	Cs_2CO_3	rt	0
3		1-octene	Grubbs II	DCE	--	--	50	0
4		1-octene	Grubbs II	DCE	--	--	50	0
5		1-octene	Grubbs II	DCM [MW]	--	--	130	8 (188)

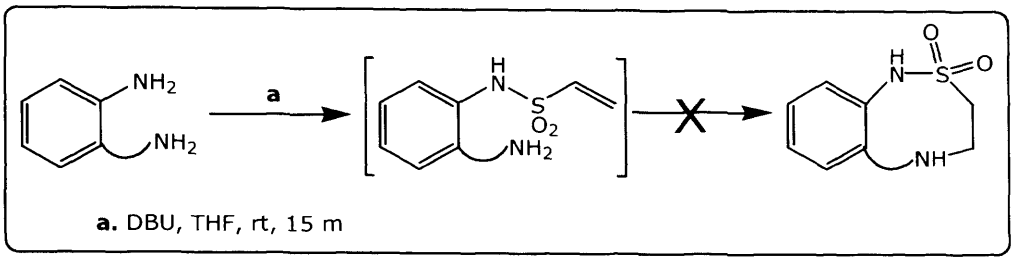
Table 15



Scheme 48

2.9 Diamine Addition to PFP Vinylsulfonate

One positive result from the preceding sulfonamide work was the possibility for amine addition at both activated portions of PFP vinylsulfonate. This principle was of importance, as it suggested that species such as diamines could be used to produce cyclic sulfonamides (Scheme 49).



Scheme 49

Hence, aminolysis was attempted stepwise with a selection of diamines using a similar protocol as that used to form the vinyl sulfonamides (Table 16). It was discovered that, despite rapid consumption of PFP vinylsulfonate, no desired product could be identified. This was perhaps inevitable for entries 1 and 2, which potentially have aniline character, but even the benzyl-based diamine (Table 16, entry 3) gave no discernible product. LCMS analysis indicated just the presence of DBU and PFPOH in the crude mixture after work-up, and nmr analysis delivered the same conclusion.

Moreover, the actual mechanism for this transformation was not clear, although it was assumed that displacement of PFPO in the first step would be the most favourable, based upon the previous vinyl sulfonamide work. It was also a possibility that steric hindrance played a part in the failure of PFP vinylsulfonate to undergo aminolysis.

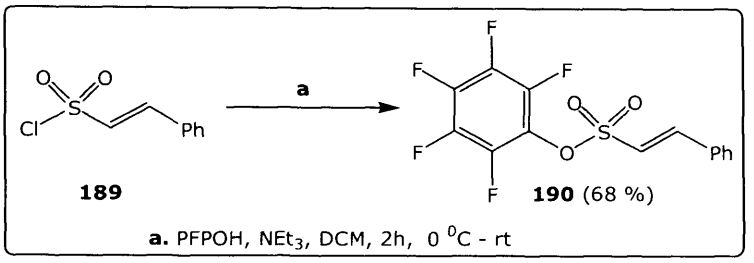
Entry	Diamine	Result
1	anthranilamide	decomposition products obtained
2	*o*-phenylenediamine	decomposition products obtained
3	2-aminobenzylamine	decomposition products obtained

Table 16

2.10 Heck Coupling and Cross Metathesis with PFP Phenyl Vinylsulfonate

With the evident incompatibility of PFP vinylsulfonate and sulfonamides with both Heck and CM conditions, it was thought that modification of the common olefinic portion would be an appropriate step. Incorporation of a phenyl group into the structure was thought a feasible synthetic step, as this would curb the electron-deficient nature of the olefin, which could have been a contributing factor to the previous lack of success.

Formation of PFP phenyl vinylsulfonate was carried out using an analogous procedure to that employed for PFP vinylsulfonate. *Trans*-β-styrenesulfonyl chloride was added to PFPOH in the presence of NEt_3 at 0 °C, and stirred at room temperature for two hours to give a white solid in good yield (190) (Scheme 50).



Scheme 50

This substrate was then employed in Heck coupling and cross metathesis under similar conditions to that formerly attempted (Table 17). Unfortunately, it was found that no desired products could be obtained, with both transformations delivering the same results as previously, namely decomposition during the Heck coupling, and recovery of starting materials in the cross metathesis.

Reaction	**Conditions**	**Result**
Heck Coupling	PhI, $Pd_2(dba)_3$, $[(^tBu)_3PH]BF_4$, Cs_2CO_3, dioxane, reflux 26 h	decomposition
Cross Metathesis	1-octene, Hoveyda, DCM, reflux 24 h	SM recovered
Cross Metathesis	1-octene, Grubbs II, DCM, reflux 24 h	SM recovered

Table 17

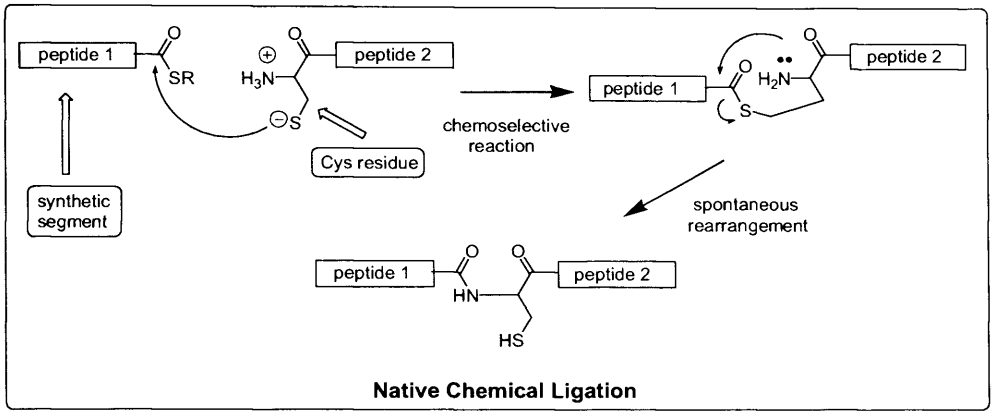
2.11 Application of PFP Vinylsulfonate to Protein Chemistry

2.11.1 Thioester formation *via* PFP vinylsulfonate

Our primary interest in thioester formation using PFP vinylsulfonate was the potential for incorporation of the acceptor into peptides (and ultimately proteins) *via* a procedure developed by Kent and Dawson known as Native Chemical Ligation.[108]

This technique for the construction of synthetic proteins allows the formation of a native peptide bond through a series of chemoselective and spontaneous

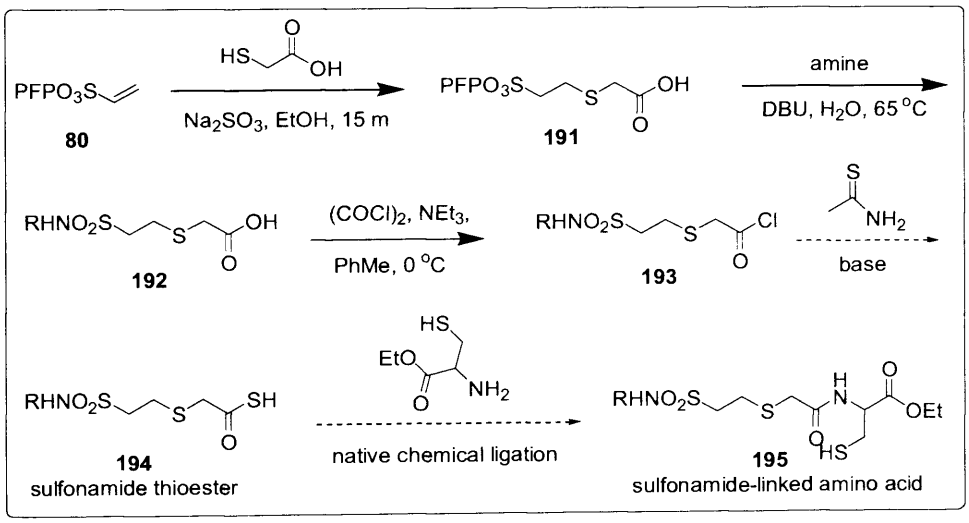
reactions between a terminal thioester on one peptide fragment, and the thiol side chain from a terminal cysteine residue on another peptide fragment (Scheme 51).



Scheme 51

It was postulated that we could exploit the proven reactivity of PFP vinylsulfonate by coupling thioester functionality onto the olefinic portion. This would then enable us to attempt chemical ligation between this species and a peptide fragment containing a terminal cysteine residue. In this way, it would be possible to incorporate PFP sulfonate esters and sulfonamides into proteins and consequently assess their biological impact.

Considering that this premise required formation of a thioester on the vinyl portion of PFP vinylsulfonate, a possible procedure to achieve this was formulated (Scheme 52).



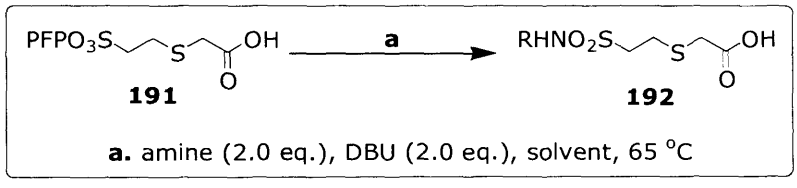
Scheme 52

As displayed above, the procedure devised firstly required Michael addition to a thioacid, followed by aminolysis to the more stable sulfonamide (192) before acid chloride formation, then conversion to the thioester (194).

Practically, it was discovered that the initial addition to mercaptoacetic acid occurred very rapidly at ambient temperature to give the product (191) as a white, tacky solid in quantitative yield without need for purification.

This product was then taken onto the next step of aminolysis (as it was thought the PFP ester would not survive the following step intact). It was initially found that standard aminolysis conditions were unsuitable for this step as the starting material was significantly insoluble in THF. However, by replacing this solvent with water, it was found that the displacement could be completed in less than 2 hours at 65 °C to give the corresponding crude sulfonamide (192) in moderate yield (Scheme 53, Table 18).

However, due to their high polarity, it required much effort to extract the products from the reaction mixture (which could explain the modest yields). In addition, they did not survive purification by column chromatography and were generally difficult to handle. Consequently, the sulfonamides formed were carried forward crude.



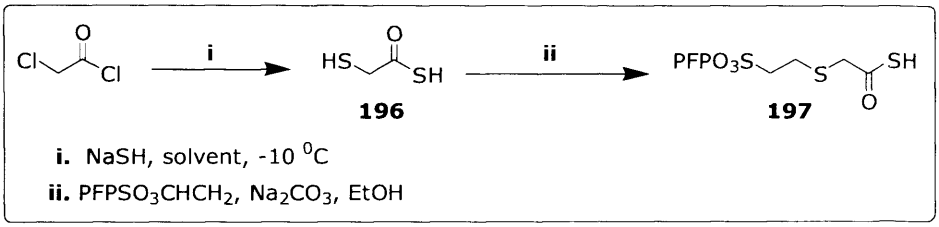
Scheme 53

Amine	Conditions	Result	No.
4-methylbenzylamine	THF, reflux	no product isolated	--
4-methylbenzylamine	H_2O, 65 °C	crude product 55 %	192a
piperidine	H_2O, 65 °C	crude product 41 %	192b

Table 18

Acid chloride formation was then carried out on the crude thio-acid. Although a product was isolated, purificaton was challenging, and determination as to whether the desired product was obtained was without confidence. At this point, the programme was terminated in order to find a similar but more straightforward route to a sulfonamide thioester.

It was considered that with a slight modification in the starting material used, we would gain direct access to the thioester without need for functional group modification. Consequently a new strategy was outlined (Scheme 54), whereby chloroacetyl chloride was reacted with sodium hydrosulfide hydrate in ethanol at -10°C to give mercapto-thioacetic acid[109] (196) in 41 % isolated yield (at best) within 1 hour (Table 19, entries 1 and 2). In addition, using a non-polar solvent did not improve the outcome of the reaction due to miscibility problems (Table 19, entry 3). The Michael addition to PFP vinylsulfonate was then attempted, but it was found that only starting materials could be isolated. (Table 19, entries 1 and 2). Subsequently, the two-step reaction was carried out *in situ*, but a yield of only 9 % of confirmed product (197) could be isolated (Table 19, entry 4). Consequently, this area of research was curtailed.



Scheme 54

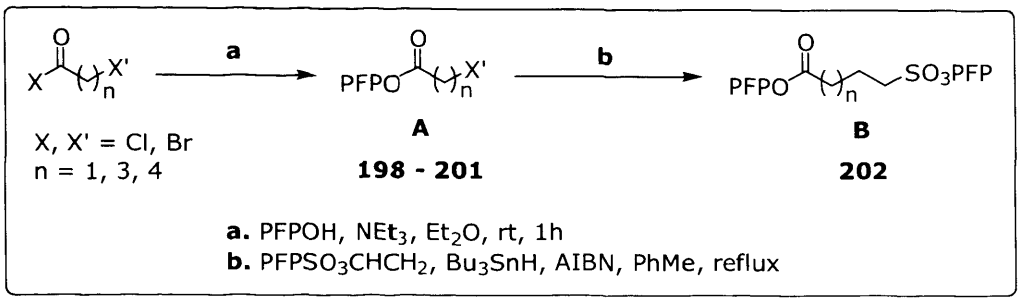
Entry	Conditions Step i	Yield % 196	Result Step ii
1	EtOH, 1 h	41	reflux 1 h, 97 % (196) recovered
2	EtOH, 1 h	23	rt 5 h, 77 % (196) recovered
3	DCM, 3 h	7	--
4	1. EtOH, 2 h; 2. Na_2CO_3, PFPVS, rt 30 m	formed *in situ*	9 % (197) isolated

Table 19

2.11.2 Formation of bifunctional PFP species

Despite the lack of success in the formation of PFP-thioesters, the notion of using PFP species as linkers between amino acids in proteins remained an intriguing proposition. The prospect of bifunctional PFP species, whereby the functionality appears at both ends of the structure, were of interest as this would allow for two points of tether within a protein, which could possibly affect biological activity.

A strategy for the production of bifunctional PFP species was planned incorporating radical chemistry, which had been successful previously in our programme (Scheme 55).[66]



Scheme 55

It was found that pentafluorophenol readily underwent addition to acetyl halides to give the corresponding PFP esters as colourless, fluid oils in moderate to excellent yield in 1 hour (Table 20).

X	X'	n	Yield % A	No.
Cl	Cl	1	36	198
Br	Br	1	61	199
Cl	Br	3	85	200
Cl	Br	4	88	201

Table 20

The proposed radical addition of PFP vinylsulfonate to the esters synthesised was then carried out. Although it has been shown that PFP vinylsulfonate will undergo radical mediated addition to simple acids,[66] it was found that addition could not be achieved very successfully in this case, with little or no consumption of the starting materials during any of the coupling attempts (Table 21).

n	Conditions	Result	No.
3	3 h reflux	SM recovered	--
4	4 h reflux	6 % B achieved	202
4	4 h reflux	8 % B achieved	202

Table 21

Although our investigation was suspended at this stage, it would be a reasonable step to repeat the reaction under modified radical conditions with alternative reagents to possibly improve the yield, as the encouraging results obtained here appear worthy of further study.

2.12 Summary and Conclusions

This research intended to demonstrate the capacity of pentafluorophenyl vinylsulfonate as a useful motif in organic synthesis, and subsequently emphasize the enduring importance of sulfonamides in current medical opinion.

Initial exploration using PFP vinylsulfonate as a radical acceptor[66] allowed us to attempt other avenues of investigation such as cycloaddition, thus exploiting the electron-deficient nature of our olefin.

It was discovered that PFP vinylsulfonate was a willing participant in Diels-Alder reactions with simple carbocycles, and also underwent cycloaddition with a variety of nitrones to form isoxazolidines.[57] However, it was found that cycloaddition was unsuccessful with all other 1,3-dipoles investigated such as azides and nitrile oxides, as well as a number of heterodienes. It was concluded from this research that PFP vinylsulfonate appeared to be a dienophile that required specific conditions or properties in the diene/dipole in order to successfully undergo cycloaddition.

Hence the scope of PFP vinylsulfonate as a dienophile is limited, but the cyclic PFP sulfonate esters formed from successful transformations are biologically attractive structures, especially the modest library of isoxazolidines produced from our research into nitrone cycloaddition. Furthermore, the aminolysis step to form a sulfonamide from the ester cycloadduct was found to be a reliable procedure and the resulting products are also appealing from a medicinal perspective.[57]

Behaviour of the olefinic portion of PFP vinylsulfonate was explored further by experimentation with procedures such as Michael addition, Heck coupling and cross metathesis. Although it was found that PFP vinylsulfonate would not undergo coupling or metathesis, it was encouraging to discover that Michael addition to oxygen nucleophiles occurred readily, prompting the conclusion that this promising area requires further attention in anticipation of fruitful results.

The propensity for PFP vinylsulfonate to undergo Michael addition with suitable nucleophiles was recognised in subsequent research on protein chemistry. The successful addition of thiol species to PFP vinylsulfonate further demonstrated the scope of this transformation, and reinforces the case for further investigation into PFP vinylsulfonate Michael addition, as initial efforts suggest this has potential to be a productive avenue of study.

In conclusion, the research described in this thesis was undertaken in an attempt to explore the reactivity of the bifunctional acceptor pentafluorophenyl vinylsulfonate in the formation of novel PFP sulfonate esters and sulfonamides. Our investigation delivered a greater knowledge on the limitations of the olefin portion of PFP vinylsulfonate, and resulted in the development of a variety of novel compounds. The most successful work involved cycloaddition of PFP vinylsulfonate with an array of functionalized nitrones, followed by aminolysis to furnish heterocyclic sulfonamides. These species are considered to be of biological importance and will presently be assessed for their applicability as therapeutic agents.

This work has also aimed to support the continuing capability of sulfonamides as diverse medicinal agents, and the straightforward and reliable methodology developed in our laboratory[66] has not only resulted in the formation of a variety of interesting sulfonamide species, but has also permitted the vision of further development in this area as the potential for PFP sulfonate esters in synthesis is acknowledged.

3.0 EXPERIMENTAL DATA

3.1 General Experimental Procedures

^1H nmr spectra were recorded on a Bruker 300 MHz machine operating at ambient probe temperature using an internal deuterium lock. Chemical shifts are reported in parts per million (ppm), using residual $CHCl_3$ as an internal standard. Standard abbreviations are used throughout (s singlet; bs broad singlet; d doublet; dd doublet of doublets; ddd double doublet of doublets; dq doublet of quartets; dt doublet of triplets; t triplet; q quartet; m multiplet). Coupling constants are reported in Hertz (Hz).

^{13}C nmr spectra were recorded at 75 MHz. Chemical shifts are reported in parts per million (ppm) using residual $CHCl_3$ as an internal standard.

Mass spectra (EI+, ES+, CI+, FAB) were recorded on a Kratos MS25 spectrometer and a Fisons autospectrometer. Mass spectra undertaken at the EPSRC mass spectrometry centre at the University of Wales Swansea were carried out on a Thermoquest Finnigan MAT 900XT spectrometer. Infra red spectra were recorded on a Perkin-Elmer FT-IR 298 spectrometer.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

Flash column chromatography was carried out using Merck 60 silica gel. Analytical thin layer chromatography was carried out using SIL G/UV_{254} plates with visualisation by UV light; iodine; alkaline potassium permanganate and anisaldehyde.

Reaction solvents were purified and dried according to literature methods.[110] Tetrahydrofuran and diethyl ether were distilled from sodiumbenzophenone ketyl, dichloromethane was distilled from calcium hydride, and toluene was distilled from sodium.

Preparations were performed under an inert (nitrogen or argon) atmosphere unless otherwise stated, and all glassware was flushed with nitrogen prior to use.

3.2 Formation of PFP Vinylsulfonate [80] [66]

To triethylamine (3.0 eq., 12.83 mL, 92.01 mmol) in dichloromethane (30 mL) at -10 °C (ice/acetone cold bath) was added pentafluorophenol (1.05 eq., 5.93 g, 32.21 mmol) dropwise, followed by 2-chloroethylsulfonyl chloride (1.0 eq., 3.21 mL, 30.67 mmol) cautiously over a 15 min period. The reaction was stirred at -10 °C for 1 hr, then quenched with 2M HCl (30 mL). The mixture was extracted with DCM (3 × 50 mL) then washed with water (2 × 50 mL) and brine (2 × 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate

concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (4.60 g, 16.78 mmol, 55 %).

R_f 0.60 (3:1 P:Et_2O)

δ_H ($CDCl_3$, 300MHz) 6.75-6.55 (m, 1H, $SO_2C\mathbf{H}$), 6.42 (dd, *J* 17.1, 0.6, 1H, $CHC\mathbf{H}_2$), 6.29 (dd, *J* 9.8, 0.5, 1H, $CHC\mathbf{H}_2$).

δ_C ($CDCl_3$, 75MHz) (Aromatic peaks not observed due to ^{19}F coupling). 133.8 ($\mathbf{C}H_2$), 131.7 (**C**H).

LRMS (EI+) 274 (M^+, 33 %), 184 (C_6F_5OH, 76 %), 136 ($CHSO_3C_2F$, 38 %), 117 ($CHSO_3C_2$, 25 %), 105 ($CHSO_3C$, 17 %), 91 (SO_2CHCH_2, 77 %), 27 ($CHCH_2$, 100 %).

3.3 Radical Addition Procedures[66]

3.3.1 Radical addition reactions

3,3-Dimethylbutane-1-sulfonic acid pentafluorophenyl ester [81]

To pentafluorophenyl vinylsulfonate (400 mg, 1.46 mmol) in dry toluene (10 mL) was added *t*-butyl iodide (3.0 eq., 0.52 mL, 4.38 mmol), the mixture was heated to reflux and tributyltinhydride (0.41 mL, 1.53 mmol) followed by AIBN (20 mg) were added. The reaction was refluxed for a further 4 hours then cooled. KF (50 mg) was added and the mixture was stirred at ambient temperature for 12 hours, filtered through Celite-545, concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (10:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (430 mg, 1.30 mmol, 89 %).

R_f 0.75 (3:1 P:Et_2O).

δ_H ($CDCl_3$, 300MHz) 3.37-3.32 (m, 2H, $SO_2C\mathbf{H_2}$), 1.89-1.84 (m, 2H, $SO_2CH_2C\mathbf{H_2}$), 0.93 (s, 9H, C ($C\mathbf{H_3}$)$_3$.

δ_C ($CDCl_3$, 75MHz) (Aromatic peaks not observed due to ^{19}F coupling). 144.3 (Ph**C**), 50.1 ($\mathbf{C}H_2$), 36.9 ($\mathbf{C}H_2$), 30.6 (**C** $(CH_3)_3$), 29.2 ($C(\mathbf{C}H_3)_3$).

LRMS (EI+) 332 (M^+, 6 %), 183 (C_6F_5O, 49 %), 155 ($SO_3HC_3F_2$, 66 %), 85 ($C_2H_4C(CH_3)_3$, 56 %), 69 ($C_2(CH_3)_3$, 84 %), 57 ($C(CH_3)_3$, 100 %), 41 (C_3H_5 78 %).

Hexane-1-sulfonic acid pentafluorophenyl ester [82]

To pentafluorophenyl vinylsulfonate (200 mg, 0.73 mmol) in dry toluene (10 mL) was added *n*-butyl iodide (3.0 eq., 0.25 mL, 2.19 mmol), the mixture was heated to reflux and tributyltinhydride (0.21 mL, 0.77 mmol) followed by AIBN (20 mg)

were added. The reaction mixture was refluxed for a further 5 hours then cooled. KF (50 mg) was added and the mixture was stirred at ambient temperature for 12 hours, filtered through Celite-545, concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (140 mg, 0.42 mmol, 58 %).

R_f 0.50 (5:1 P:Et_2O).

δ_H ($CDCl_3$, 300MHz) 3.39-3.34 (m, 2H, SO_2CH_2), 2.01-1.91 (m, 2H, $SO_2CH_2CH_2$), 1.52-1.31 (m, 2H, $SO_2CH_2CH_2CH_2$), 1.30-1.26 (m, 2H, CH_2CH_3), 0.84 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75MHz) (Aromatic peaks not observed due to ^{19}F coupling). 144.1-136.6 (Ph**C**), 53.2 (SO_2CH_2), 31.4 ($SO_2CH_2CH_2$), 28.1 ($SO_2CH_2CH_2CH_2$), 23.8 (CH_2CH_3), 22.6 (CH_2CH_3), 14.2 (CH_3).

LRMS (EI+) 333 (M^+, H, 39 %), 183 (C_6F_5O, 67 %), 155 ($SO_3HC_3F_2$, 55 %), 84 (C_6H_{12}, 70 %), 43 (C_3H_7, 100 %), 29 (C_2H_5, 51 %).

3-Methylbutane-1-sulfonic acid pentafluorophenyl ester [83]

To pentafluorophenyl vinylsulfonate (200 mg, 0.73 mmol) in dry toluene (10 mL) was added 2-bromopropane (3.0 eq., 0.21 mL, 2.19 mmol), the mixture was heated to reflux and tributyltinhydride (0.21 mL, 0.77 mmol) followed by AIBN (20 mg) were added. The reaction mixture was refluxed for a further 7 hours then cooled. KF (50 mg) was added and the mixture was stirred at ambient temperature for 12 hours, filtered through Celite-545, concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (66 mg, 0.21 mmol, 29 %).

R_f 0.60 (5:1 P:Et_2O).

δ_H ($CDCl_3$, 300MHz) 3.40-3.34 (m, 2H, SO_2CH_2), 1.82-1.90 (m, 2H, $SO_2CH_2CH_2$), 0.93 (d, 6H, $CH(CH_3)_2$).

δ_C ($CDCl_3$, 75MHz) (Aromatic peaks not observed due to ^{19}F coupling). 144.3 (Ph**C**), 136.7 (Ph**C**), 51.6 (SO_2CH_2), 32.2 ($SO_2CH_2CH_2$), 27.5 (CH_3), 22.3 (CH_3).

LRMS (EI+) 319 (M^+, H, 36 %), 231 ($C_6F_5SO_2$, 14 %), 184 (C_6F_5OH, 42 %), 86 (SC_4H_6, 100 %), 71 (C_5H_{11}, 68 %), 55 (C_4H_7, 73 %).

5-Iodomethyl-2,2,7,7-tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β,4', 5'-α] pyran

To 2,2,7,7-tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β, 4',5'-α] pyran-5-yl-methanol (5.00 g, 19.23 mmol) in dry toluene (40 mL) was added triphenylphosphine (2.0 eq., 10.08 g, 38.46 mmol) followed by imidazole (3.0

eq., 3.92 g, 57.69 mmol) and iodine (2.0 eq., 9.77 g, 38.46 mmol), and the mixture was refluxed for 4 hours. The mixture was diluted with ether (50 mL), and the filtrate was decanted and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (3.50 g, 9.46 mmol, 49 %).

R_f 0.75 (2:1 P:Et_2O).

δ_H ($CDCl_3$, 300MHz) 5.74 (d, *J* 4.9, 1H, ICH_2CHOCH), 4.81 (dd, *J* 7.8, 2.4, 1H, $ICH_2CHCHCH$), 4.57 (dd, *J* 7.9, 1.7, 1H, ICH_2CHCH), 4.49 (dd, *J* 5.0, 2.5, 1H, $ICH_2CHOCHCH$), 4.13 (dd, *J* 12.4, 7.1, 1H, ICH_2CH), 3.55-3.38 (m, 2H, ICH_2), 1.74-1.53 (m, 12H, 2 × $C(CH_3)_2$).

δ_C ($CDCl_3$, 75MHz) 109.9 ($C(CH_3)_2$), 109.3 ($C(CH_3)_2$), 97.1 (ICH_2CHOCH), 72.0 ($ICH_2CHCHCH$), 71.5 (ICH_2CHCH), 71.0 ($ICH_2CHOCHCH$), 69.3 (ICH_2CH), 26.4 (CH_3), 26.4 (CH_3), 25.3 (CH_3), 24.8 (CH_3), 2.7 (ICH_2).

LRMS (FAB+) 371 (M^+, H, 16 %), 355 (M^+ -CH_3, 36 %), 313 (M^+ -$(CH_3)_2CO$, 26 %), 237 ($C_5O_2H_4CH_2I$, 11 %), 209 ($ICH_2C(CO)_2$, 16 %), 169 (ICH_2CO, 12 %), 127 (I, 14 %), 113 ($C_5O_3H_5$, 13 %), 59 (CH_3CO_2, 100 %).

3-(2,2,7,7-Tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β,4',5'-α]pyran-5-yl)-propane-1-sulfonic acid pentafluorophenyl ester [84]

To pentafluorophenyl vinylsulfonate (260 mg, 0.95 mmol) in dry toluene (15 mL) was added 5-iodomethyl-2,2,7,7-tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β, 4',5'-α] pyran (2.5 eq., 880 mg, 2.37 mmol), the mixture was heated to reflux and tributyltinhydride (0.27 mL, 0.98 mmol) followed by AIBN (30 mg) were added. The reaction mixture was refluxed for a further 3 hours then cooled. KF (50 mg) was added and the mixture was stirred at ambient temperature for 12 hours, filtered through Celite-545, concentrated *in vacuo,* and the crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (350 mg, 0.68 mmol, 71 %).

R_f 0.40 (2:1 P:Et_2O).

δ_H ($CDCl_3$, 300MHz) 5.45 (d, *J* 5.1, 1H, CH_2CHOCH), 4.52 (dd, *J* 7.9, 2.7, 1H, $CH_2CHCHCH$), 4.23 (dd, *J* 5.1, 2.3, 1H, $CH_2CHOCHCH$), 4.05 (dd, *J* 7.9, 1.6, 1H, CH2CHCH), 3.68 (dd, *J* 7.7, 1.5, 1H, CH_2CH), 3.57-3.37 (m, 2H, SO_2CH_2), 2.18-2.04 (m, 2H, $SO_2CH_2CH_2$), 1.86-1.65 (m, 2H, CH_2CHO), 1.51-1.25 (m, 12H, 2 × $(CH_3)_2$).

δ_C ($CDCl_3$, 75MHz) (Aromatic peaks not observed due to ^{19}F coupling). 121.8 (PhC), 109.6 ($C(CH_3)_2$), 108.8 ($C(CH_3)_2$), 96.9 (CH_2CHOCH), 73.1 ($CH_2CHCHCH$), 71.3 ($CH_2CHOCHCH$), 70.7 (CH2CHCH), 67.0 (CH_2CH), 52.6 (SO_2CH_2), 28.4 ($SO_2CH_2CH_2$), 26.3 (CH_3), 25.1 (CH_3), 24.7 (CH_3), 23.7 (CH_3), 20.8 (CH_2CHO).

LRMS (EI+) 503 (M^+ -CH_3, 37 %), 461 (M^+ -$(CH_3)_3C$, 16 %), 445 (M^+ -$(CH_3)_3CO$, 6 %), 385 (M^+ -$C_2(CH_3)_4O_3$, H, 12 %), 357 (M^+ -$C_2(CH_3)_4O_4$, CH, 30 %), 335 (M^+ -C_6F_5O, 7 %), 184 (C_6F_5OH, 10 %), 100 ($C_2(CH_3)_4O$, 68 %), 85 ($C_2(CH_3)_3O$, 29 %), 59 (CH_3CO_2, 49 %), 43 (CH_3CO, 100 %).

3.3.2 Aminolysis procedures for radical addition products

2-(3,3-dimethylbutane-1-sulfonylamino)-3-phenylpropionic acid ethyl ester [85]

To 3,3-dimethylbutane-1-sulfonic acid pentafluorophenyl ester [81] (69 mg, 0.21 mmol) in dry toluene (10 mL) was added phenylalanine ethyl ester (5.0 eq., 200 mg, 1.04 mmol) followed by DBU (1.00 eq., 0.03 mL, 0.21 mmol), and the mixture was refluxed for 8 hours, then stirred at ambient temperature for 12 hours. The reaction was diluted with dichloromethane (50 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$) filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow solid (50 mg, 0.16 mmol, 77 %).

R_f 0.30 (1:1 P:Et_2O).

Mp 85-87 °C

δ_H ($CDCl_3$, 300MHz) 7.27-7.12 (m, 5H, Ph**H**), 4.77 (d, *J* 9.4, 1H, N**H**), 4.27-4.21 (m, 1H, C**H**CH_2Ph), 4.14 (q, *J* 7.1, 2H, $CH_3C\mathbf{H_2}$), 3.08-2.89 (m, 2H, $SO_2C\mathbf{H_2}$), 2.69-2.59 (m, 2H, C$\mathbf{H_2}$Ph), 1.47-1.41 (m, 2H, C$\mathbf{H_2}(CH_3)_3$), 1.20 (t, *J* 7.1, 3H, C$\mathbf{H_3}$), 0.74 (s, 9H, (C$\mathbf{H_3}$)$_3$).

δ_C ($CDCl_3$, 75MHz) 172.0 (**C**O), 136.0-127.8 (Ph**C**), 62.4 ($CH_3\mathbf{C}H_2$), 57.7 (**C**HCH_2Ph), 50.7 ($SO_2\mathbf{C}H_2$), 40.1 (**C**H_2Ph), 36.7 (**C**$H_2(CH_3)_3$), 30.3 (**C**$(CH_3)_3$), 29.3 ((**C**H_3)$_3$), 14.5 (**C**H_3).

LRMS (EI+) 268 (M^+ -$C_2H_5CO_2$, 74 %), 250 (M^+ -Ph, CH_3, 72 %), 194 (M^+ -$SO_2C_6H_{11}$, 29 %), 176 (M+ -$PhCH_3CO_2C_2H_5$, 78 %), 120 (PhC_2H_4NH, 70 %), 102 ($C_4H_8NO_2$, 88 %), 91 ($PhCH_2$, 66 %), 69 ($C(CH_3)_3C$, 27 %), 57 ($C(CH_3)_3$, 100 %), 43 ($CH(CH_3)_2$, 54 %).

3-(2,2,7,7-tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β, 4',5'-α]pyran-5-yl)-propane-1-sulfonic acid allylamide [86]

To 3-(2,2,7,7-tetramethyl-tetrahydro-bis [1,3] dioxolo [4,5-β, 4',5'-α] pyran-5-yl)-propane-1-sulfonic acid pentafluorophenyl ester [84] (68 mg, 0.13 mmol) in dry THF (10 mL) was added allylamine (5.0 eq., 0.05 mL, 0.66 mmol) and DMAP

(1.0 eq., 0.13 mmol, 17 mg), and the mixture was refluxed for 5 hours, then stirred at ambient temperature for 12 hours. The reaction was diluted with dichloromethane (50 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$) filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:4 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (35 mg, 0.09 mmol, 69 %).

R_f 0.10 (1:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 3583 w, 3287 w, 2987 m, 1724 m, 1645 m, 1383 m, 1319 m, 1256 m, 1211 m, 1070 m.

δ_H ($CDCl_3$, 300MHz) 6.11-5.98 (m, 1H, C**H**CH_2NH), 5.70 (d, *J* 4.8, 1H, CH_2CHOCH), 5.47 (d, *J* 16.9, 1H, C**H**$_2$$CHCH_2NH$), 5.38 (d, *J* 10.1, 1H, C**H**$_2$$CHCH_2NH$), 4.77 (dd, *J* 5.8, 2.1, 1H, $CH_2CHCHCH$), 4.62 (dd, *J* 5.5, 4.0, 1H, CH_2CHCH), 4.48 (dd, *J* 4.9, 2.3, 1H, $CH_2CHOCHCH$), 4.29 (dd, *J* 7.9, 1.9, 1H, CH_2CHO), 3.92-3.91 (m, 3H, C**H**$_2$N**H**), 3.26-3.24 (m, 2H, SO_2CH_2), 2.17-1.86 (m, 4H, $SO_2CH_2CH_2CH_2$), 1.70-1.51 (m, 12H, 2 × C(C**H**$_3$)$_2$).

δ_C ($CDCl_3$, 75MHz) 134.1 (**C**HCH_2NH), 118.1 (**C**H_2CHCH_2NH), 109.5 (**C**$(CH_3)_2$), 108.8 (**C**$(CH_3)_2$), 96.9 (CH_2CHOCH), 73.1 ($CH_2CHCHCH$), 71.2 (CH_2CHCH), 70.8 ($CH_2CHOCHCH$), 67.1 (CH_2CHO), 53.0 (SO_2CH_2), 46.1 (**C**H_2NH), 28.8 ($SO_2CH_2CH_2$), 26.4 (**C**H_3), 26.4 (**C**H_3), 25.3 (**C**H_3), 24.7 (**C**H_3), 20.7 (**C**H_2CHO).

LRMS (FAB+) 414 (MNa^+, 21 %), 392 (M^+, H, 100 %), 376 (M^+ -CH_3, 37 %), 334 (M+ -C_3H_6NH, 52 %), 258 ($C_{11}H_{17}O_5(CH_2)_2H$, 29 %), 173 ($C_5H_5O_5CH_2CH_2$, 29 %), 154 ($C_6H_2O_5$, 89 %), 137 ($C_8H_9O_2$, 100 %), 77 (C_5OH, 44 %).

HRMS (ES+) MNa^+ Calcd for $C_{17}H_{29}NO_7S$, 414.1562, found 414.1551.

3.4 Nitrone Cycloaddition Procedures

3.4.1 Typical procedure for the preparation of nitrones[68]

C-Phenyl-*N*-methylnitrone [76][68]

To *N*-methylhydroxylamine hydrochloride (1.2 eq.) in dry dichloromethane (20 mL) was added benzaldehyde (1.0 eq.) and sodium hydrogen carbonate (3.0 eq.). The mixture was refluxed at 40 °C for 2 hours, and the resulting suspension was filtered and washed with dichloromethane (4 × 20 mL). The organic fractions were combined and concentrated *in vacuo* to yield a white solid which was recrystallised (5:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as white needles (92 %).

R_f 0.45 (Et_2O:AcOH 20:1).

δ_H ($CDCl_3$, 300 MHz) 8.38-8.35 (m, 2H, Ph**H**), 7.58-7.41 (m, 4H, C**H**N, Ph**H**), 4.04 (s, 3H, C**H_3**).
δ_C ($CDCl_3$, 75 MHz) 135.6 (**C**H), 130.8 (Ph**C**), 128.9 (Ph**C**), 128.8 (Ph**C**), 54.8 (**C**H_3).
LRMS (EI+) 134 (M^+, 100 %), 118 (M^+-O, 40 %), 89 (PhC, 30 %), 77 (Ph, 27 %), 28 (CO, 25 %).

***C*-(2-Fluorophenyl)-*N*-methylnitrone [87]**[68] (white solid 78 %)
δ_H ($CDCl_3$, 300 MHz) 9.15 (t, *J* 7.7, 1H, Ph**H**), 7.60 (s, 1H, C**H**N), 7.36-7.24 (m, 1H, Ph**H**), 7.20-7.10 (m, 1H, Ph**H**), 7.00 (t, *J* 10.0, 1H, Ph**H**), 3.80 (s, 3H, C**H_3**).
δ_C ($CDCl_3$, 75 MHz) 161.9 (Ph**C**), 158.6 (Ph**C**), 132.1 (**C**HN), 129.0-114.9 (Ph**C**H), 55.3 (**C**H_3).
LRMS (EI+) 153 (M^+, 100 %), 134 (M^+-F, 85 %), 125 (M^+-CO, 90 %), 107 (M^+-$NHCH_3O$, 85 %), 77 (Ph, 40 %), 28 (CO, 15 %).

***C*-(3-Chlorophenyl)-*N*-methylnitrone [88]**[68] (white solid 88 %)
δ_H ($CDCl_3$, 300 MHz) 8.15 (s, 1H, Ph**H**), 7.19 (d, *J* 7.0, 1H, Ph**H**), 7.18-7.12 (m, 3H, Ph**H**, C**H**N), 3.56 (s, 3H, C**H_3**).
δ_C ($CDCl_3$, 75 MHz) 134.9 (**C**HN), 134.2 (Ph**C**), 132.4 (Ph**C**), 130.7-126.8 (Ph**C**H), 55.0 (**C**H_3).
LRMS (EI+) 171 (M^+, ^{37}Cl, 35 %), 170 (M^+-H, ^{37}Cl, 40 %), 169 (M^+, ^{35}Cl, 95 %), 168 (M^+-H, ^{35}Cl, 100 %), 141 (M^+-CO, %), 111 (ClPh, 15 %), 89 (PhCH, 35 %), 77 (Ph, 35 %), 42 (CNO, 60 %).

***C*-(4-Methoxyphenyl)-*N*-methylnitrone [91]**[68] (pale yellow solid 99 %)
δ_H ($CDCl_3$, 300 MHz) 8.15 (d, *J* 8.9, 2H, Ph**H**), 7.20 (s, 1H, C**H**N), 6.85 (d, *J* 9.0, 2H, Ph**H**), 3.71 (s, 6H, OC**H_3**, NC**H_3**).
δ_C ($CDCl_3$, 75 MHz) 161.4 (Ph**C**H), 135.3 (**C**HN), 130.8 (Ph**C**H), 123.8 (Ph**C**), 114.7- 114.2 (Ph**C**H), 55.7 (N**C**H_3), 54.3 (O**C**H_3).
LRMS (EI+) 165 (M^+, 100 %), 135 (M^+-CH_3O, 50 %), 91 (OPh, 15 %), 42 (CNO, 15 %).

***C*-(3-Bromophenyl)-*N*-methylnitrone [92]**[68] (pale brown solid 100 %)
δ_H ($CDCl_3$, 300 MHz) 8.27 (s, 1H, Ph**H**), 7.82 (d, *J* 7.9, 1H, Ph**H**), 7.40 (d, 1H, *J* 8.1, Ph**H**), 7.34 (s, 1H, C**H**N), 7.07 (t, *J* 7.9, 1H, Ph**H**), 3.63 (s, 3H, C**H_3**).
δ_C ($CDCl_3$, 75 MHz) 134.1 (**C**HN), 133.6 (Ph**C**H), 132.6 (Ph**C**), 131.1-127.2 (Ph**C**H), 123.0 (Ph**C**), 55.0 (**C**H_3).
LRMS (EI+) 214 (M^+, 45 %), 184 (^{81}BrPhCHN, 30 %), 84 (92 %), 49 (100 %).

***C*-(4-Nitrophenyl)-*N*-methylnitrone [93]**[68] (yellow solid 93 %)

δ_H ($CDCl_3$, 300 MHz) 8.23-8.06 (m, 4H, Ph**H**), 7.11 (s, 1H, C**H**N), 3.75 (s, 3H, C**H$_3$**).

δ_C ($CDCl_3$, 75 MHz) 129.1 (**C**HN), 124.2 (Ph**C**H), 55.6 (**C**H$_3$).

LRMS (EI+) 179 (M^+, 100 %), 133 (M^+-CH_3ON, 2H, 15 %), 105 (NOPh, 25 %), 77 (Ph, 25 %), 42 (CNO, 40 %).

***C*-(5-Bromo-2-furyl)-*N*-methylnitrone [95]**[68] (white solid 97 %)

δ_H ($CDCl_3$, 300 MHz) 7.61 (d, *J* 3.4, 1H, C**H**CO,), 7.40 (s, 1H, C**H**N), 6.39 (d, *J* 3.4, 1H, C**H**CBr), 3.74 (s, 3H, C**H$_3$**).

δ_C ($CDCl_3$, 75 MHz) 149.1 (**C**O), 125.6 (**C**Br), 124.7 (**C**HN), 117.8 (**C**HCBr), 114.5 (**C**HCO), 53.2 (**C**H$_3$).

LRMS (EI+) 203 (M^+, 92 %), 124 (M^+-Br, 10 %), 79 (M^+-Br, $NOCH_3$, 100 %), 51 (C_4H_3, 90 %), 42 ($CHNCH_3$, 96 %).

***C*-(2-Furyl)-*N*-methylnitrone [96]**[68] (yellow needles 91 %)

δ_H ($CDCl_3$, 300 MHz) 7.70 (d, *J* 3.4, 1H, C**H**COCHN,), 7.48 (s, 1H, C**H**O), 7.40 (s, 1H, C**H**N), 6.45 (s, 1H, C**H**CHCOCHN), 3.70 (s, 3H, C**H$_3$**).

δ_C ($CDCl_3$, 75 MHz) 147.0 (**C**O), 144.1 (**C**HO), 126.8 (**C**HN), 115.7 (**C**HCHO), 112.7 (**C**HCHCHO), 53.1 (**C**H$_3$).

LRMS (EI+) 125 (M^+, 100 %), 108 (M^+-OH, 20 %), 95 (M^+-CHOH, 35 %), 52 (CO, 2C, 45 %), 42 (CNO, 75 %), 28 (CO, 27 %).

***C*-(2-Naphthyl)-*N*-methylnitrone [97]**[68] (yellow solid 86 %)

δ_H ($CDCl_3$, 300 MHz) 9.10 (s, 1H, C**H**N), 7.89-7.40 (m, 7H, Ph**H**), 3.88 (s, 3H, C**H$_3$**).

δ_C ($CDCl_3$, 75 MHz) 135.6 (**C**HN), 134.5-133.5 (Ph**C**), 129.6-126.0 (Ph**C**H), 54.9 (**C**H$_3$).

LRMS (EI+) 185 (M^+, 100 %), 168 (M^+-OH, 45 %), 139 (M^+-$NHCH_3O$, 65 %), 127 ($C_{10}H_7$, 65 %), 115 (C_9H_7, 90 %), 42 (CNO, 70 %), 28 (CO, 10 %).

***C*-(Cyclohexyl)-*N*-methylnitrone [98]**[68] (pale yellow oil 99 %)

δ_H ($CDCl_3$, 300 MHz) 6.42 (d, *J* 7.5, 1H, C**H**N,), 3.49 (s, 3H, C**H$_3$**), 1.70-1.61 (m, 1H, CH_2C**H**), 1.60-1.40 (m, 4H, C**H$_2$**), 1.21-0.90 (m, 6H, C**H$_2$**).

δ_C ($CDCl_3$, 75 MHz) 147.0 (**C**HN), 52.8 (**C**H$_3$), 35.6 (CH_2**C**H), 29.0-25.4 (**C**H$_2$).

LRMS (EI+) 141 (M^+, H, 25 %), 124 (M^+-O, 15 %), 95 (M^+-CH_3NO, 60 %), 84 (C_6H_{12}, 85 %), 49 (100 %), 42 (CNO, 40 %).

***C*-(Cyclopropyl)-*N*-methylnitrone [99]**[68] (yellow oil 100 %)

δ_H ($CDCl_3$, 300 MHz) 5.90 (d, *J* 8.7, 1H, C**H**N,), 3.25 (s, 3H, C$\mathbf{H_3}$), 2.00-1.87 (m, 1H, C**H**CHN), 0.70-0.60 (m, 2H, C$\mathbf{H_2}$), 0.39-0.30 (m, 2H, C$\mathbf{H_2}$).

δ_C ($CDCl_3$, 75 MHz) 143.6 (**C**HN), 52.0 (**C**H_3), 9.5 (**C**HCHN), 7.2 (**C**H_2), 6.8 (**C**H_2).

LRMS (EI+) 99 (M^+, 100 %), 84 (C_3H_5CHNO, 36 %), 68 (C_3H_5CHN, 35 %), 42 (CNO, 67 %), 28 (CO, 42 %).

***C*-(Pentyl)-*N*-methylnitrone [103]**[68] (colourless oil 62 %)

δ_H ($CDCl_3$, 300 MHz) 6.45 (t, *J* 5.8, 1H, C**H**N,), 3.40 (s, 3H, C$\mathbf{H_3}$), 2.21-2.10 (m, 2H, NCHC$\mathbf{H_2}$), 1.30-1.16 (m, 2H, $NCHCH_2C\mathbf{H_2}$), 1.09-0.97 (m, 4H, $CH_3C\mathbf{H_2}C\mathbf{H_2}$), 0.60 (s, 3H, $CH_2C\mathbf{H_3}$).

δ_C ($CDCl_3$, 75 MHz) 140.2 (**C**HN), 51.8 (N**C**H_3), 31.0(**C**H_2CHN), 26.2 (**C**H_2CH_2CHN), 24.6 (**C**$H_2CH_2CH_3$), 21.8 (**C**H_2CH_3), 13.4 (CH_2**C**H_3).

LRMS (EI+) 130 (M^+, H, 70 %), 84 ($CH_3(CH_2)_4CH$, 85 %), 49 (100 %), 42 (CNO, 25 %).

***C*-(4-Allyloxy-phenyl)-*N*-methylnitrone [104]**[68] (white solid 100 %)

δ_H ($CDCl_3$, 300 MHz) 8.08 (d, *J* 8.9, 2H, Ph**H**), 7.17 (s, 1H, C**H**N), 6.82 (d, *J* 9.0, 2H, Ph**H**), 6.01-5.87 (m, 1H, C**H**CH_2O), 5.38-5.16 (m, 2H, C$\mathbf{H_2}$O), 4.46 (d, *J* 5.3, 2H, C$\mathbf{H_2}CHCH_2O$), 3.70 (s, 3H, C$\mathbf{H_3}$).

δ_C ($CDCl_3$, 75 MHz) 160.4 (Ph**C**O), 135.2 (**C**HN), 133.1 (Ph**C**H), 130.7 (Ph**C**H), 124.0 (Ph**C**), 118.4 (**C**H_2CH), 114.9 (CH_2**C**H), 69.2 (**C**H_2O), 54.3 (**C**H_3).

LRMS (EI+) 191 (M^+, 80 %), 175 (M^+-O, 20 %), 150 (M^+-C_3H_5, 30 %), 133 ($PhCNOCH_3$, 25 %), 105 (PhOCH, 12 %), 84 (C_4H_6NO, 23 %), 77 (Ph, 15 %), 42 (CNO, 100 %).

3.4.2 1,3-dipolar cycloaddition reactions[57]

4-Benzenesulfonyl-2-methyl-3-phenyl-isoxazolidine

To phenyl vinyl sulfone (622 mg, 3.70 mmol) in dry toluene (15 mL) was added *C*-phenyl-*N*-methylnitrone [76] (1.0 eq., 500 mg, 3.70 mmol) and the mixture was heated to reflux for 10 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (733 mg, 2.42 mmol, 65 %).

R_f 0.50 (2:1 P:EtOAc).

Mp 96-98 °C

ν_{max} (thin film, cm^{-1}) 3433s, 3063 s, 1633 s, 1447 m, 1306 m, 1149 m.

δ_H ($CDCl_3$, 300 MHz) 7.73-7.08 (m, 5H, Ph**H**), 4.41 (dd, *J* 10.0, 3.4, 1H, C**H**$_2$), 4.18 (dd, *J* 10.0, 8.3, 1H, C**H**$_2$), 4.03-3.97 (m, 1H, C**H**CH_2), 3.78 (d, *J* 6.7, 1H, C**H**N), 2.51 (s, 3H, C**H**$_3$).

δ_C ($CDCl_3$, 75 MHz) 138.4-128.2 (Ph**C**), 76.0 (**C**HCH_2), 73.9 (**C**HN), 66.6 (**C**H_2), 43.1 (**C**H_3).

LRMS (EI+) 303 (M^+, 30 %), 160 (M^+-$PhSO_2$, 2H, 75 %), 134 ($PhCNCH_3O$, 35 %), 117 (M^+-$PhSO_2$, Ph, 47 %), 84 (M^+-$C_6H_5SO_2$, PhH, 85 %), 49 (SO, H, 100 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{17}NO_3S$, 304.1002, found 304.1001.

2-Methyl-3-phenyl-isoxazolidine-4-sulfonic acid phenyl ester

To phenyl vinylsulfonate (109 mg, 0.59 mmol) in dry toluene (10 mL) was added *C*-phenyl-*N*-methylnitrone [76] (2.5 eq., 200 mg, 1.48 mmol) and the mixture was heated to reflux for 24 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (145 mg, 0.45 mmol, 77 %).

R_f 0.55 (1:1 P:Et_2O).

Mp 72-75 °C

ν_{max} (thin film, cm^{-1}) 3435 s, 1641 s, 1487 m, 1378 m, 1192 m, 1142 m.

δ_H ($CDCl_3$, 300 MHz) 6.40-5.54 (m, 10H, Ph**H**), 4.43 (dd, *J* 10.0, 3.4, 1H, C**H**$_2$), 4.30 (dd, *J* 9.8, 8.1, 1H, C**H**$_2$), 4.10 (dt, *J* 7.9, 2.8, 1H, C**H**CH_2), 3.97 (d, *J* 6.9, 1H, C**H**N), 2.60 (s, 3H, C**H**$_3$).

δ_C ($CDCl_3$, 75 MHz) 149.1-122.0 (Ph**C**), 74.5 (**C**HCH_2), 71.9 (**C**HN), 66.9 (**C**H_2), 42.9 (**C**H_3).

LRMS (EI+) 319 (M^+, 100 %), 160 (M^+-$PhSO_3$, 2H, 75 %), 242 (M^+-Ph, 10 %), 134 ($PhCNCH_3O$, 65 %), 117 (M^+-PhO_3, Ph, 52 %), 91 (M^+-$C_6H_5O_3$, PhCN, 35 %), 77 (Ph, 25 %), 65 (SO_2, H, 28 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{17}NO_4S$, 320.0951, found 320.0945.

Elemental analysis Anal. calcd for $C_{16}H_{17}NO_4S$: C 60.17, H 5.37, N 4.39, S 10.04; found: C 59.95, H 5.38, N 4.29, S 9.89.

2-Methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [105]

To pentafluorophenyl vinylsulfonate [80] (120 mg, 0.44 mmol) in dry toluene (10 mL) was added *C*-phenyl-*N*-methylnitrone [76] (2.5 eq., 148 mg, 1.09 mmol) and the mixture was heated to reflux for 20 hours. The reaction was concentrated

in vacuo, and the crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (120 mg, 0.29 mmol, 67 %).

R_f 0.45 (3:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2969s, 2881 s, 1650 s, 1519 m, 1458 m, 1393 m, 1183 m.

δ_H ($CDCl_3$, 300 MHz) 7.41-7.18 (m, 5H, Ph**H**), 4.53 (dd, *J* 10.2, 3.0, 1H, C**H**$_2$), 4.41 (dd, *J* 10.0, 7.9, 1H, C**H**$_2$), 4.25 (dt, J 7.7, 2.8, 1H, C**H**CH_2), 3.98 (d, *J* 6.8, 1H, C**H**N), 2.62 (s, 3H, C**H**$_3$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 144.2-128.4 (Ph**C**), 74.5 (**C**HCH_2), 74.2 (**C**HN), 67.2 (**C**H_2), 43.1 (**C**H_3).

LRMS (EI+) 409 (M^+, 100 %), 183 (C_6F_5O, 15 %), 162 (M^+-$C_6F_5O_3S$, 60 %), 134 (PhCNCH_3O, 57 %), 117 (M^+-$C_6F_5O_3$, Ph, 100 %), 91 (M^+-$C_6F_5O_3$, PhCN, 58 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{12}NO_4F_5S$, 410.0480, found 410.0461.

2-Methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid pentafluoro-phenyl ester [106]

To pentafluorophenyl vinylsulfonate [80] (331 mg, 1.21 mmol) in dry toluene (10 mL) was added *C*-(4-nitrophenyl)-*N*-methylnitrone [93] (1.5 eq., 238 mg, 1.81 mmol) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow solid (355 mg, 0.78 mmol, 65 %).

R_f 0.35 (2:1 P:Et_2O).

Mp 126-128 °C

ν_{max} (thin film, cm^{-1}) 3432 s, 1642 s, 1520 m, 1352 w, 1183 w, 997 w.

δ_H ($CDCl_3$, 300 MHz) 8.19 (d, *J* 8.7, 2H, Ph**H**), 7.62 (d, *J* 8.7, 2H, Ph**H**), 4.53 (dd, *J* 10.2, 3.2, 1H, SO_2CHCH**H**), 4.42 (t, *J* 9.1, 1H, SO_2CHCH**H**), 4.21 (dt, *J* 7.2, 3.2, 1H, SO_2CH**H**), 4.11 (d, *J* 7.0, 1H, SO_2CHCH**H**), 2.63 (s, 3H, C**H**$_3$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 148.8 (Ph**C**), 143.5 (Ph**C**), 129.4 (Ph**C**H), 124.7 (Ph**C**H), 74.1 (**C**HSO_2), 73.3 (SO_2CH**C**H), 67.3 (**C**H_2), 43.2 (**C**H_3).

LRMS (EI+) 454 (M^+, 90 %), 207 (M^+–$C_6H_5SO_3$, 75 %), 161 (M^+-$C_6H_5SO_3$, NO_2, 55 %), 133 (M^+-$C_6H_5O_2$, PhNO_2, 35 %), 116 (C_4H_6NOS, 100 %), 69 (C_3H_3NO, 66 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{12}N_2O_6F_5S$, 455.0336, found 455.0307.

Elemental analysis: Anal. calcd for $C_{16}H_{11}N_2O_6F_5S$: C 42.30, H 2.44, N 6.17; found C 42.38, H 2.44, N 5.83.

3-(4-Methoxy-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid penta-fluorophenyl ester [107]

To pentafluorophenyl vinylsulfonate [80] (201 mg, 0.73 mmol) in dry toluene (5 mL) was added *C*-(4-methoxyphenyl)-*N*-methylnitrone [91] (1.2 eq., 145 mg, 0.88 mmol) and the mixture was heated to reflux for 1 hour. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow solid (250 mg, 0.57 mmol, 78 %).

R_f 0.50 (2:1 P:Et_2O).

Mp 64-68 °C

ν_{max} (thin film, cm^{-1}) 3440 m, 2967 m, 2842 m, 1684 m, 1612 m, 1519 s, 1469 m, 1392 s, 1305 m, 1392 s, 1305 m, 1251 s, 1181 s, 996 s.

δ_H ($CDCl_3$, 300 MHz) 7.18 (d, *J* 8.7, 2H, Ph**H**), 6.67 (d, *J* 8.7, 2H, Ph**H**), 4.42 (dd, *J* 10.4, 3.4, 1H, SO_2CHCH_2), 4.32 (t, *J* 9.0, 1H, SO_2CHCH_2), 4.15 (dt, *J* 7.5, 3.0, 1H, SO_2CH), 3.81 (d, *J* 7.2, 1H, SO_2CHCH), 3.60 (s, 3H, OCH_3), 2.49 (s, 3H, NCH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 165.1 (Ph**C**), 160.6 (Ph**C**), 132.3-114.8 (Ph**C**H), 74.1 (**C**HSO_2), 67.1 (**C**H_2), 55.6 (SO_2CHCH), 42.8 (NCH_3), 15.5 (OCH_3).

LRMS (EI+) 439 (M^+, 95 %), 165 ($CH_3OPhCHNOCH_3$, 97 %), 147 ($CH_3OPhCHCHCH_2$, 100 %), 135 (CH_3OPhCH_2N, 77 %), 121 (CH_3OPhCH_2, 40 %), 77 (Ph, 50 %).

HRMS (ES+) MH^+ Calcd for $C_{17}H_{15}NO_5F_5S$, 440.0591, found 440.0612.

3-Furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [108]

To pentafluorophenyl vinylsulfonate [80] (164 mg, 0.60 mmol) in dry toluene (10 mL) was added *C*-(2-furyl)-*N*-methylnitrone [96] (2.0 eq., 150 mg, 1.20 mmol) and the mixture was heated to reflux for 1 hour. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (4:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (180 mg, 0.45 mmol, 75 %).

R_f 0.50 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2970 m, 2882 m, 1518 s, 1392 s, 1190 s, 997 s.

δ_H ($CDCl_3$, 300 MHz) 7.30 (s, 1H, C**H**O), 6.29 (d, *J* 3.2, 1H, CHCHC**H**O), 6.16 (dd, *J* 3.2, 1.9, 1H, CHC**H**O), 4.51 (dt, *J* 7.9, 3.2, 1H, SO_2CH), 4.38 (dd, *J* 10.2, 2.8, 1H, SO_2CHCH_2), 4.28 (d, *J* 8.7, 1H, SO_2CHCH), 3.91 (s, 1H, SO_2CHCH_2), 2.54 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 147.2 (**C**O), 144.3 (**C**HO), 111.4 (**C**HCO), 111.1 (**C**HCHO), 70.1 (**C**HSO_2), 67.9 (**C**$HCHSO_2$), 67.1 (**C**H_2), 43.1 (**C**H_3).

LRMS (EI+) 399 (M^+, H, 90 %), 353 (M^+-CH_3NO, H, 20 %), 150 ($C_8H_8NO_2$, 30 %), 125 ($C_6H_7NO_2$, 95 %), 107 (C_7H_7O, 100 %), 79 (C_5H_3O, 45 %), 42 (CNO, 45 %).

HRMS (ES+) MH^+ Calcd for $C_{14}H_{11}NO_4F_5S$, 400.0278, found 400.0262.

3-(3-Chloro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluoro-phenyl ester [109]

To pentafluorophenyl vinylsulfonate [80] (606 mg, 2.21 mmol) in dry toluene (5 mL) was added *C*-(3-chlorophenyl)-*N*-methylnitrone [88] (1.5 eq., 562 mg, 3.32 mmol) and the mixture was heated to reflux for 6 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a pale orange oil (649 mg, 1.46 mmol, 66 %).

R_f 0.40 (3:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 3275 w, 2880 m, 1736 m, 1517 m, 1395 m, 1184 m, 995 m.

δ_H ($CDCl_3$, 300 MHz) 7.52 (s, 1H, Ph**H**), 7.41-7.30 (m, 3H, Ph**H**), 4.62 (dd, *J* 10.2, 3.0, 1H, SO_2CHCH_2), 4.49 (t, *J* 7.9, 1H, SO_2CHCH_2), 4.31 (dt, *J* 7.5, 3.2, 1H, SO_2CH), 4.08 (d, *J* 7.0, 1H, SO_2CHCH), 2.69 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 138.2 (Ph**C**), 135.4 (Ph**C**), 130.8-126.8 (Ph**C**H), 74.1 (**C**HSO_2), 73.7 (SO_2CHCH), 67.2 (**C**H_2), 43.0 (**C**H_3).

LRMS (EI+) 443 (M^+, ^{35}Cl, 90 %), 196 ($M^+-C_6F_5SO_3$, 75 %), 168 ($ClPhC_3H_5O$, 65 %), 151 ($ClPhCHCHCH_2$, 85 %), 115 (PhC_3H_3, 80 %), 102 (PhCHCH, 22 %), 85 ($M^+-C_6F_5SO_3$, ClPh, 65 %), 42 (CNO, 100 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{12}NO_4F_5SCl$, 444.0096, found 444.0083.

3-(2-Fluoro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluoro-phenyl ester [110]

To pentafluorophenyl vinylsulfonate [80] (598 mg, 2.18 mmol) in dry toluene (5 mL) was added *C*-(2-fluorophenyl)-*N*-methylnitrone [87] (1.5 eq., 501 mg, 3.27 mmol) and the mixture was heated to reflux for 6 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a pale brown oil (429 mg, 1.00 mmol, 46 %).

R_f 0.50 (3:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2969 m, 2882 m, 1736 m, 1590 m, 1520 s, 1520 s, 1395 s, 1186 s, 998 s.

δ_H ($CDCl_3$, 300 MHz) 7.50-7.03 (m, 4H, Ph**H**), 4.64 (m, 1H, SO_2C**H**), 4.55 (m, 2H, SO_2CHCH_2), 4.34 (s, 1H, SO_2CHCH), 2.69 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 163.2 (Ph**C**), 159.9 (Ph**C**), 131.5-116.6 (Ph**C**H), 72.6 (**C**HSO_2), 68.9 (SO_2CHCH), 67.3 (CH_2), 43.1 (CH_3).

LRMS (EI+) 427 (M^+, 90 %), 180 ($M^+-C_6H_5SO_3$, 75 %), 135 ($FPhCHCHCH_2$, 100 %), 109 ($FPhCH_2$, 70 %), 84 (C_4H_6NO, 50 %), 49 (NO, F, 65 %).

HRMS (ES+) MNa^+ Calcd for $C_{16}H_{11}NO_4F_6SNa$, 450.0211, found 450.0213.

2-Methyl-3-pentyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [111]

To pentafluorophenyl vinylsulfonate [80] (520 mg, 1.90 mmol) in dry toluene (5 mL) was added *C*-(pentyl)-*N*-methylnitrone [103] (1.5 eq., 367 mg, 2.85 mmol) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (4:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (508 mg, 1.26 mmol, 66 %).

R_f 0.75 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3400 w, 2931 m, 1775 m, 1519 m, 1390 m, 1184 m, 997 m.

δ_H ($CDCl_3$, 300 MHz) 4.61-4.53 (m, 1H, SO_2CHCH_2), 4.45-4.38 (m, 1H, SO_2CHCH_2), 4.25-4.15 (m, 1H, SO_2C**H**), 3.40 (s, 1H, SO_2CHCH), 2.82 (s, 3H, NCH_3), 1.59-1.47 (m, 2H, CH_2CHNCH_3), 1.39-1.19 (m, 6H, CH_3CH_2, $CH_3CH_2CH_2$, $CH_2CH_2CHNCH_3$), 0.82 (s, 3H, CH_2CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 71.5 (**C**HSO_2), 70.1 (SO_2CHCH), 66.7 (SO_2CHCH_2), 61.4 (CH_2CHNCH_3), 43.9 (NCH_3), 32.2 ($CH_2CH_2CHNCH_3$), 25.8 ($CH_3CH_2CH_2$), 22.8 (CH_3CH_2), 13.9 (CH_3CH_2).

LRMS (EI+) 403 (M^+, 60 %), 332 ($M^+-C_5H_{11}$, 100 %), 156 ($C_9H_{18}NO$, 55 %), 135 (C_8H_9NO, 75 %), 109 ($C_5H_{11}C_3H_2$, 53 %), 85 ($C_5H_{11}CH_2$, 93 %), 42 (CNO, 52 %).

HRMS (ES+) MH^+ Calcd for $C_{15}H_{19}NO_4F_5S$, 404.0955, found 404.0945.

3-Cyclohexyl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [112]

To pentafluorophenyl vinylsulfonate [80] (450 mg, 1.64 mmol) in dry toluene (5 mL) was added *C*-cyclohexyl-*N*-methylnitrone [98] (2.0 eq., 460 mg, 3.28 mmol)

and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a brown oil (370 mg, 0.89 mmol, 54 %).

R_f 0.50 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2930 s, 1519 s, 1388 m, 1158 m, 997 s.

δ_H ($CDCl_3$, 300 MHz) 4.60-4.50 (m, 1H, $SO_2C\mathbf{H}$), 4.32-4.11 (m, 2H, $SO_2C\mathbf{H_2}$), 3.25-3.18 (m, 1H, $SO_2CHC\mathbf{H}$), 2.78 (s, 3H, $C\mathbf{H_3}$), 1.81-1.47 (m, 6H, $C\mathbf{H_2}$), 1.20-0.94 (m, 5H, $C\mathbf{H_2}$, $C\mathbf{H}$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 73.2 ($\mathbf{C}HSO_2$), 67.6 ($SO_2CH\mathbf{C}H$), 65.7 ($SO_2CH\mathbf{C}H_2$), 44.1 ($\mathbf{C}H_3$), 40.4 ($\mathbf{C}HCHN$), 28.9-24.0 ($\mathbf{C}H_2$).

LRMS (EI+) 415 (M^+, 35 %), 332 (M^+-C_6H_{11}, 95 %), 184 (C_6F_5OH, 65 %), 85 ($CHCHCH_2ONCH_3$, 100 %), 41 (CH_2CHCH_2, 55 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{19}NO_4F_5S$, 416.0949, found 416.0948.

2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid pentafluoro-phenyl ester [113]

To pentafluorophenyl vinylsulfonate [80] (375 mg, 1.37 mmol) in dry toluene (5 mL) was added *C*-(2-naphthyl)-*N*-methylnitrone [97] (1.5 eq., 380 mg, 2.05 mmol) and the mixture was heated to reflux for 6 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (10:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow solid (406 mg, 0.88 mmol, 65 %).

R_f 0.40 (3:1 P:Et_2O).

Mp 91-97 °C

ν_{max} (thin film, cm^{-1}) 3432 bs, 2091 w, 1646 s, 1522 s, 1395 m, 1184 m, 996 s.

δ_H ($CDCl_3$, 300 MHz) 8.06-7.81 (m, 4H, Ph**H**), 7.65-7.48 (m, 3H, Ph**H**), 4.68-4.55 (m, 2H, $C\mathbf{H_2}$), 4.48 (dt, *J* 7.7, 3.0, 1H, $SO_2C\mathbf{H}$), 4.30 (d, *J* 6.8, 1H, $SO_2CHC\mathbf{H}$), 2.79 (s, 3H, $C\mathbf{H_3}$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 136.9-125.1 (Ph**C**H), 74.7 ($SO_2\mathbf{C}H$), 74.1 ($SO_2CH\mathbf{C}H$), 67.4 ($\mathbf{C}H_2$), 43.1 ($\mathbf{C}H_3$).

LRMS (EI+) 459 (M^+, 30 %), 184 (C_6F_5OH, 80 %), 155 (M^+-$C_{10}H_7$, 100 %), 127 ($C_{10}H_7$, 95 %).

HRMS (ES+) MH^+ Calcd for $C_{20}H_{14}NO_4F_5S$, 459.0558, found 459.0561.

Elemental analysis: Anal. calcd for $C_{20}H_{14}NO_4F_5S$: C 52.29, H 3.07, N 3.05; found C 52.20, H 2.99, N 2.92.

3-Cyclopropyl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [114]

To pentafluorophenyl vinylsulfonate [80] (213 mg, 0.78 mmol) in dry toluene (5 mL) was added *C*-cyclopropyl-*N*-methylnitrone [99] (1.5 eq., 115 mg, 1.17 mmol) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a pale yellow oil (156 mg, 0.42 mmol, 54 %).

R_f 0.40 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 3011 m, 2881 s, 2463 w, 1651 w, 1520 s, 1471 m, 1387 s, 1185 s, 997 s.

δ_H ($CDCl_3$, 300 MHz) 4.40 (d, *J* 6.6, 1H, SO_2CHCH), 4.31-4.20 (m, 2H, SO_2CHCH_2), 2.79 (s, 3H, CH_3), 1.02-0.90 (m, 1H, $CHCH_2CH_2$), 0.73-0.52 (m, 3H, CH_2CH_2), 0.41-0.31 (m, 1H, CH_2).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 72.2 ($CHSO_2$), 69.8 (SO_2CHCH), 64.5 (SO_2CHCH_2), 42.0 (CH_3), 10.9 (CH_2CH_2CH), 2.6 (CH_2CH_2), 0.0 (CH_2CH_2).

LRMS (EI+) 373 (M^+, 95 %), 332 (M^+-C_3H_5, 35 %), 184 (C_6F_5OH, 15 %), 126 (M^+-$C_6F_5SO_3$, 40 %), 99 (C_5H_9NO, 37 %), 85 (C_4H_7NO, 82 %), 49 (SO, H, 100 %).

HRMS (ES+) MH^+ Calcd for $C_{13}H_{13}NO_4F_5S$, 374.0480, found 374.0478.

3-(4-Allyloxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [115]

To pentafluorophenyl vinylsulfonate [80] (725 mg, 2.65 mmol) in dry toluene (10 mL) was added *C*-(4-allyloxyphenyl)-*N*-methylnitrone [104] (1.1 eq., 556 mg, 2.91 mmol) and the mixture was heated to reflux for 1 hour. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (4:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (1.09 g, 2.34 mmol, 88 %).

R_f 0.45 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2967 m, 2878 m, 1692 m, 1601 m, 1520 s, 1392 s, 1247 s, 996 s.

δ_H ($CDCl_3$, 300 MHz) 7.22 (d, *J* 8.9, 2H, PhH), 6.77 (d, *J* 8.9, 2H, PhH), 5.99-5.86 (m, 1H, $CHCH_2O$), 5.31-5.10 (m, 2H, CH_2O), 4.52-4.31 (m, 4H, SO_2CHCH_2, CH_2CHCH_2O), 4.15 (dt, *J* 4.9, 3.0, 1H, SO_2CH), 3.86 (d, *J* 6.8, 1H, SO_2CHCH), 2.51 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 164.0 (Ph**C**), 159.6 (Ph**C**), 133.4 (**C**HCH_2O), 132.7-129.6 (Ph**C**H), 127.8 (Ph**C**), 118.2 (**C**H_2CHCH_2O), 115.6 (Ph**C**H), 115.4 (Ph**C**H), 74.1 (**C**HSO_2), 69.2 (**C**H_2O), 67.1 (SO_2CH**C**H_2), 53.8 (**C**$HCHSO_2$), 42.9 (**C**H_3).

LRMS (EI+) 465 (M^+, 50 %), 191 (M^+-$C_6F_5SO_3$, C_2H_3, 80 %), 162 (M^+-$C_6F_5SO_3$, C_3H_4O, 70 %), 120 ($PhOCH_2CH_2$, 42 %), 105 (PhOCH, 47 %), 79 (C_5H_5N, 55 %), 41 (C_3H_5, 100 %).

HRMS (ES+) MH^+ Calcd for $C_{19}H_{17}NO_5F_5S$, 466.0748, found 466.0727.

3-(5-Bromo-furan-2-yl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [116]

To pentafluorophenyl vinylsulfonate [80] (172 mg, 0.63 mmol) in dry toluene (5 mL) was added *C*-(5-bromo-2-furyl)-*N*-methylnitrone [95] (1.2 eq., 154 mg, 0.75 mmol) and the mixture was heated to reflux for 4 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (166 mg, 0.35 mmol, 55 %).

R_f 0.50 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 3140 w, 2971 m, 2882 m, 1651 w, 1471 m, 1394 s, 1189 s, 1122 m, 996 s.

δ_H ($CDCl_3$, 300 MHz) 6.40 (d, *J* 3.3, 1H, C**H**CO), 6.24 (d, *J* 3.3, 1H, C**H**CBr), 4.63-4.57 (m, 1H, C**H**SO_2), 4.53-4.37 (m, 2H, SO_2CHCH_2), 4.03 (bs, 1H, SO_2CHCH), 2.69 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 149.1 (**C**O), 124.1 (**C**Br), 114.2 (**C**HCBr), 113.0 (**C**HCO), 70.0 (**C**HSO_2), 67.8 (**C**$HCHSO_2$), 67.1 (**C**H_2), 43.2 (**C**H_3).

LRMS (EI+) 479 (M^+, H, 70 %), 433 (M^+-CH_3NOH, 35 %), 203 (M^+-$C_6F_5SO_3$, NCH_3, 90 %), 184 (C_6F_5OH, 75 %), 117 (C_4H_7NOS, 17 %), 84 (C_4H_6NO, 100 %).

HRMS (ES+) MH^+ Calcd for $C_{14}H_{10}NO_5F_5SBr$, 477.9383, found 477.9378.

3-(3-Bromo-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [117]

To pentafluorophenyl vinylsulfonate [80] (1.25 g, 4.56 mmol) in dry toluene (10 mL) was added *C*-(3-bromophenyl)-*N*-methylnitrone [92] (1.2 eq., 1.17 g, 5.47 mmol) and the mixture was heated to reflux for 1 hour. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (8:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (1.34 g, 2.74 mmol, 60 %).

R_f 0.55 (2:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 2966 m, 2928 m, 2879 m, 1572 m, 1520 s, 1474 m, 1394 s, 1184 s, 998 s, 792 m.

δ_H ($CDCl_3$, 300 MHz) 7.62-7.19 (m, 4H, Ph**H**), 4.62-4.52 (m, 1H, SO_2C**H**), 4.50-4.38 (m, 1H, SO_2CHCH_2), 4.30-4.20 (m, 1H, SO_2CHCH_2), 4.01 (bs, 1H, SO_2CHCH), 2.70 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 138.4 (Ph**C**), 132.8-127.3 (Ph**C**H), 123.5 (Ph**C**), 74.1 (**C**HSO_2), 73.6 (SO_2CHCH), 67.2 (CH_2), 43.1 (CH_3).

LRMS (EI+) 489 (M^+, ^{81}Br, 78 %), 487 (M^+, ^{79}Br, 77 %), 240 ($C_{10}H_{11}NO^{79}Br$, 67 %), 212 ($C_8H_7NO^{79}Br$, 47 %), 197 ($C_7H_4NO^{79}Br$, 36 %), 183 (C_6F_5O, 42 %), 155 ($C_6H_4{}^{79}Br$, 49 %), 116 (C_9H_8, 100 %), 102 (C_3H_4NOS, 33 %), 85 (C_4H_7NO, 46 %), 42 (CNO, 54 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{12}NO_4F_5SBr$, 487.9591, found 487.9610.

3.4.3 Aminolysis procedures for isoxazolidine sulfonate esters[66]

2-Methyl-3-phenyl-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide [122]

To 2-methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [105] (94 mg, 0.23 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.09 mL, 0.69 mmol) followed by DBU (1.4 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (58 mg, 0.17 mmol, 73 %).

R_f 0.50 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3546 m, 3292 s, 2875 m, 2254 m, 1603 w, 1516 m, 1455 m, 1328 s, 1149 s, 1043 m, 911 m.

δ_H ($CDCl_3$, 300 MHz) 7.40-7.18 (m, 5H, Ph**H**), 7.07-6.81 (m, 4H, CH_3Ph**H**), 4.42-4.33 (m, 1H, SO_2C**H**), 4.20 (t, *J* 9.1, 1H, N**H**), 4.17-4.03 (m, 2H, SO_2CHCH_2), 4.00-3.90 (m, 1H, SO_2CHCH), 3.85-3.65 (m, 2H, $NHCH_2$), 2.50 (s, 3H, NCH_3), 2.20 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) 138.3-133.5 (Ph**C**), 129.8-128.4 (Ph**C**H), 73.6 (**C**HSO_2), 68.8 (SO_2CHCH), 67.2 (SO_2CHCH_2), 47.5 ($NHCH_2$), 43.1 (NCH_3), 21.5 (PhCH_3).

LRMS (EI+) 346 (M^+, 15 %), 160 (M^+-$CH_3PhCH_2NHSO_2$, 2H, 95 %), 134 ($PhCHCHCH_2O$, H, 75 %), 117 ($PhCHCHCH_2$, 100 %), 91 (CH_3Ph, 65 %), 77 (Ph, 45 %).

HRMS (ES+) MH^+ Calcd for $C_{11}H_{17}N_2O_4S$, 347.1429, found 347.1423.

2-Methyl-3-phenyl-isoxazolidine-4-sulfonic acid 4-methyl-benzaldehyde [133]

To 2-methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [105] (105 mg, 0.26 mmol) in dry tetrahydrofuran (5 mL) was added phenylalanine ethyl ester (3.0 eq., 149 mg, 0.77 mmol) followed by DBU (1.3 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (63 mg, 0.15 mmol, 58 %).

R_f 0.65 (20:10:1 P:EtOAc:AcOH).

ν_{max} (thin film, cm^{-1}) 3274 s, 2929 s, 2255 w, 1738 s, 1604 w, 1455 m, 1331 m.

δ_H ($CDCl_3$, 300 MHz) 7.40-6.90 (m, 10H, Ph**H**), 5.10 (dd, *J* 24.5, 9.4, 1H, SO_2CHCH_2), 4.20-4.00 (m, 6H, SO_2CHCH_2, N**H**, CH_3CH_2, $PhCH_2$), 3.90-3.75 (m, 1H, SO_2CH), 2.82 (d, *J* 6.2, 1H, SO_2CHCH), 2.80-2.72 (m, 1H, NHC**H**), 2.53 (s, 3H, NCH_3), 1.09 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) 137.4-135.3 (Ph**C**), 129.7-127.8 (Ph**C**H), 74.5 ($CHSO_2$), 76.6 (SO_2CHCH_2), 62.5 ($PhCH_2$), 58.0 (SO_2CHCH), 57.5 (NH**C**H), 43.1 (NCH_3), 39.7 (CH_3CH_2), 14.4 (CH_3CH_2).

LRMS (EI+) 418 (M^+, 45 %), 161 (PhC_4H_6NO, 100 %), 146 (PhC_3H_3NO, 30 %), 134 (PhC_2H_3NO, 65 %), 117 (PhCHCHN, 82 %), 91 ($PhCH_2$, 80 %), 77 (Ph, 20 %).

HRMS (ES+) MH^+ Calcd for $C_{21}H_{27}N_2O_5S$, 419.1641, found 419.1635.

3-Furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid allylamide [125]

To 3-furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [108] (97 mg, 0.24 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.05 mL, 0.73 mmol) followed by DBU (1.4 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$),

filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow solid (52 mg, 0.19 mmol, 80 %).

R_f 0.25 (2:1 P:EtOAc).

Mp 56-61 °C

ν_{max} (thin film, cm^{-1}) 3432 s, 2095 m, 1645 s, 1438 w, 1322 s, 1248 w, 1150 s, 1038 w.

δ_H ($CDCl_3$, 300 MHz) 7.38 (s, 1H, C**H**O), 6.40 (d, *J* 3.2, 1H, CHCHC**H**O), 6.32-6.29 (m, 1H, CHC**H**O), 5.60-5.42 (m, 1H, C**H**CH_2NH), 5.16-5.02 (m, 2H, NHC**H_2**), 4.80 (s, 1H, N**H**), 4.35-4.20 (m, 3H, NHCH_2CHC**H_2**, SO_2CHC**H_2**), 3.85 (s, 1H, NHCH_2CHC**H_2**), 3.69-3.57 (m, 1H, SO_2C**H**), 3.49-3.35 (m, 1H, SO_2CHC**H**), 2.59 (s, 3H, NC**H_3**).

δ_C ($CDCl_3$, 75 MHz) 148.8 (**C**O), 143.8 (**C**HO), 133.5 (**C**HCH_2NH), 118.4 (**C**H_2CHCH_2NH), 111.2 (**C**HCO), 110.8 (**C**HCHO), 69.6 (**C**HSO_2), 68.2 (**C**HCHSO_2), 67.1 (SO_2CH**C**H_2), 46.2 (NH**C**H_2), 43.3 (**C**H_3).

LRMS (EI+) 272 (M^+, 15 %), 150 (M^+-$C_3H_8NO_2S$, 100 %), 125 ($C_6H_7NO_2$, 75 %), 107 (C_6H_5NO, 90 %), 79 (C_5H_3O, 55 %), 57 (CHNOCH_2, 75 %), 43 (CHNO, 95 %).

HRMS (ES+) MH^+ Calcd for $C_{11}H_{17}N_2O_4S$, 273.0909, found 273.0903.

3-Furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid 4-methyl-benzyl-amide [118]

To 3-furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [108] (115 mg, 0.29 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.11 mL, 0.86 mmol) followed by DBU (1.1 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (84 mg, 0.25 mmol, 86 %).

R_f 0.30 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3550 w, 3291 s, 2877 s, 2255 w, 1732 m, 1616 m, 1516 w, 1435 m, 1327 s, 1148 s.

δ_H ($CDCl_3$, 300 MHz) 7.07-6.90 (m, 5H, CH_3Ph**H**, CHO), 6.30 (s, 2H, CHC**H**O, CHCHC**H**O), 4.95 (s, 1H, N**H**), 4.40-4.00 (m, 4H, SO_2CHC**H_2**, SO_2CHC**H**, SO_2C**H**), 3.82 (d, *J* 13.8, 2H, NHC**H_2**), 2.55 (s, 3H, NC**H_3**), 2.21 (s, 3H, C**H_3**).

δ_C ($CDCl_3$, 75 MHz) 148.9 (**C**O), 143.8 (**C**HO), 138.2 (Ph**C**), 133.7 (Ph**C**), 129.8 (Ph**C**H), 128.3 (Ph**C**H), 111.2 (**C**HCO), 110.7 (**C**HCHO), 69.6 (**C**HSO_2), 68.1 (**C**HCHSO_2), 67.1 (SO_2CH**C**H_2), 47.4 (NH**C**H_2), 43.4 (N**C**H_3), 21.4 (Ph**C**H_3).
LRMS (EI+) 336 (M^+, 15 %), 150 (M^+-$C_8H_{12}NO_2S$, 60 %), 125 ($C_6H_7NO_2$, 30 %), 107 (C_6H_5NO, 45 %), 84 (C_4H_6NO, 75 %), 49 (SO, H, 100 %).
HRMS (ES+) MH^+ Calcd for $C_{16}H_{21}N_2O_4S$, 337.1222, found 337.1209.

2-Methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid allylamide [131]

To 2-methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [106] (151 mg, 0.33 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.07 mL, 1.00 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 1 hour. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow solid (51 mg, 0.15 mmol, 47 %).
R_f 0.40 (2:1 P:EtOAc).
Mp 148-153 °C
ν_{max} (thin film, cm^{-1}) 3432 s, 2098 w, 1643 s, 1522 w, 1350 w, 1149 w.
δ_H ($CDCl_3$, 300 MHz) 8.18 (d, *J* 8.7, 2H, Ph**H**), 7.61 (d, *J* 8.7, 2H, Ph**H**), 5.72-5.59 (m, 1H, $NHCH_2C$**H**), 5.10 (t, *J* 13.2, 2H, NHC**H_2**), 4.68-4.59 (m, 1H, $NHCH_2CHCH_2$), 4.32-4.24 (m, 2H, SO_2CHCH_2), 4.02-3.85 (m, 2H, SO_2CH, N**H**), 3.60 (d, *J* 3.2, 2H, SO_2CHCH, $NHCH_2CHCH_2$), 2.60 (s, 3H, NC**H_3**).
δ_C ($CDCl_3$, 75 MHz) 148.4 (Ph**C**), 145.4 (Ph**C**), 133.5 (**C**HCH_2NH), 129.4 (Ph**C**H), 124.5 (Ph**C**H), 118.7 (**C**H_2CHCH_2NH), 74.5 (**C**HSO_2), 73.4 (SO_2CH**C**H), 67.5 (SO_2CHCH_2), 46.4 (NH**C**H_2), 43.4 (**C**H_3).
LRMS (EI+) 327 (M^+, 15 %), 205 ($NO_2PhC_4H_5NO$, 100 %), 179 ($NO_2PhC_2H_3NO$, 25 %), 116 (C_4H_6NOS, 60 %).
HRMS (ES+) MH^+ Calcd for $C_{13}H_{18}N_3O_5S$, 328.0967, found 328.0964.

2-Methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide [128]

To 2-methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [106] (155 mg, 0.34 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.13 mL, 1.02 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.34 mmol), and the mixture was refluxed for 1 hour. The reaction was

diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow solid (67 mg, 0.17 mmol, 50 %).

R_f 0.50 (2:1 P:EtOAc).

Mp 146-150 °C

ν_{max} (thin film, cm^{-1}) 3436 s, 1641 s, 1521 m, 1349 m, 1148 m, 1042 w.

δ_H ($CDCl_3$, 300 MHz) 8.10 (d, *J* 8.9, 2H, Ph**H**), 7.50 (d, *J* 8.7, 2H, Ph**H**), 7.02-6.90 (m, 4H, CH_3Ph**H**), 4.28 (dd, *J* 9.8, 3.8, 1H, SO_2CHCH_2), 4.18-4.07 (m, 4H, SO_2CHCH_2, N**H**, SO_2CH, SO_2CHCH), 3.90 (d, *J* 6.8, 1H, $NHCH_2$), 3.65 (dt, *J* 8.1, 3.8, 1H, $NHCH_2$), 2.52 (s, 3H, NCH_3), 2.20 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) 148.3-133.6 (Ph**C**), 129.9-124.4 (Ph**C**H), 74.4 (**C**HSO_2), 73.3 (SO_2CHCH), 67.5 (SO_2CHCH_2), 47.5 ($NHCH_2$), 43.3 (NCH_3), 21.5 (PhCH_3).

LRMS (EI+) 391 (M^+, 10 %), 205 (M^+-$CH_3PhCH_2NHSO_2$, 2H, 100 %), 120 (CH_3PhCH_2NH, 87 %), 105 (CH_3PhCH_2, 100 %), 91 (CH_3Ph, 32 %), 69 (C_3H_3NO, 60 %), 57 (C_2H_3NO, 35 %), 43 (C_2H_3O, 30 %).

HRMS (ES+) MH^+ Calcd for $C_{18}H_{22}N_3O_5S$, 392.1280, found 392.1269.

3-(4-Methoxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid allylamide [126]

To 3-(4-methoxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluoro-phenyl ester [107] (145 mg, 0.33 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.07 mL, 0.99 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 1 hour. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (84 mg, 0.27 mmol, 81 %).

R_f 0.30 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3293 s, 2875 s, 1612 s, 1515 s, 1440 m, 1326 s, 1250 s, 1178 m, 1149 s, 1033 s, 923 m, 838 s.

δ_H ($CDCl_3$, 300 MHz) 7.30 (d, *J* 8.7, 2H, Ph**H**), 6.82 (d, *J* 8.7, 2H, Ph**H**), 5.63-5.40 (m, 1H, $NHCH_2CH$), 5.12-5.02 (m, 2H, $NHCH_2$), 4.75 (t, *J* 5.9, 1H, N**H**), 4.37-4.25 (m, 2H, SO_2CHCH_2), 4.00-3.90 (m, 1H, SO_2CH), 3.74 (s, 3H, OCH_3), 3.57-3.20 (m, 3H, SO_2CHCH, $NHCH_2CHCH_2$), 2.51 (s, 3H, NCH_3).

δ_C ($CDCl_3$, 75 MHz) 160.3 (Ph**C**), 133.6 (**C**HCH_2NH), 130.9 (Ph**C**H), 129.8 (Ph**C**H), 128.8 (Ph**C**), 118.3 (**C**H_2CHCH_2NH), 114.3 (Ph**C**H), 73.4 (**C**HSO_2), 67.1 (SO_2CHCH_2), 55.7 (**C**$HCHSO_2$), 46.1 ($NHCH_2$), 43.0 (NCH_3), 14.6 (OCH_3).

LRMS (EI+) 312 (M^+, 45 %), 190 (M^+-CH_3OPhCH_3, 100 %), 165 ($C_9H_{11}NO_2$, 90 %), 147 ($CH_3OPhCHCHN$, 95 %), 91 (OPh, 25 %), 41 (CH_2CHCH_2, 25 %).

HRMS (ES+) MH^+ Calcd for $C_{14}H_{21}N_2O_4S$, 313.1222, found 313.1217.

3-(4-Methoxy-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid 4-methyl-benzylamide [123]

To 3-(4-methoxy-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluoro-phenyl ester [107] (136 mg, 0.31 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.12 mL, 0.93 mmol) followed by DBU (1.1 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 1 hour. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (107 mg, 0.28 mmol, 91 %).

R_f 0.45 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3307 m, 2923 m, 1614 m, 1515 m, 1456 m, 1149 w.

δ_H ($CDCl_3$, 300 MHz) 7.08-6.72 (m, 8H, Ph**H**), 4.35-4.25 (m, 1H, SO_2C**H**), 4.20 (t, *J* 8.3, 1H, N**H**), 4.10-4.00 (m, 3H, SO_2CHCH_2, SO_2CHCH), 3.92-3.82 (m, 2H, $NHCH_2$), 3.72 (s, 3H, OCH_3), 2.48 (s, 3H, NCH_3), 2.22 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) 171.6-133.7 (Ph**C**), 130.9-114.3 (Ph**C**H), 73.3 (**C**HSO_2), 67.0 (SO_2CHCH_2), 55.7 (**C**$HCHSO_2$), 47.4 ($NHCH_2$), 42.9 (NCH_3), 21.5 ($PhCH_3$), 14.6 (OCH_3).

LRMS (EI+) 376 (M^+, 15 %), 190 ($CH_3OPhC_4H_5NO$, 89 %), 165 ($CH_3OPhCHNOCH_3$, 75 %), 147 ($CH_3OPhCHCHCH_2$, 100 %), 120 (CH_3PhCH_2NH, 62 %), 105 (CH_3PhCH_2, 70 %), 91 (CH_3Ph, 30 %), 77 (Ph, 20 %).

HRMS (ES+) MH^+ Calcd for $C_{19}H_{24}N_2O_4S$, 377.1535, found 377.1535.

3-(2-Fluoro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid 4-methyl-benzylamide [124]

To 3-(2-fluoro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [110] (143 mg, 0.33 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.13 mL, 1.00 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.33 mmol), and the mixture was refluxed for 3 hours. The reaction was

diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (73 mg, 0.20 mmol, 61 %).

R_f 0.55 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3546 w, 3293 s, 2877 m, 1733 w, 1587 m, 1517 m, 1493 m, 1329 m, 1148 m, 1044 m.

δ_H ($CDCl_3$, 300 MHz) 7.35-6.80 (m, 8H, Ph**H**), 4.34-4.23 (m, 1H, SO_2C**H**), 4.19 (t, *J* 8.1, 1H, N**H**), 4.12-4.05 (m, 2H, SO_2CHC**H_2**), 3.98-3.85 (m, 3H, NHC**H_2**, SO_2CHC**H**), 2.50 (s, 3H, NC**H_3**), 2.20 (s, 3H, PhC**H_3**).

δ_C ($CDCl_3$, 75 MHz) 163.1-133.7 (Ph**C**), 129.8-116.3 (Ph**C**H), 72.5 (**C**HSO_2), 68.5 (SO_2CHC**C**H), 67.6 (**C**H_2CHSO_2), 47.4 (NHC**C**H_2), 43.2 (NC**C**H_3), 21.5 (PhC**C**H_3).

LRMS (EI+) 364 (M^+, 15 %), 178 (M^+-FPh, CH_3Ph, 100 %), 135 (CH_3PhCH_2NH, CH_3, 85 %), 120 (CH_3PhCH_2NH, 75 %), 105 (CH_3PhCH_2, 85 %), 91 ($CHNSO_2$, 30 %), 42 (CH_3NCH, 30 %).

HRMS (ES+) MH^+ Calcd for $C_{18}H_{22}N_2O_3S$, 365.1335, found 365.1322.

3-(3-Chloro-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid allylamide [135]

To 3-(3-chloro-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [109] (154 mg, 0.35 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.08 mL, 1.04 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.35 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (64 mg, 0.20 mmol, 58 %).

R_f 0.45 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3302 s, 2875 m, 1709 w, 1646 w, 1575 m, 1519 m, 1434 m, 1323 s, 1149 m.

δ_H ($CDCl_3$, 300 MHz) 7.40 (s, 1H, Ph**H**), 7.30-7.15 (m, 3H, Ph**H**), 5.60-5.45 (m, 1H, $NHCH_2C$**H**), 5.14-5.02 (m, 2H, NHC**H_2**), 4.61 (t, *J* 6.2, 1H, N**H**), 4.35-4.20 (m, 2H, SO_2CHC**H_2**), 3.90 (dt, *J* 7.5, 4.0, 1H, SO_2C**H**), 3.62-3.38 (m, 2H, C**H_2**$CHCH_2$), 2.55 (s, 3H, NC**H_3**).

δ_C ($CDCl_3$, 75 MHz) 139.6 (Ph**C**), 135.2 (Ph**C**), 133.4 (**C**HCH_2NH), 130.6-128.5 (Ph**C**H), 126.9 (**C**$HCHSO_2$), 118.6 (**C**H_2CHCH_2NH), 73.9 (SO_2**C**H), 67.3 (**C**H_2CHSO_2), 46.3 (NH**C**H_2), 43.2 (N**C**H_3).

LRMS (EI+) 316 (M^+, ^{35}Cl, 40 %), 194 (PhC_4H_7NOS, H, 100 %), 168 ($ClPhCHNOCH_2$, 55 %), 151 (ClPhCHCHN, 70 %), 115 (C_4H_5NOS, 67 %), 84 (C_4H_6NO, 45 %), 56 (C_3H_4O, 35 %), 28 (CO, 60 %).

HRMS (ES+) MNa^+ Calcd for $C_{13}H_{17}N_2O_3SClNa$, 339.0546, found 339.0547.

3-(3-Chloro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid 4-methyl-benzylamide [127]

To 3-(3-chloro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [109] (1.23 g, 2.77 mmol) in dry tetrahydrofuran (15 mL) was added 4-methylbenzylamine (3.0 eq., 1.06 mL, 8.32 mmol) followed by DBU (1.05 eq., 0.44 mL, 2.91 mmol), and the mixture was refluxed for 1 hour. The reaction was diluted with dichloromethane (50 mL) and washed with 2M HCl (2 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (540 mg, 1.93 mmol, 69 %).

R_f 0.50 (2:1 P:EtOAc).

Mp 89-93 °C

ν_{max} (thin film, cm^{-1}) 3366 s, 2091 m, 1638 s, 1433 w, 1323 w, 1147 w, 1040 w.

δ_H ($CDCl_3$, 300 MHz) 7.30-6.80 (m, 8H, Ph**H**), 4.49 (s, 1H, SO_2C**H**), 4.24-4.16 (m, 1H, N**H**), 4.12-3.98 (m, 2H, SO_2CHCH_2), 3.93-3.84 (m, 1H, SO_2CHC**H**), 3.66 (bs, 2H, NHCH_2), 2.49 (s, 3H, NCH_3), 2.20 (s, 3H, PhCH_3).

δ_C ($CDCl_3$, 75 MHz) 139.6-133.3 (Ph**C**), 130.6-126.9 (Ph**C**H), 74.0 (**C**HSO_2), 67.3 (SO_2CHCH_2), 47.7 (NH**C**H_2), 43.2 (N**C**H_3), 21.5 (Ph**C**H_3).

LRMS (EI+) 380 (M^+, ^{35}Cl, 12 %), 194 ($C_{10}H_{12}NOS$, 100 %), 151 ($ClPhCHCHCH_2$, 37 %), 120 (CH_3PhCH_2NH, 66 %), 105 (CH_3PhCH_2, 62 %).

HRMS (ES+) MNa^+ Calcd for $C_{18}H_{21}N_2O_3SClNa$, 403.0859, found 403.0859.

2-Methyl-3-pentyl-isoxazolidine-4–sulfonic acid 4-methyl-benzylamide [129]

To 2-methyl-3-pentyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [111] (140 mg, 0.35 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.13 mL, 1.04 mmol) followed by DBU (1.0 eq., 0.05 mL, 0.35 mmol), and the mixture was refluxed for 5 hours. The reaction was

diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (73 mg, 0.21 mmol, 61 %).

R_f 0.40 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3547 w, 3286 s, 2928 s, 1749 w, 1650 m, 1516 m, 1458 s, 1323 s, 1146 s, 1068 m.

δ_H ($CDCl_3$, 300 MHz) 7.18-7.02 (m, 4H, Ph**H**), 4.20-4.13 (m, 2H, NHC**H_2**), 4.07-3.98 (m, 1H, SO_2CHCH_2), 3.83 (t, *J* 8.9, 1H, SO_2CHCH_2), 3.50-3.40 (m, 1H, SO_2CH), 2.95 (s, 1H, SO_2CHCH), 2.62 (s, 3H, NC**H_3**), 2.49 (s, 1H, N**H**), 2.22 (s, 3H, PhC**H_3**), 1.57-1.40 (m, 2H, C**H_2**CHNCH_3), 1.31-1.12 (m, 6H, CH_3CH_2, $CH_3CH_2CH_2$, C**H_2**CH_2CHNCH_3), 0.78 (s, 3H, CH_2CH_3).

δ_C ($CDCl_3$, 75 MHz) 138.4 (Ph**C**), 134.3 (Ph**C**), 130.0-128.4 (Ph**C**H), 71.7 (**C**HSO_2), 69.5 (SO_2CHCH), 66.7 (SO_2CHCH_2), 47.6 (**C**H_2CHNCH_3), 47.3 (NHC**H_2**), 44.5 (N**C**H_3), 32.2 (**C**H_2CH_2CHNCH_3), 25.7 ($CH_3CH_2CH_2$), 23.0 (CH_3CH_2), 21.5 (Ph**C**H_3), 14.4 (**C**H_3CH_2).

LRMS (EI+) 340 (M^+, 10 %), 269 (M^+-C_5H_{11}, 95 %), 120 (CH_3PhCH_2NH, 85 %), 105 (CH_3PhCH_2, 100 %), 85 (C_4H_7NO, 98 %), 42 (CH_3CH_2CH, 45 %).

HRMS (ES+) MH^+ Calcd for $C_{17}H_{29}N_2O_3S$, 341.1899, found 341.1904.

2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid allylamide [121]

To 2-methyl-3-naphthalene-2-yl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [113] (132 mg, 0.29 mmol) in dry tetrahydrofuran (10 mL) was added allylamine (3.0 eq., 0.06 mL, 0.86 mmol) followed by DBU (1.0 eq., 0.04 mL, 0.29 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (60 mg, 0.18 mmol, 62 %).

R_f 0.40 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3306 m, 1645 w, 1436 w, 1317 w, 1149 w.

δ_H ($CDCl_3$, 300 MHz) 7.72-7.60 (m, 4H, Ph**H**), 7.39-7.23 (m, 3H, Ph**H**), 5.32-5.20 (m, 1H, $NHCH_2CH$), 4.78-4.67 (m, 2H, SO_2CHCH_2), 4.57 (t, *J* 6.0, 1H, N**H**SO_2), 4.28-4.15 (m, 2H, NHC**H_2**), 4.00-3.90 (m, 1H, SO_2CH), 3.85-3.78 (m,

1H, SO_2CHCH), 3.40-3.30 (m, 1H, $NHCH_2CHCH_2$), 3.19-3.08 (m, 1H, $NHCH_2CHCH_2$) 2.44 (s, 3H, CH_3).

δ_C ($CDCl_3$, 75 MHz) 134.5-133.6 (Ph**C**), 133.3 (**C**HCH_2NH), 129.4-125.4 (Ph**C**H), 118.3 (**C**H_2CHCH_2NH), 75.1 (SO_2**C**H), 73.6 (**C**$HCHSO_2$), 67.4 (SO_2CHCH_2), 46.1 ($NHCH_2$), 43.2 (CH_3).

LRMS (EI+) 332 (M^+, 40 %), 210 (95 %), 167 (95 %), 56 (CH_2CHCH_2NH, 56 %), 41 (CH_2CHCH_2 45 %).

HRMS (ES+) MH^+ Calcd for $C_{17}H_{21}N_2O_3S$, 333.1267, found 333.1262.

3-Cyclohexyl-2-methyl-isoxazolidine-4–sulfonic acid allylamide [134]

To 3-cyclohexyl-2-methyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester [112] (115 mg, 0.28 mmol) in dry tetrahydrofuran (10 mL) was added allylamine (3.0 eq., 0.06 mL, 0.83 mmol) followed by DBU (1.0 eq., 0.04 mL, 0.28 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow solid (56 mg, 0.19 mmol, 69 %).

R_f 0.45 (2:1 P:EtOAc).

Mp 73-76 °C

ν_{max} (thin film, cm^{-1}) 3445 s, 2926 s, 1645 m, 1448 m, 1319 m, 1148 m.

δ_H ($CDCl_3$, 300 MHz) 5.90-5.75 (m, 1H, $NHCH_2CH$), 5.30-5.11 (m, 2H, $NHCH_2$), 4.77-4.68 (m, 1H, N**H**), 4.30-4.20 (m, 1H, SO_2CH), 3.99 (t, *J* 9.8, 1H, SO_2CHCH_2), 3.82-3.67 (m, 3H, $NHCH_2CHCH_2$, SO_2CHCH_2), 2.95-2.90 (m, 1H, SO_2CHCH), 2.68 (s, 3H, CH_3), 1.78-1.58 (m, 4H, CH_2), 1.42-1.30 (m, 1H, CHCHN), 1.21-0.92 (m, 6H, CH_2).

δ_C ($CDCl_3$, 75 MHz) 134.0 (**C**HCH_2NH), 118.4 (**C**H_2CHCH_2NH), 74.0 (SO_2**C**H), 69.7 (SO_2CHCH), 69.0 (SO_2CHCH_2), 46.5 ($NHCH_2$), 45.6 (C**H**CHN), 42.1 (CH_3), 30.1-26.5 (CH_2).

LRMS (EI+) 288 (M^+, 20 %), 205 (M^+-C_6H_{10}, 100 %), 85 ($CHCHCH_2ONCH_3$, 95 %), 55 (CH_2CHCH_2N, 35 %), 41 (CH_2CHCH_2, 50 %).

HRMS (ES+) MH^+ Calcd for $C_{13}H_{25}N_2O_3S$, 289.1580, found 289.1582.

Elemental analysis: Anal. calcd for $C_{13}H_{24}N_2O_3S$: C 54.14, H 8.39, N 9.71, S 11.12; found: C 54.35, H 8.55, N 9.49, S 10.78.

3-Cyclopropyl-2-methyl-isoxazolidine-4-sulfonic acid allylamide [120]

To 3-cyclopropyl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester

[114] (105 mg, 0.28 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.06 mL, 0.84 mmol) followed by DBU (1.05 eq., 0.04 mL, 0.30 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (58 mg, 0.24 mmol, 84 %).

R_f 0.40 (1:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3564 m, 3292 s, 2924 s, 2451 m, 1738 m, 1646 s, 1436 s, 1317 s, 1147 s.

δ_H ($CDCl_3$, 300 MHz) 6.90-5.77 (m, 1H, $NHCH_2C\mathbf{H}$), 5.32-5.15 (m, 2H, $NHC\mathbf{H_2}$), 4.43 (bs, 1H, N**H**), 4.26-4.07 (m, 3H, $SO_2CHC\mathbf{H_2}$, $SO_2C\mathbf{H}$), 3.87 (bs, 1H, $SO_2CHC\mathbf{H}$), 3.81-3.74 (m, 2H, $NHCH_2CHC\mathbf{H_2}$), 2.76 (s, 3H, $C\mathbf{H_3}$), 0.98-0.88 (m, 1H, $CH_2CH_2C\mathbf{H}$), 0.73 (d, J 8.1, 1H, $CH_2C\mathbf{H_2}$), 0.65-0.52 (m, 2H, $C\mathbf{H_2}CH_2$), 0.40-0.29 ($C\mathbf{H_2}CH_2$).

δ_C ($CDCl_3$, 75 MHz) 131.7 ($\mathbf{C}HCH_2NH$), 115.9 ($\mathbf{C}H_2CHCH_2NH$), 71.6 ($SO_2\mathbf{C}H$), 70.0 ($SO_2CH\mathbf{C}H$), 64.7 ($SO_2CH\mathbf{C}H_2$), 44.1 ($NH\mathbf{C}H_2$), 42.3 ($\mathbf{C}H_3$), 11.7 ($CH_2CH_2\mathbf{C}H$), 2.5 ($\mathbf{C}H_2CH_2$), 0.0 ($CH_2\mathbf{C}H_2$).

LRMS (EI+) 246 (M^+, 35 %), 205 (M^+-C_3H_5, 20 %), 124 ($C_7H_{10}NO$, 99 %), 99 (C_5H_9NO, 40 %), 81 (C_6H_9, 100 %), 41 (C_3H_5, 68 %).

HRMS (ES+) MH^+ Calcd for $C_{10}H_{19}N_2O_3S$, 247.1111, found 247.1110.

3-(5-Bromo-furan-2-yl)-2-methyl-isoxazolidine-4-sulfonic acid allylamide [130]

To 3-(5-bromo-furan-2-yl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluoro-phenyl ester [116] (133 mg, 0.28 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.06 mL, 0.83 mmol) followed by DBU (1.05 eq., 0.04 mL, 0.29 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (63 mg, 0.18 mmol, 64 %).

R_f 0.50 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3292 m, 2924 m, 1646 w, 1503 w, 1435 w, 1317 m, 1149 m.

δ_H ($CDCl_3$, 300 MHz) 6.35 (d, *J* 3.2, 1H, C**H**CO), 6.21 (d, *J* 3.4, 1H, C**H**CBr), 5.63-5.50 (m, 1H, C**H**CH_2NH), 5.18-5.04 (m, 2H, NHC**H_2**), 4.80 (bs, 1H, N**H**), 4.34-4.15 (m, 3H, SO_2CHCH_2, SO_2CH), 3.78 (bs, 1H, SO_2CHCH), 3.63-3.45 (m, 2H, C**H_2**$CHCH_2NH$), 2.60 (s, 3H, C**H_3**).

δ_C ($CDCl_3$, 75 MHz) 150.9 (**C**O), 133.4 (**C**HCH_2NH), 123.4 (**C**Br), 118.7 (**C**H_2CHCH_2NH), 113.5 (**C**HCBr), 112.9 (**C**HCO), 69.6 (SO_2CH), 68.1 (SO_2CHCH), 67.1 (SO_2CHCH_2), 46.3 ($NHCH_2$), 43.4 (CH_3).

LRMS (EI+) 352 (M^+, H, 20 %), 230 (M^+-C_3H_5 NH_2SO_2, 100 %), 203 ($BrC_6H_5NO_2$, 30 %), 187 (BrC_7H_7O, 35 %), 159 (BrC_5H_3O, 15 %), 78 (C_5H_2O, 40 %).

HRMS (ES+) MH^+ Calcd for $C_{11}H_{16}N_2O_4BrS$, 351.0014, found 351.0011.

3-(4-Allyloxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide [119]

To 3-(4-allyloxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [115] (1.07g, 2.30 mmol) in dry tetrahydrofuran (15 mL) was added 4-methylbenzylamine (3.0 eq., 0.88 mL, 6.90 mmol) followed by DBU (1.05 eq., 0.36 mL, 2.42 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (50 mL) and washed with 2M HCl (2 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (818 mg, 2.03 mmol, 88 %).

R_f 0.45 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3544 w, 3291 s, 2923 s, 1735 w, 1611 s, 1456 s, 1328 s, 1245 s, 1149 s.

δ_H ($CDCl_3$, 300 MHz) 7.27-6.74 (m, 8H, Ph**H**), 6.05-5.82 (m, 1H, C**H**CH_2O), 5.40-5.12 (m, 2H, C**H_2**O), 4.69 (bs, 1H, N**H**), 4.40-4.21 (m, 2H, SO_2CHCH_2), 4.08-3.92 (m, 3H, C**H_2**$CHCH_2O$, Ph**CH_2**), 3.88-3.76 (m, 2H, SO_2CH, Ph**CH_2**), 3.68-3.61 (m, 1H, SO_2CHCH), 2.47 (s, 3H, N**CH_3**), 2.20 (s, 3H, Ph**CH_3**).

δ_C ($CDCl_3$, 75 MHz) 159.4 (Ph**C**), 138.2 (Ph**C**), 133.4 (**C**HCH_2O), 130.9-128.4 (Ph**C**H), 125.1 (Ph**C**), 118.3 (**C**H_2CHCH_2O), 115.5 (Ph**C**H), 115.1 (Ph**C**H), 73.3 (**C**HSO_2), 69.2 (**C**H_2O), 67.1 (SO_2CHCH_2), 59.4 (**C**$HCHSO_2$), 47.4 (Ph**C**H_2), 43.0 (N**C**H_3), 21.5 (Ph**C**H_3).

LRMS (EI+) 402 (M^+, 45 %), 216 (M^+-$C_8H_{12}NO_2S$, 100 %), 173 ($C_{11}H_{11}NO$, 77 %), 150 ($C_4H_8NO_3S$, 50 %), 120 (CH_3PhCH_2NH, 70 %), 105 (CH_3PhCH_2, 85 %), 91 (CH_3Ph, 46 %), 77 (Ph, 40 %), 41 (C_3H_5, 60 %).

HRMS (ES+) MH^+ Calcd for $C_{21}H_{27}N_2O_4S$, 403.1686, found 403.1679.

3-(3-Bromo-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide [132]

To 3-(3-bromo-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [117] (1.24 g, 2.54 mmol) in dry tetrahydrofuran (10 mL) was added 4-methylbenzylamine (3.0 eq., 0.97 mL, 7.62 mmol) followed by DBU (1.05 eq., 0.40 mL, 2.67 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (50 mL) and washed with 2M HCl (2 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (603 mg, 1.42 mmol, 56 %).

R_f 0.55 (2:1 P:EtOAc).

Mp 93-95 °C

ν_{max} (thin film, cm^{-1}) 3293 s, 2082 w, 1640 m, 1430 m, 1324 m, 1042 w.

δ_H ($CDCl_3$, 300 MHz) 7.52-6.91 (m, 8H, Ph**H**), 4.44 (bs, 1H, SO_2C**H**), 4.32-4.26 (m, 1H, N**H**), 4.22-4.06 (m, 2H, SO_2CHCH**$_2$**), 4.02-3.92 (m, 1H, SO_2CHCH**H**), 3.74 (bs, 2H, $NHCH$**$_2$**), 2.55 (s, 3H, NCH**$_3$**), 2.25 (s, 3H, $PhCH$**$_3$**).

δ_C ($CDCl_3$, 75 MHz) 132.2-127.4 (Ph**C**H), 74.0 (**C**HSO_2), 67.3 (SO_2CH**C**H_2), 47.7 (NH**C**H_2), 43.4 (N**C**H_3), 21.5 (Ph**C**H_3).

LRMS (EI+) 426 (M^+, ^{81}Br, 52 %), 240 (M^{+79}Br-$MePhCH_2NHSO_2$, 100 %), 212 ($^{79}BrPhCHNOCH_2$, 36 %), 197 ($^{81}BrPhCHCHCH_2$, 42 %), 120 (CH_3PhCH_2NH, 78 %), 105 (CH_3PhCH_2, 64 %), 91 (CH_3Ph, 43 %), 77 (Ph, 36 %), 42 (CNO, 33 %).

HRMS (ES+) MNa^+ Calcd for $C_{18}H_{21}N_2O_3SBrNa$, 447.0354, found 447.0360.

Elemental analysis: Anal. calcd for $C_{18}H_{21}N_2O_3SBr$: C 50.83, H 4.98, N 6.59, S 7.54, Br 18.79; found: C 51.01, H 5.04, N 6.46, S 7.30, Br 18.55.

3.4.3.1 Aminolysis procedures incorporating microwave techniques[73]

3-(4-Methoxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid benzyl-methylamide [136]

To 3-(4-methoxy-phenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluoro-phenyl ester (78 mg, 0.18 mmol) in dry tetrahydrofuran (5 mL) in a microwave reaction vessel was added *N*-benzylmethylamine (3.0 eq., 0.07 mL, 0.53 mmol) followed by DBU (2.0 eq., 0.05 mL, 0.36 mmol), and the mixture was subjected to microwave irradiation at 110 °C for 45 minutes. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by

flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (36 mg, 0.10 mmol, 53 %).

R_f 0.30 (2:1 P:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 7.46-6.88 (m, 9H, Ph**H**), 4.52-4.41 (m, 2H, SO_2CHCH_2), 4.39-4.22 (m, 2H, SO_2CH, SO_2CHCH), 4.19-4.02 (m, 2H, $PhCH_2$), 3.82 (s, 3H, OCH_3), 2.60 (s, 3H, $ONCH_3$), 2.53 (s, 3H, CH_2NCH_3).

δ_C ($CDCl_3$, 75 MHz) 160.0 (Ph**C**), 135.8-113.7 (Ph**C**H), 73.9 ($CHSO_2$), 67.2 (SO_2CHCH_2), 55.2 (SO_2CHCH), 53.1 ($PhCH_2$), 34.2 ($ONCH_3$), 21.1 (CH_2NCH_3), 14.2 (OCH_3).

3-Cyclopropyl-2-methyl-isoxazolidine-4-sulfonic acid methylcyclohexyl-amide [137]

To 3-cyclopropyl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (90 mg, 0.24 mmol) in dry tetrahydrofuran (5 mL) in a microwave reaction vessel was added *N*-methylcyclohexylamine (3.0 eq., 0.09 mL, 0.72 mmol) followed by DBU (2.0 eq., 0.09 mL, 0.48 mmol), and the mixture was subjected to microwave irradiation at 110 °C for 45 minutes. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a pale yellow oil (51 mg, 0.17 mmol, 70 %).

R_f 0.25 (2:1 P:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 4.20-4.04 (m, 2H, SO_2CHCH_2), 3.92-3.81 (m, 1H, SO_2CH), 3.63 (t, *J* 8.4, 1H, SO_2CHCH), 2.83 (s, 3H, $ONCH_3$), 2.78 (s, 3H, $CHNCH_3$), 1.87-0.67 (m, 16H, 7 × CH_2, 2 × C**H**).

δ_C ($CDCl_3$, 75 MHz) 66.3 (SO_2CHCH_2), 57.4 (SO_2CHCH), 31.1-25.3 (CH_2).

2-Methyl-3-naphthalen-2-yl-isoxazolidine-4–sulfonic acid methyl-*t*-butyl-amide [138]

To 2-methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (61 mg, 0.13 mmol) in dry tetrahydrofuran (3 mL) in a microwave reaction vessel was added tert-butylmethylamine (3.0 eq., 0.05 mL, 0.40 mmol) followed by DBU (2.0 eq., 0.04 mL, 0.27 mmol), and the mixture was subjected to microwave irradiation at 110 °C for 30 minutes. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by

flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a colourless oil (12 mg, 0.03 mmol, 25 %).

R_f 0.75 (2:1 P:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 7.93-7.81 (m, 4H, Ph**H**), 7.59-7.47 (m, 3H, Ph**H**), 4.52-4.44 (m, 1H, $SO_2CHCH\mathbf{H}_2$), 4.39 (t, *J* 6.6, 1H, $SO_2C\mathbf{H}$), 4.22 (dt, *J* 2.8, 1.9, 1H, $SO_2CHCH\mathbf{H}_2$), 3.93 (d, *J* 8.4, 1H, $SO_2CHC\mathbf{H}$), 2.81 (s, 3H, $ONC\mathbf{H}_3$), 2.67 (s, 3H, $CNC\mathbf{H}_3$), 1.12 (s, 9H, $(C\mathbf{H}_3)_3$).

3-(2-Fluoro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid methylallyl-amide [139]

To 3-(2-fluoro-phenyl)-2-methyl-isoxazolidine-4–sulfonic acid pentafluorophenyl ester (54 mg, 0.13 mmol) in dry 1-methyl-2-pyrrolidinone (NMP) (3 mL) in a microwave reaction vessel was added *N*-methylallylamine (3.0 eq., 0.04 mL, 0.38 mmol) followed by DBU (2.0 eq., 0.04 mL, 0.25 mmol), and the mixture was subjected to microwave irradiation at 80 °C for 45 minutes. The reaction was diluted with dichloromethane (20 mL) and washed with 2M HCl (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (22 mg, 0.07 mmol, 54 %).

R_f 0.40 (2:1 P:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 7.49-7.05 (m, 4H, Ph**H**), 5.61-5.45 (m, 1H, $NCH_3CH_2C\mathbf{H}$), 5.17-5.09 (m, 2H, NCH_3CH_2), 4.47-4.31 (m, 2H, $SO_2CHCH\mathbf{H}_2$), 4.24 (dt, *J* 4.7, 3.8, 1H, $SO_2C\mathbf{H}$), 4.17-4.09 (m, 1H, $SO_2CHC\mathbf{H}$), 3.75 (dd, *J* 7.5, 6.6, 1H, $NCH_3CH_2CHCH\mathbf{H}_2$), 3.52 (dd, *J* 7.5, 6.6, 1H, $NCH_3CH_2CHCH\mathbf{H}_2$), 2.68 (s, 3H, $ONC\mathbf{H}_3$), 2.63 (s, 3H, $CH_2NC\mathbf{H}_3$).

δ_C ($CDCl_3$, 75 MHz) 162.8 (Ph**C**), 159.5 (Ph**C**), 132.4 ($\mathbf{C}HCH_2NCH_3$), 130.7-123.3 (Ph**C**H), 119.3 ($\mathbf{C}H_2CHCH_2NCH_3$), 86.6 ($SO_2CH\mathbf{C}H$), 71.1 ($\mathbf{C}HSO_2$), 67.0 ($SO_2CH\mathbf{C}H_2$), 52.8 ($\mathbf{C}H_2NCH_3$), 42.8 ($ON\mathbf{C}H_3$), 34.1 ($CH_2N\mathbf{C}H_3$).

3.5 Diels-Alder Reactions with Cyclic Dienes

3.5.1 [4+2] cycloaddition procedures

Bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [157a]

To pentafluorophenyl vinylsulfonate [80] (1.0 g, 3.60 mmol) in dry toluene (20 mL) was added cyclopentadiene (3.0 eq., 720 mg, 10.90 mmol) and the mixture

was refluxed at 110 °C for 4 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (970 mg, 2.90 mmol, 78 %).

R_f 0.55 (3:1 P:Et_2O).

Mp 48-49 °C

ν_{max} (thin film, cm^{-1}) 3430 s, 2990 s, 1650 s, 1518 m, 1378 m.

δ_H ($CDCl_3$, 300 MHz) 6.25 (dd, *J* 5.7, 3.2, 1H, $SO_2CHCHC\mathbf{H}$), 6.02 (dd, *J* 5.5, 2.8, 1H, $SO_2CHCH_2CHC\mathbf{H}$), 4.02-3.99 (m, 1H, $SO_2C\mathbf{H}$), 3.42 (s, 1H, $SO_2CHC\mathbf{H}$), 3.02 (s, 1H, $SO_2CHCH_2C\mathbf{H}$), 2.25 (dt, *J* 5.7, 3.6, 1H, $CH_2CHC\mathbf{H}_2$), 1.54-1.50 (m, 2H, $SO_2CHC\mathbf{H}_2$), 1.33 (d, *J* 9.0, 1H, $CH_2CHC\mathbf{H}_2$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 138.8 ($SO_2CHCH\mathbf{C}H$), 131.4 ($SO_2CHCH_2CH\mathbf{C}H$), 63.3 ($SO_2\mathbf{C}H$), 50.0 ($CH_2CH\mathbf{C}H_2$), 46.3 ($SO_2CH\mathbf{C}H$), 43.1 ($SO_2CHCH_2\mathbf{C}H$), 30.3 ($SO_2CH\mathbf{C}H_2$).

LRMS (EI+) 340 (M^+, 20 %), 155 (SO_2C_6F, 10 %), 93 (M^+-$C_6F_5OSO_2$, 100 %), 77 (SO_2CH, 42 %), 66 (SO_2, 2H, 23 %).

HRMS (ES+) MNa^+ Calcd for $C_{13}H_9O_3F_5SNa$, 363.0085, found 363.0074.

Bicyclo [2.2.2] oct-5-ene-2-sulfonic acid pentafluorophenyl ester [160a]

To pentafluorophenyl vinylsulfonate [80] (155 mg, 0.57 mmol) in dry toluene (5 mL) was added 1,3-cyclohexadiene (3.0 eq., 0.16 mL, 1.70 mmol) and the mixture was refluxed at 110 °C for 24 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (94 mg, 0.27 mmol, 47 %).

R_f 0.60 (3:1 P:Et_2O).

Mp 52-54 °C

ν_{max} (thin film, cm^{-1}) 3434 s, 2954 m, 1649 m, 1519 s, 1372 s, 1186 s, 996 s.

δ_H ($CDCl_3$, 300 MHz) 6.36 (t, *J* 7.1, 1H, $SO_2CHCHCHC\mathbf{H}$), 6.22 (t, *J* 7.1, 1H, $SO_2CHCHC\mathbf{H}$), 3.65 (m, 1H, $SO_2C\mathbf{H}$), 3.17 (s, 1H, $SO_2CHC\mathbf{H}$), 2.68 (s, 1H, $SO_2CHCH_2C\mathbf{H}$), 2.05 (dt, *J* 9.8, 2.6, 1H, $SO_2CHC\mathbf{H}_2$), 1.85-1.73 (m, 1H, $SO_2CHC\mathbf{H}_2$), 1.62-1.52 (m, 1H, $SO_2CHC\mathbf{H}_2$), 1.50-1.15 (m, 3H, $CH_2CHC\mathbf{H}_2SO_2CHC\mathbf{H}_2$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 135.4 ($\mathbf{C}HCHCHSO_2$), 130.2 ($\mathbf{C}HCHCHCHSO_2$), 62.9 ($SO_2\mathbf{C}HCH_2$), 31.0 ($SO_2CH\mathbf{C}HCH$), 30.1 ($SO_2CH\mathbf{C}H_2$), 29.4 ($SO_2CHCH_2\mathbf{C}H$), 26.2 ($SO_2CHCH\mathbf{C}H_2$), 23.1 ($CH_2CH\mathbf{C}H_2$).

LRMS (EI+) 355 (M^+, H, 15 %), 183 (C_6F_5O, 40 %), 155 (M^+-$C_6F_5O_2$, 60 %), 108 ($C_6F_5O_3$, H, 85 %), 91 (C_7H_7, 90 %), 78 (C_6H_6, 100 %).

HRMS (ES+) MNa^+ Calcd for $C_{14}H_{11}O_3F_5SNa$, 377.0247, found 377.0228.

1-Methoxy-bicyclo [2.2.2] oct-5-ene-2-sulfonic acid pentafluorophenyl ester [161a]

To pentafluorophenyl vinylsulfonate [80] (116 mg, 0.42 mmol) in dry toluene (5 mL) was added 1-methoxy-1,3-cyclohexadiene (5.0 eq., 0.25 mL, 2.12 mmol) and the mixture was refluxed at 110 °C for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (140 mg, 0.36 mmol, 87 %).

R_f 0.50 (3:1 P:Et_2O).

ν_{max} (thin film, cm^{-1}) 3412 w, 2951 s, 2666 w, 2459 w, 1519 s, 1389 m, 995 s.

δ_H ($CDCl_3$, 300 MHz) 6.29-6.20 (m, 2H, CHC**H**$COCH_3$, C**H**$COCH_3$), 3.91 (dd, *J* 10.0, 5.8, 1H, SO_2C**H**), 3.30 (s, 3H, OC**H$_3$**), 2.62 (s, 1H, CHC**H$_2$**), 2.21 (dt, *J* 10.2, 2.5, 1H, SO_2CHCH_2), 2.05-1.94 (m, 1H, SO_2CHCH_2), 1.70-1.57 (m, 3H, $CHCH_2$, CH_2COCH_3), 1.47-1.35 (m, 1H, $CHCH_2$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 133.3 (**C**$HCOCH_3$), 132.2 (**C**$HCHCOCH_3$), 78.5 (**C**OCH_3), 66.5 (SO_2**C**H), 51.6 (O**C**H_3), 32.6 (SO_2CHCH_2), 29.4 (CH_3CO**C**H_2), 28.9 (SO_2CHCH_2**C**H), 24.3 (CH_2CHCH_2).

LRMS (EI+) 384 (M^+, 30 %), 356 (M^+-CO, 63 %), 201 (M^+-C_6F_5O, 40 %), 183 (C_6F_5O, 80 %), 155 (M^+-$C_6F_5O_3$, CH_2, 95 %), 138 (M^+-$C_6F_5SO_3$, H, 65 %), 108 (C_8H_{12}, 100 %), 94 (C_7H_{10}, 98 %), 77 (C_6H_5, 94 %).

HRMS (ES+) MNa^+ Calcd for $C_{15}H_{13}O_4F_5SNa$, 407.0352, found 407.0338.

7-Oxa-bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [175 & 176]

To pentafluorophenyl vinylsulfonate [80] (104 mg) in furan (0.5 mL) was added ZnI_2 (36 mg) and stirred at 40 °C for 4 d. The reaction was diluted with ethyl acetate (10 mL) and washed with aqueous $Na_2S_2O_3$ solution (2 x 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ether) to give the *exo* cycloadduct [175] as a pale yellow solid (56 mg, 0.16 mmol, 43 %), and the *endo* cycloadduct [176] as a pale yellow solid (46 mg, 0.13 mmol, 35 %).

***Exo* product:**

R_f 0.20 (2:1 P:Et_2O).

Mp 83-86 °C

ν_{max} (thin film, cm^{-1}) 3434 s, 2093 m, 1651 s, 1520 m, 1385 m.

δ_H ($CDCl_3$, 300 MHz) 6.50 (dd, *J* 5.7, 1.5, 1H, $SO_2CHCHCHCH$**H**), 6.35 (dd, *J* 5.7, 1.5, 1H, $SO_2CHCHCH$**H**), 5.48-5.40 (m, 1H, SO_2CH**H**), 5.21-5.10 (s, 1H, C**H**CH_2), 3.41-3.30 (m, 1H, SO_2C**H**), 2.40-2.28 (m, 1H, C**H**$_2$), 1.91-1.80 (m, 1H, C**H**$_2$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 138.5 ($SO_2CHCHCH$**C**H), 131.7 (SO_2CHCH**C**H), 80.0 (**C**HCH_2), 78.9 (SO_2CH**C**H), 60.3 (SO_2**C**H), 29.6 (**C**H_2).

LRMS (EI+) 343 (M^+, 35 %), 183 (C_6F_5O, 45 %), 155 (57 %), 95 (C_6H_7O, 60 %), 68 (100 %), 41 (65 %), 27 (57 %).

HRMS (ES+) MNa^+ Calcd for $C_{12}H_7O_4F_5SNa$, 364.9883, found 364.9895.

***Endo* product:**

R_f 0.40 (2:1 P:Et_2O).

δ_H ($CDCl_3$, 300 MHz) 6.51 (dd, *J* 5.7, 1.5, 1H, $SO_2CHCHCHCH$**H**), 6.33 (dd, *J* 5.7, 1.5, 1H, $SO_2CHCHCH$**H**), 5.30 (dd, *J* 5.7, 1.5, 1H, SO_2CH**H**), 5.10 (dd, *J* 5.7, 1.5, 1H, SO_2CHCH_2CH**H**), 4.17-4.00 (m, 1H, SO_2C**H**), 2.50-2.38 (m, 1H, SO_2CHCH**H**$_2$), 1.68. (dd, *J* 12.0, 2.4, 1H, SO_2CHCH**H**$_2$).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 138.5 ($SO_2CHCHCH$**C**H), 131.7 (SO_2CHCH**C**H), 80.0 (SO_2CHCH_2**C**H), 78.9 (SO_2CH**C**H), 60.3 (SO_2**C**H), 29.7 (**C**H_2).

3.5.2 Aminolysis procedures for bicyclic sulfonate esters[66]

Bicyclo [2.2.1] hept-5-ene-2-sulfonic acid allylamide [157b]

To bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [157a] (104 mg, 0.31 mmol) in dry toluene (10 mL) was added allylamine (3.0 eq., 0.07 mL, 0.92 mmol) followed by DBU (1.1 eq., 0.05 mL, 0.34 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow solid (34 mg, 0.16 mmol, 52 %).

R_f 0.25 (2:1 P:Et_2O).

Mp 51-56 °C

ν_{max} (thin film, cm^{-1}) 3285 w, 2978 s, 2871 s, 1645 m, 1429 m, 1320 m, 1290 m, 1146 s.

δ_H ($CDCl_3$, 300 MHz) 6.21 (dd, *J* 5.5, 3.0, 1H, $SO_2CHCHCH$**H**), 6.06 (dd, *J* 5.7, 2.8, 1H, SO_2CHCH_2CHCH**H**), 5.86-5.73 (m, 2H, C**H**$_2$$CHCH_2NH$), 5.25-5.10 (ddd, *J*

10.2, 1.32, 1H, C**H**CH_2NH), 5.00-4.93 (q, *J* 5.5, 1H, N**H**), 4.33-4.31 (m, 1H, SO_2C**H**), 3.22 (s, 1H, SO_2CHCH**H**), 2.92 (s, 1H, SO_2CHCH_2CH**H**), 2.05 (dt, *J* 9.4, 3.8, 1H, CH_2CHCH**H**$_2$), 1.49-1.14 (m, 3H, SO_2CHCH**H**$_2$, CH_2CHCH**H**$_2$).

δ_C ($CDCl_3$, 75 MHz) 137.5 ($SO_2CHCHCH$), 134.2 (**C**HCH_2NH), 131.9 (SO_2CHCH_2CHCH), 117.5 (**C**H_2CHCH_2NH), 62.7 (SO_2CH), 50.0 (CH_2CHCH_2), 46.0 (**C**H_2NH), 45.6 (SO_2CHCH), 43.0 (SO_2CHCH_2CH), 29.7 (SO_2CHCH_2).

LRMS (EI+) 214 (M^+, H, 20 %), 148 (C_7H_9, C_3H_5N, 25 %), 108 ($SO_2NHC_2H_5$, 15 %), 91 (SO_2NHC, 65 %), 83 (C_3NHS, 55 %), 77 ($SONHCH_2$, 50 %), 66 (C_5H_6, 100 %), 56 (C_3H_5NH, 10 %), 41 (C_3H_5, 25 %).

HRMS (ES+) MH^+ Calcd for $C_{10}H_{15}NO_2S$, 214.0896, found 214.0892.

2-(Bicyclo [2.2.1] hept-5-ene-2-sulfonylamino)-4-phenyl butyric acid ethyl ester [158]

To bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [157a] (105 mg, 0.31 mmol) in dry toluene (10 mL) was added phenylalanine ethyl ester (3.0 eq., 179 mg, 0.93 mmol) followed by DBU (1.1 eq., 0.05 mL, 0.34 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a yellow oil (47 mg, 0.13 mmol, 44 %).

R_f 0.50 (2:1 P:EtOAc).

ν_{max} (thin film, cm^{-1}) 3303 w, 3064 s, 2980 s, 1731 m, 1604 m, 1497 m, 1455 m.

δ_H ($CDCl_3$, 300MHz) 7.30-7.10 (m, Ph**H**), 6.16-6.10 (m, 1H, $SO_2CHCHCH$**H**), 5.98-5.90 (m, 1H, SO_2CHCH_2CHCH**H**), 4.70-4.60 (m, 1H, N**H**), 4.30-4.20 (m, 1H, SO_2C**H**), 3.99 (dq, *J* 7.2, 3.0, 2H, CH_3CH**H**$_2$), 3.30-3.12 (m, 1H, SO_2CHCH**H**), 3.10-2.95 (m, 2H, $PhCH$**H**$_2$), 2.82 (s, 1H, SO_2CHCH_2CH**H**), 1.77 (dq, *J* 9.2, 3.8, 1H, NHC**H**), 1.40-1.32 (m, 1H, CH_2CHCH**H**$_2$), 1.17 (dt, *J* 7.2, 2.6, 4H, C**H**$_3$, CH_2CHCH**H**$_2$), 1.10-1.02 (m, 2H, SO_2CHCH**H**$_2$).

δ_C ($CDCl_3$, 75MHz) 172.2 (**C**O), 137.6 ($SO_2CHCHCH$), 136.1 (Ph**C**), 136.0 (Ph**C**), 131.9 (SO_2CHCH_2CHCH), 130.0-127.7 (Ph**C**), 63.4 (SO_2CH), 62.3 (**C**H_2CH_3), 57.6 (**C**HNH), 50.0 (CH_2CHCH_2), 45.6 (SO_2CHCH), 43.0 (SO_2CHCH_2CH), 40.3 (**C**H_2CHNH), 29.8 (SO_2CHCH_2), 14.5 (**C**H_3).

LRMS (EI+) 214 (M^+, H), 148 ($C_{10}H_{14}N$), 108 ($SO_2NHC_2H_3$, 2H), 91 (SO_2NHC), 83 (C_3NHS), 77 ($SONHCH_2$), 66 (C_5H_6), 56 (C_3H_5NH), 41 (C_3H_5).

HRMS (ES+) MNa^+ Calcd for $C_{18}H_{23}NO_4SNa$, 372.1245, found 372.1240.

Bicyclo [2.2.1] hept-5-ene-2-sulfonic acid (4-ethyl-phenyl)-amide [159]

To bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [157a] (90 mg, 0.26 mmol) in dry toluene (10 mL) was added 4-methylbenzylamine (3.0 eq., 0.10 mL, 0.79 mmol) followed by DBU (1.3 eq., 0.05 mL, 0.34 mmol), and the mixture was refluxed for 24 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a white solid (48 mg, 0.17 mmol, 67 %).

R_f 0.20 (2:1 P:EtOAc).

Mp 105-109 °C

ν_{max} (thin film, cm^{-1}) 3434 w, 2978 s, 1644 m, 1426 m, 1319 m, 1292 m, 1140 w.

δ_H ($CDCl_3$, 300 MHz) 7.20-7.04 (m, 4H, Ph**H**), 6.14 (m, 1H, SO_2CHCHC**H**), 6.00 (m, 1H, SO_2CHCH_2CHC**H**), 4.52 (m, 1H, N**H**), 4.16 (m, 2H, C**H_2**NH), 3.48 (m, 1H, SO_2C**H**), 3.14 (s, 1H, SO_2CHC**H**), 2.86 (s, 1H, SO_2CHCH_2C**H**), 2.24 (s, 3H, C**H_3**), 2.00-1.88 (dt, *J* 9.2, 3.6, 1H, SO_2CHCHC**H_2**), 1.43 (d, *J* 8.9, 1H, SO_2CHCHC**H_2**), 1.38-1.21 (m, 1H, SO_2CHCH_2), 1.18 (d, *J* 8.5, 1H, SO_2CHCH_2).

δ_C ($CDCl_3$, 75 MHz) 138.0 (Ph**C**), 137.6 (SO_2CHCH**C**H), 134.7 (Ph**C**), 132.1 (SO_2CHCH_2CH**C**H), 129.8 (Ph**C**), 128.2 (Ph**C**), 62.9 (SO_2**C**H), 50.2 (CH_2CH**C**H_2), 47.4 (**C**H_2NH), 45.7 (SO_2CH**C**H), 43.1 (SO_2CHCH_2**C**H), 29.8 (SO_2CH**C**H_2), 21.5 (**C**H_3).

LRMS (EI+) 278 (M^+, H, 10 %), 213 (M^+-SO_2, 50 %), 170 ($CH_3CH_2PhNHSO$, 2H, 20 %), 120 (CH_3CH_2PhNH, 85 %), 105 (CH_3CH_2Ph, 100 %), 91 (SO_2NHC, 65 %), 77 (Ph, 45 %), 66 (SO_2, 2H, 55 %).

HRMS (ES+) MH^+ Calcd for $C_{15}H_{19}NO_2S$, 278.1209, found 278.1203.

Elemental analysis: Anal. calcd for $C_{15}H_{19}NO_2S$: C 64.95, H 6.90, N 5.05, S 11.56; found C 65.05, H 7.02, N 4.91, S 11.40.

Bicyclo [2.2.2] oct-5-ene-2-sulfonic acid 4-methyl-benzylamide [160b]

To bicyclo [2.2.2] oct-5-ene-2-sulfonic acid pentafluorophenyl ester [160a] (50 mg, 0.14 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.05 mL, 0.42 mmol) followed by DBU (1.05 eq., 0.02 mL, 0.15 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by

flash column chromatography (4:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (27 mg, 0.09 mmol, 66 %).

R_f 0.45 (4:1 P:EtOAc).

Mp 92-95 °C

ν_{max} (thin film, cm^{-1}) 3293 s, 2103 w, 1641 m, 1314 w, 1140 w.

δ_H ($CDCl_3$, 300 MHz) 7.18-6.99 (m, 4H, Ph**H**), 6.27-6.18 (m, 1H, $SO_2CHCHCHC$**H**), 6.17-6.09 (m, 1H, SO_2CHCHC**H**), 4.40-4.32 (m, 1H, N**H**), 4.19-4.10 (t, *J* 4.7, 2H, NHC**H_2**), 3.05 (t, *J* 7.7, 1H, SO_2C**H**), 2.93 (bs, 1H, SO_2CHC**H**), 2.55 (bs, 1H, SO_2CHCH_2C**H**), 2.24 (s, 3H, C**H_3**), 1.85-1.72 (m, 1H, SO_2CHC**H_2**), 1.57-1.45 (m, 1H, SO_2CHC**H_2**), 1.41-1.11 (m, 4H, SO_2CHCHC**H_2CH_2**, $SO_2CHCHCH_2C$**H_2**).

δ_C ($CDCl_3$, 75 MHz) 138.1 (Ph**C**), 134.5 ($SO_2CHCHCHC$**C**H), 131.2 (SO_2CHCHC**C**H), 129.8 (Ph**C**H), 128.3 (Ph**C**H), 61.8 (SO_2**C**H), 47.6 (NHC**H_2**), 30.9 (SO_2CHC**C**H), 30.3 (SO_2CHC**H_2**), 29.8 (SO_2CHCH_2C**C**H), 26.7 (SO_2CHCHC**H_2**), 23.3 ($SO_2CHCHCH_2C$**H_2**), 21.5 (**C**H_3).

LRMS (EI+) 291 (M^+, 60 %), 227 ($C_{11}H_{17}NO_2S$, 64 %), 186 (M^+-CH_3PhCH_2, 25 %), 120 (CH_3PhCH_2NH, 100 %), 105 (CH_3PhCH_2, 95 %), 91 (CH_3Ph, 65 %), 79 (C_6H_7, 93 %).

HRMS (ES+) MH^+ Calcd for $C_{16}H_{22}NO_2S$, 292.1366, found 292.1364.

1-Methoxy-bicyclo [2.2.2] oct-5-ene-2-sulfonic acid allylamide [161b]

To 1-methoxy-bicyclo [2.2.2] oct-5-ene-2-sulfonic acid pentafluorophenyl ester [161a] (148 mg, 0.39 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.09 mL, 1.16 mmol) followed by DBU (1.0 eq., 0.06 mL, 0.39 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (56 mg, 0.22 mmol, 56 %).

R_f 0.40 (2:1 P:EtOAc).

Mp 48-52 °C

ν_{max} (thin film, cm^{-1}) 3435 s, 2088 w, 1644 m, 1320 w, 1151 w.

δ_H ($CDCl_3$, 300 MHz) 6.31-6.15 (m, 2H, C**H**CHCOCH$_3$, C**H**COCH$_3$), 5.88-5.72 (m, 1H, $NHCH_2C$**H**), 5.22 (d, *J* 17.1, 1H, NHC**H_2**), 5.10 (d, *J* 10.2, 1H, NHC**H_2**), 4.66 (t, *J* 10.2, 5.8, 1H, SO_2C**H**), 3.70-3.53 (m, 2H, $NHCH_2CHC$**H_2**), 3.30 (s, 3H, OC**H_3**), 2.52 (bs, 1H, SO_2CHCH_2C**H**), 1.97 (dt, *J* 13.4, 3.6, 1H, SO_2CHC**H_2**), 1.78-

1.60 (m, 1H, SO_2CHCH_2), 1.57-1.48 (m, 1H, CH_2COCH_3), 1.41-1.29 (m, 3H, CH_2COCH_3, $CH_2CH_2COCH_3$).

δ_C ($CDCl_3$, 75 MHz) 134.4 ($CHCH_2NH$), 132.9 ($CHCOCH_3$), 131.5 ($CHCHCOCH_3$), 117.5 (CH_2CHCH_2NH), 79.2 ($COCH_3$), 62.7 (SO_2CH), 51.9 (OCH_3), 46.6 ($NHCH_2$), 31.5 (SO_2CHCH_2), 29.4 (SO_2CHCH_2CH), 29.3 (CH_3COCH_2), 24.4 (CH_2CHCH_2).

LRMS (EI+) 257 (M^+, 30 %), 165 ($C_9H_{11}NS$, 75 %), 137 (M^+-$CH_2CHCH_2NHSO_2$, 55 %), 108 (C_8H_{12}, 100 %), 94 (C_7H_{10}, 67 %), 77 (C_6H_5, 65 %), 41 (C_3H_5, 52 %).

HRMS (ES+) MH^+ Calcd for $C_{12}H_{20}NO_3S$, 258.1158, found 258.1158.

1-Methoxy-bicyclo [2.2.2] oct-5-ene-2-sulfonic acid 4-methyl-benzyl-amide [162]

To 1-methoxy-bicyclo [2.2.2] oct-5-ene-2-sulfonic acid pentafluorophenyl ester [161a] (158 mg, 0.41 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.16 mL, 1.23 mmol) followed by DBU (1.0 eq., 0.06 mL, 0.41 mmol), and the mixture was refluxed for 2 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a white solid (69 mg, 0.22 mmol, 53 %).

R_f 0.45 (2:1 P:EtOAc).

Mp 110-114 °C

ν_{max} (thin film, cm^{-1}) 3433 s, 2094 w, 1638 m, 1323 w, 1151 w.

δ_H ($CDCl_3$, 300 MHz) 7.18-6.96 (m, 4H, Ph**H**), 6.28-6.09 (m, 2H, $CHCHCOCH_3$, $CHCOCH_3$), 4.91-4.81 (m, 1H, SO_2CH), 4.20-4.01 (m, 2H, $NHCH_2$), 3.19 (s, 3H, OCH_3), 3.15 (m, 1H, N**H**), 2.49 (bs, 1H, SO_2CHCH_2CH), 2.18 (s, 3H, $PhCH_3$), 1.99-1.83 (m, 1H, SO_2CHCH_2), 1.76-1.55 (m, 1H, SO_2CHCH_2), 1.51-1.42 (m, 1H, CH_2COCH_3), 1.32-1.21 (m, 3H, CH_2COCH_3, $CH_2CH_2COCH_3$).

δ_C ($CDCl_3$, 75 MHz) 137.8 (Ph**C**), 134.6 (Ph**C**), 132.9 ($CHCOCH_3$), 131.6 ($CHCHCOCH_3$), 129.7 (Ph**C**H), 128.5 (Ph**C**H), 79.2 ($COCH_3$), 62.4 (SO_2CH), 51.8 (OCH_3), 47.9 ($NHCH_2$), 31.5 (SO_2CHCH_2), 29.2 (SO_2CHCH_2CH), 29.0 (CH_3COCH_2), 24.4 (CH_2CHCH_2), 21.5 ($PhCH_3$).

LRMS (CI+) 339 (M^+, NH_4, 83 %), 322 (M^+, H, 68 %), 122 ($C_8H_{10}O$, 26 %), 120 (CH_3PhCH_2NH, 100 %), 110 ($C_7H_{10}O$, 28 %).

HRMS (ES+) MH^+ Calcd for $C_{17}H_{24}NO_3S$, 322.1471, found 322.1470.

Elemental analysis: Anal. calcd for $C_{17}H_{23}NO_3S$: C 63.52, H 7.21, N 4.36, S 9.98; found C 62.97, H 7.35, N 4.23, S 9.54.

7-Oxa-bicyclo [2.2.1] hept-5-ene-2-sulfonic acid allylamide [177]

To *exo* 7-oxa-bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [175] (59 mg, 0.17 mmol) in dry tetrahydrofuran (5 mL) was added allylamine (3.0 eq., 0.04 mL, 0.51 mmol) followed by DBU (1.05 eq., 0.03 mL, 0.18 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the *exo* title compound as a white solid (28 mg, 0.13 mmol, 76 %).

R_f 0.20 (2:1 P:EtOAc).

Mp 61-64 °C

ν_{max} (thin film, cm^{-1}) 3435 s, 2093 m, 1642 s, 1313 w, 1146 w.

δ_H ($CDCl_3$, 300 MHz) 6.49-6.40 (m, 1H, $SO_2CHCHCHC\mathbf{H}$), 6.39-6.30 (m, 1H, $SO_2CHCHC\mathbf{H}$), 5.88-5.70 (m, 1H, $NHCH_2C\mathbf{H}$), 5.22-5.03 (m, 4H, $SO_2CHC\mathbf{H}$, $CH_2C\mathbf{H}$, $NHC\mathbf{H_2}$), 4.77-4.68 (m, 1H, N**H**), 3.73-3.61 (m, 2H, $NHCH_2CHC\mathbf{H_2}$), 3.08-2.99 (m, 1H, $SO_2C\mathbf{H}$), 2.11-1.98 (m, 1H, $SO_2CHC\mathbf{H_2}$), 1.72-1.59 (m, 1H, $SO_2CHC\mathbf{H_2}$).

δ_C ($CDCl_3$, 75 MHz) 138.5 ($SO_2CHCHCH\mathbf{C}H$), 134.8 ($\mathbf{C}HCHCHSO_2$), 134.4 ($\mathbf{C}HCH_2NH$), 117.8 ($\mathbf{C}H_2CHCH_2NH$), 80.0 ($SO_2CHCH_2\mathbf{C}H$), 78.5 ($SO_2CH\mathbf{C}H$), 61.9 ($SO_2\mathbf{C}H$), 46.4 ($NH\mathbf{C}H_2$), 28.9 ($SO_2CH\mathbf{C}H_2$).

LRMS (EI+) 199 (M^+-O, 35 %), 95 (M^+-$CH_2CHCH_2NHSO_2$, 62 %), 68 (C_4H_4O, 100 %), 56 (CH_2CHCH_2NH, 69 %), 41 (CH_2CHCH_2, 76 %), 28 (CO, 52 %).

HRMS (ES+) MNa^+ Calcd for $C_9H_{13}NO_3SNa$, 238.0514, found 238.0506.

7-Oxa-bicyclo [2.2.1] hept-5-ene-2-sulfonic acid 4-methyl-benzylamide [178]

To *endo* 7-oxa-bicyclo [2.2.1] hept-5-ene-2-sulfonic acid pentafluorophenyl ester [176] (47 mg, 0.14 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (3.0 eq., 0.05 mL, 0.41 mmol) followed by DBU (1.05 eq., 0.02 mL, 0.14 mmol), and the mixture was refluxed for 3 hours. The reaction was diluted with dichloromethane (30 mL) and washed with 2M HCl (2 x 15 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the *exo* title compound as a pale yellow solid (21 mg, 0.08 mmol, 54 %).

R_f 0.25 (2:1 P:EtOAc).

Mp 122-125 °C

ν_{max} (thin film, cm^{-1}) 3430 s, 2090 m, 1644 s, 1319 w, 1135 w.

δ_H ($CDCl_3$, 300 MHz) 7.20-7.03 (m, 4H, Ph**H**), 6.32 (dd, *J* 5.8, 1.7, 1H, $SO_2CHCHCHC$**H**), 6.18 (dd, *J* 5.7, 1.5, 1H, SO_2CHCHC**H**), 5.19 (s, 1H, SO_2CHC**H**), 5.05 (d, *J* 4.1, 1H, SO_2CHCH_2C**H**), 4.81-4.71 (m, 1H, N**H**), 4.21 (d, *J* 5.8, 2H, Ph**CH_2**), 2.97-2.90 (m, 1H, SO_2C**H**), 2.25 (s, 3H, **CH_3**), 2.10-2.00 (m, 1H, SO_2CHC**H_2**), 1.66-1.57 (m, 1H, SO_2CHC**H_2**).

δ_C ($CDCl_3$, 75 MHz) 138.4 ($SO_2CHCHCHC$**C**H), 134.8 (**C**HCHCHSO_2), 132.3 (Ph**C**), 130.0-128.2 (Ph**C**H), 79.9 (SO_2CHCH_2**C**H), 78.6 (SO_2CHC**C**H), 61.9 (SO_2**C**H), 47.7 (Ph**C**H_2), 28.9 (SO_2CHC**C**H_2), 21.5 (Ph**C**H_3).

LRMS (EI+) 279 (M^+, 12 %), 148 ($C_4H_6NO_3S$, 50 %), 120 (CH_3PhCH_2NH, 83 %), 105 (CH_3PhCH_2, 100 %), 95 (C_6H_7O, 61 %), 68 (C_4H_4O, 77 %), 28 (CO, 41 %).

HRMS (ES+) MNa^+ Calcd for $C_{14}H_{17}NO_3SNa$, 302.0827, found 302.0847.

3.6 Procedures for 1,3-Dipoles and Dienes Unsuccessful in Cycloaddition with PFP Vinylsulfonate

3.6.1 General procedures for the preparation of aromatic azides[111]

a) Aryl azides: To the corresponding amine (1.0 eq.) in a 50 % sulfuric acid solution (10 mL) at −5 °C was added dropwise sodium nitrite (1.2 eq.) in water (2 mL). The reaction was stirred for 10 minutes at −5 °C then filtered. The filtrate was added to a stirred slurry of sodium azide (1.5 eq.) and sodium acetate (20.0 eq.) in ice water (25 mL) The suspension was stirred for 30 minutes, extracted into ether (2 × 20 mL) and washed with sodium carbonate solution (20 mL). The organic fraction were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aryl azide as a solid which did not require further purification

1-Azido-4-methoxy-benzene [140]

δ_H ($CDCl_3$, 300 MHz) 6.80-6.62 (m, 4H, Ph**H**), 3.58 (s, 3H, **CH_3**).

1-Azido-4-nitro-benzene [141]

δ_H ($CDCl_3$, 300 MHz) 8.04 (d, *J* 9.2, 2H, Ph**H**), 6.94 (d, *J* 9.2, 2H, Ph**H**).

b) Benzyl azides: To the corresponding bromide (1.0 eq) in acetonitrile (10 mL) was added sodium azide (2.0 eq.) followed by potassium iodide (0.02 eq.) and stirred at reflux for 16 hours. The solution was then concentrated *in vacuo* and the resulting residue was dissolved in water (10 mL) and dichloromethane (10 mL), and then shaken with sodium sulfite (0.1 eq.). The organic layer was

isolated, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude benzyl azide, which did not require further purification.

Azidomethyl-benzene [142]

δ_H ($CDCl_3$, 300 MHz) 7.36-7.11 (m, 5H, Ph**H**), 4.22 (s, 2H, C**H_2**).

1-Azidomethyl-4-fluoro-benzene [143]

δ_H ($CDCl_3$, 300 MHz) 7.20-7.05 (m, 2H, Ph**H**), 6.92-6.80 (m, 2H, Ph**H**), 4.10 (s, 2H, C**H_2**).

1-Azidomethyl-4-methoxy-benzene [144]

δ_H ($CDCl_3$, 300 MHz) 7.06 (d, *J* 8.7, 2H, Ph**H**), 6.75 (d, *J* 8.7, 2H, Ph**H**), 4.08 (s, 2H, C**H_2**), 3.60 (s, 3H, C**H_3**).

3.6.2 General procedures for the preparation of nitrile oxides and precursors

a) Formation of hydroxamic acid chlorides using $TiCl_4$ [146]:[83] To benzaldehyde (2.00 mL, 19.70 mmol) in methanol (5 mL) was added nitromethane (1.2 eq., 1.28 mL, 23.64 mmol) at −10 °C. Sodium hydroxide solution (1.2 eq., 900 mg, 23.64 mmol in 2 mL water) was added dropwise, and the reaction was stirred for 15 minutes. Water (10 mL) was added to dissolve any precipitate, and the solution was poured slowly into 4M HCl (10 mL). The solid formed was filtered and washed with ice-cold water, and dried with suction to give the crude nitro-olefin as a yellow solid, which did not require further purification (1.57 g, 10.54 mmol, 53 %).

To the nitro-olefin (509 mg, 3.42 mmol) and triethylsilane (1.1 eq., 0.60 mL, 3.76 mL) was added $TiCl_4$ (1.2 eq., 4.10 mL of a 1M solution in dichloromethane, 4.10 mmol) dropwise. The reaction was then stirred at r.t. for 1 hour, quenched with water (10 mL), and extracted with dichloromethane (2 × 20 mL). The organic fraction was washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitrile oxide precursor as a white solid, which did not require further purification (321 mg, 1.89 mmol, 55 %).

δ_H ($CDCl_3$, 300 MHz) 7.25-7.08 (m, 5H, Ph**H**), 3.65 (s, 2H, C**H_2**).

b) Nitrile oxide formation *via* oxidation of aldoximes:[81] To the corresponding aldehyde (1.0 eq.) in ethanol (10 mL) and water (10 mL) was added hydroxylamine hydrochloride (1.2 eq.) and sodium hydrogen carbonate (2.0 eq.). The reaction was stirred at r.t. for 2 hours and then extracted with

ether (2 × 20 mL). The organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aldoxime, which did not require further purification.
To the aldoxime (1.0 eq.) in 2M sodium hydroxide (10 mL) at 0 °C was added bromine (1.05 eq.) in carbon tetrachloride (9 mL) dropwise over 1 hour. The reaction was stirred at r.t. for 30 minutes, and then extracted into ether (2 × 20 mL), washed with water (20 mL), dried, ($MgSO_4$) and then concentrated *in vacuo* to give the crude nitrile oxide, which did not require further purification.

2,4,6-Trimethyl-benzonitrile *N*-oxide [152]
δ_H ($CDCl_3$, 300 MHz) 6.82 (s, 2H, PhH), 2.35 (s, 6H, CH_3), 2.20 (s, 3H, CH_3).

2,4,6-Trimethoxy-benzonitrile *N*-oxide [153]
δ_H ($CDCl_3$, 300 MHz) 6.20 (s, 2H, PhH), 3.98 (s, 9H, CH_3).
δ_C ($CDCl_3$, 75 MHz) 163.8 (PhC), 90.9 (PhCH), 56.4-56.0 (CH_3).

3.6.3 Procedure for the preparation of 2-azadiene [163][90]

To LiHMDS (10 mL/1.67 g of a 1M solution in tetrahydrofuran, 10.00 mmol) in dry ether (50 mL) at 0 °C was added dropwise benzaldehyde (1.0 eq.) in dry ether (5 mL). The reaction was stirred at 0 °C for 1 hour, followed by addition of triethylamine (1.1 eq.) and dropwise addition of acetyl chloride (1.0 eq.) in dry ether (5 mL). The reaction was stirred at r.t. for 2 hours, filtered through Celite-545, and the filtrate concentrated *in vacuo* to give the crude product as a yellow oil which did not require further purification 1.51 g, 6.89 mmol, 34 %.
δ_H ($CDCl_3$, 300 MHz) 8.40 (s, 1H, CH), 7.80-7.70 (m, 2H, PhH), 7.31-7.21 (m, 3H, PhH), 4.61 (s, 1H, CH), 4.23 (s, 1H, CH), 0.20 (s, 9H, CH_3).

3.6.4 Procedure for the preparation of 4-methyl-2,5-diphenyl-oxazole [169][91,92]

To norephedrine (411 mg, 2.72 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (1.0 eq.) followed by dropwise addition of benzoyl chloride (1.0 eq.) in dichloromethane (5 mL). The reaction was stirred at r.t. for 3 hours followed by addition of water (10 mL). The organic phase was separated and washed with brine (2 x 20 mL). The organic phase was separated, dried ($MgSO_4$) filtered and the filtrate concentrated *in vacuo* to give a white solid which did not require further purification (470 mg, 1.84 mmol, 68 %). To this precursor (1.0 eq.) in dichloromethane (10 mL) was added Dess-Martin periodinane (1.2 eq.) and stirred at r.t. for 1 hour. The solution was filtered through a plug of Grade 1 aluminium oxide and sand, and washed with dichloromethane into a pre-prepared

solution of triphenylphosphine (2.0 eq.) and iodine (2.0 eq.) in triethylamine (4.0 eq.). The reaction was stirred at r.t. for 12 hours, washed with saturated sodium thiosulfate solution and extracted with ether. The organic phase was separated and washed with saturated sodium bicarbonate solution, the organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (279 mg, 1.19 mmol, 50 %).

δ_H ($CDCl_3$, 300 MHz) 7.98-7.20 (m, 10H, Ph**H**), 1.40 (s, 3H, C**H**$_3$).

3.6.5 Procedure for the synthesis of pyran-2-one [173][96]

To *N*-bromosuccinimide (890 mg, 5.00 mmol) in carbon tetrachloride (30 mL) was added 5,6-dihydro-2*H*-pyran-2-one (1.0 eq.) and benzoyl peroxide (0.1 eq.), and the reaction was refluxed for 2 hours. The solution was filtered, concentrated *in vacuo* and diluted with triethylamine (15 mL). The reaction was refluxed for 30 minutes, concentrated *in vacuo* and purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ethyl acetate) to give the title compound as a yellow oil (179 mg, 1.87 mmol, 37 %).

δ_H ($CDCl_3$, 300 MHz) 7.45-7.21 (m, 2H, C**H**), 6.25-6.10 (m, 2H, C**H**).

δ_C ($CDCl_3$, 75 MHz) 162.4 (**C**O), 152.4 (**C**H), 143.6 (**C**H), 116.9 (**C**H), 106.5 (**C**H).

3.7 Formation of Vinyl Sulfonamides

4-Methylbenzyl vinylsulfonamide [183]

To pentafluorophenyl vinylsulfonate [80] (154 mg, 0.56 mmol) in dry tetrahydrofuran (5 mL) was added 4-methylbenzylamine (1.0 eq., 0.07 mL, 0.56 mmol) followed by DBU (1.0 eq., 0.08 mL, 0.56 mmol) and the reaction was stirred at ambient temperature for 10 minutes. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (1:1 Hexanes:Ethyl acetate) to give the title compound as a pale brown solid (69 mg, 0.33 mmol, 58 %).

R_f 0.70 (2:1 H:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 7.28-7.11 (m, 4H, Ph**H**), 6.52-6.45 (m, 1H, SO_2C**H**), 6.26 (d, *J* 23.2, 1H, SO_2CHCH_2), 5.92 (d, *J* 19.0, 1H, SO_2CHCH_2), 4.59 (bs, 1H, N**H**), 4.16 (dd, *J* 6.3, 2H, NHC**H**$_2$), 2.34 (s, 3H, C**H**$_3$).

δ_C ($CDCl_3$, 75 MHz) 135.9 (SO_2**C**H), 129.4 (Ph**C**H), 127.9 (Ph**C**H), 126.8 (SO_2CHCH_2), 46.8 (Ph**C**H_2), 21.1 (**C**H_3).

Benzylmethyl vinylsulfonamide [184]

To pentafluorophenyl vinylsulfonate [80] (411 mg, 1.50 mmol) in dry tetrahydrofuran (7 mL) was added benzylmethylamine (1.0 eq., 0.19 mL, 1.50 mmol) followed by DBU (1.0 eq., 0.22 mL, 1.50 mmol) and the reaction was stirred at ambient temperature for 10 minutes. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (6:1 Hexanes:Ethyl acetate) to give the title compound as a yellow oil (175 mg, 0.83 mmol, 55 %).

R_f 0.35 (2:1 H:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 7.40-7.28 (m, 5H, Ph**H**), 6.51-6.40 (m, 1H, SO_2C**H**), 6.28 (d, *J* 23.2, 1H, SO_2CHC**H_2**), 6.00 (d, *J* 16.9, 1H, SO_2CHC**H_2**), 4.24 (s, 2H, PhC**H_2**), 2.68 (s, 3H, NC**H_3**).

δ_C ($CDCl_3$, 75 MHz) 133.0 (SO_2**C**H), 128.6-128.0 (Ph**C**H), 127.9 (SO_2CH**C**H_2), 53.7 (Ph**C**H_2), 34.0 (N**C**H_3).

1-Vinylsulfonyl-pyrrolidine-2-carboxylic acid methyl ester [185]

To pentafluorophenyl vinylsulfonate [80] (474 mg, 1.73 mmol) in dry tetrahydrofuran (10 mL) was added *L*-proline methyl ester (1.0 eq., 223 mg, 1.73 mmol) followed by DBU (1.0 eq., 0.26 mL, 1.73 mmol) and the reaction was stirred at ambient temperature for 10 minutes. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (2:1 Hexanes:Ethyl acetate) to give the title compound as a yellow oil (104 mg, 0.47 mmol, 27 %).

R_f 0.15 (4:1 H:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 6.65-6.57 (m, 1H, SO_2C**H**), 6.23 (d, *J* 21.1, 1H, SO_2CH C**H_2**), 5.98 (d, *J* 19.0, 1H, SO_2CHC**H_2**), 3.75 (s, 3H, OC**H_3**), 4.40 (dd, *J* 10.5, 2.2, 1H, NC**H**), 3.49-3.37 (m, 2H, $NCHC$**H_2**), 2.31-2.18 (m, 1H, NCH_2C**H_2**), 2.10-1.92 (m, 3H, NC**H_2C**H_2).

Methylpropyl vinylsulfonamide [186]

To pentafluorophenyl vinylsulfonate [80] (427 mg, 1.56 mmol) in dry tetrahydrofuran (7 mL) was added *N*-methylpropylamine (1.0 eq., 0.16 mL, 1.56 mmol) followed by DBU (1.0 eq., 0.23 mL, 1.56 mmol) and the reaction was stirred at ambient temperature for 10 minutes. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (4:1 Hexanes:Ethyl acetate) to give the title compound as a yellow oil (202 mg, 1.24 mmol, 79 %).

R_f 0.20 (4:1 H:EtOAc).

δ_H ($CDCl_3$, 300 MHz) 6.47-6.38 (m, 1H, SO_2CH), 6.20 (d, *J* 20.8, 1H, SO_2CHCH_2), 5.98 (d, *J* 19.0, 1H, SO_2CHCH_2), 3.10-3.01 (m, 2H, NCH_3CH_2), 2.75 (s, 3H, NCH_3), 1.64-1.53 (m, 2H, CH_3CH_2), 0.09 (s, 3H, CH_3).
δ_C ($CDCl_3$, 75 MHz) 132.8 (SO_2CH), 127.4 (SO_2CHCH_2), 51.5 (CH_2NCH_3), 34.2 (NCH_3), 21.1 (CH_2CH_3), 10.9 (CH_3).

3.8 Procedures for the Formation of PFP Thioesters

3.8.1 Formation of a PFP thioacid

(2-Pentafluorophenyloxysulfonyl-ethylsulfanyl)-acetic acid [191]
To pentafluorophenyl vinylsulfonate [80] (1.02 g, 3.72 mmol) in absolute ethanol (20 mL) was added mercaptoacetic acid (1.0 eq., 0.26 mL, 3.72 mmol) followed by sodium carbonate (2.0 eq., 789 mg, 7.44 mmol). The reaction was stirred for 15 minutes at ambient temperature, then filtered, washed with absolute ethanol (10 mL) and concentrated *in vacuo* to give the title compound as a white solid (1.36 g, 3.72 mmol, 100 %).
R_f 0.15 (2:1 P:Et_2O + 5% AcOH)
δ_H ($CDCl_3$, 300 MHz) 5.26 (bs, 1H, OH), 4.31 (dt, *J* 10.3, 7.5, 1H, SO_2CH_2), 3.86-3.80 (m, 1H, SO_2CH_2), 3.47-3.39 (m, 1H, $SO_2CH_2CH_2$), 3.34 (s, 1H, $COCH_2$), 3.27 (s, 1H, $COCH_2$), 3.05-2.98 (m, 1H, $SO_2CH_2CH_2$).
δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 177.0 (CO), 51.1 (SO_2CH_2), 37.9 ($COCH_2$), 26.9 ($SO_2CH_2CH_2$).

3.8.2 Formation of thioacid sulfonamides

2-(4-Methyl-benzylsulfamoyl)-ethylsulfanyl-acetic acid [192a]
To (2-pentafluorophenyloxysulfonyl-ethylsulfanyl)-acetic acid [191] (201 mg, 0.55 mmol) in water (20 mL) was added 4-methylbenzylamine (2.0 eq., 0.14 mL, 1.10 mmol) followed by DBU (2.0 eq., 0.16 mL, 1.10 mmol) and the reaction was heated at 65 °C for 1 hour. The mixture was acidified with conc. HCl (5 drops), and the product was extracted into dichloromethane (10 × 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to give the title compound as a pale yellow solid (58 mg, 0.19 mmol, 55 %).
R_f 0.30 (2:1 P:Et_2O + 5% AcOH)
δ_H ($CDCl_3$, 300 MHz) 7.25-7.08 (m, 4H, PhH), 4.18 (s, 2H, $PhCH_2$), 3.58 (dt, *J* 11.2, 4.7, 1H, SO_2CH_2), 3.32 (s, 1H, NH), 3.21-3.14 (m, 2H, CH_2CO_2H, SO_2CH_2),

2.97-2.85 (m, 2H, C**H**$_2$CO$_2$H, SO$_2$CH$_2$C**H**$_2$), 2.69-2.60 (m, 1H, SO$_2$CH$_2$C**H**$_2$), 2.29 (s, 3H, PhC**H**$_3$).

δ_C (CDCl$_3$, 75 MHz) 170.0 (CO), 138.6-129.1 (Ph**C**H), 53.6 (SO$_2$**C**H$_2$), 47.5 (Ph**C**H$_2$), 34.6 (CO**C**H$_2$), 27.0 (SO$_2$CH$_2$**C**H$_2$), 21.1 (Ph**C**H$_3$).

2-(Piperidine-1-sulfonyl)-ethylsulfanyl-acetic acid [192b]

To (2-pentafluorophenyloxysulfonyl-ethylsulfanyl)-acetic acid [191] (79 mg, 0.22 mmol) in water (5 mL) was added piperidine (2.0 eq., 0.04 mL, 0.43 mmol) followed by DBU (2.0 eq., 0.06 mL, 0.43 mmol) and the reaction was heated at 65 °C for 1 hour. The mixture was acidified with conc. HCl (5 drops), and the product was extracted into dichloromethane (10 × 20 mL). The organic phase was separated, dried (MgSO$_4$), filtered and the filtrate concentrated *in vacuo* to give the title compound as a yellow oil (24 mg, 0.09 mmol, 41 %).

R$_f$ 0.05 (2:1 P:Et$_2$O + 5% AcOH)

δ_H (CDCl$_3$, 300 MHz) 5.26 (bs, 1H, O**H**), 3.38-3.31 (m, 2H, SO$_2$C**H$_2$**), 3.11 (t, *J* 3.7, 1H, C**H**$_2$CO$_2$H), 3.02-2.93 (m, 1H, C**H**$_2$CO$_2$H), 2.64 (dt, *J* 10.3, 8.4, 2H, SO$_2$CH$_2$C**H$_2$**), 2.10-1.51 (m, 10H, 5 × C**H$_2$**).

3.8.3 Procedure for the preparation of mercapto-thioacetic acid [196][109]

To chloroacetyl chloride (5.00 mL, 62.83 mmol) in absolute ethanol at -10 °C (ice/acetone cold bath) was added sodium hydrosulfide hydrate (3.0 eq., 10.60 g, 188.50 mmol) in portions over 15 minutes. The reaction mixture was stirred at -10 °C for 1 hour, filtered and the filtrate washed with absolute ethanol (20 mL). The filtrate was concentrated *in vacuo* and then purified by flash column chromatography (6:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (2.80 g, 25.88 mmol, 41 %)

R$_f$ 0.50 (2:1 P:Et$_2$O)

δ_H (CDCl$_3$, 300 MHz) 4.26-4.11 (m, 2H, C**H$_2$**).

4.9 Formation of Bifunctional PFP Esters

Chloroacetic acid pentafluorophenyl ester [198]

To pentafluorophenol (210 mg, 1.14 mmol) in dry ether (20 mL) was added chloroacetyl chloride (1.0 eq., 0.09 mL, 1.14 mmol), followed by triethylamine (1.0 eq., 0.16 mL, 1.14 mmol). The reaction was stirred at ambient temperature for 1 hour, diluted with dichloromethane (20 mL) and washed with 2M HCl (1 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried (MgSO$_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue

was purified by flash column chromatography (20:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (107 mg, 0.41 mmol, 36 %).

R_f 0.80 (3:1 P:Et_2O)

δ_H ($CDCl_3$, 300 MHz) 4.41 (s, 2H, C**H_2**).

Bromoacetic acid pentafluorophenyl ester [199]

To pentafluorophenol (1.11 g, 6.03 mmol) in dry ether (50 mL) was added bromoacetyl bromide (1.05 eq., 0.55 mL, 6.33 mmol), followed by triethylamine (1.05 eq., 0.88 mL, 6.33 mmol). The reaction was stirred at ambient temperature for 1 hour, diluted with dichloromethane (30 mL) and washed with 2M HCl (1 x 30 mL), water (2 x 30 mL) and brine (2 x 30 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (1.12 g, 3.68 mmol, 61 %).

R_f 0.80 (3:1 P:Et_2O)

δ_H ($CDCl_3$, 300 MHz) 4.14 (s, 2H, C**H_2**).

δ_C ($CDCl_3$, 75 MHz) 163.5 (**C**O), 142.8-136.1 (Ph**C**F), 124.6 (Ph**C**), 23.3 (**C**H_2).

4-Bromobutyric acid pentafluorophenyl ester [200]

To pentafluorophenol (600 mg, 3.26 mmol) in dry ether (15 mL) was added 4-bromobutyryl chloride (1.05 eq., 0.40 mL, 3.42 mmol), followed by triethylamine (1.05 eq., 0.48 mL, 3.42 mmol). The reaction was stirred at ambient temperature for 1 hour, diluted with dichloromethane (30 mL) and washed with 2M HCl (1 x 30 mL), water (2 x 30 mL) and brine (2 x 30 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (920 mg, 2.76 mmol, 85 %).

R_f 0.90 (3:1 P:Et_2O)

δ_H ($CDCl_3$, 300 MHz) 3.52 (q, *J* 7.5, 6.6, 2H, C**H_2**Br), 2.89 (q, *J* 8.4, 6.6, 2H, COC**H_2**), 2.30 (dt, *J* 8.4, 5.6, 2H, C**H_2**CH_2Br).

δ_C ($CDCl_3$, 75 MHz) (Aromatic peaks not observed due to ^{19}F coupling). 168.6 (**C**O), 31.8 (**C**H_2Br), 31.6 (CO**C**H_2), 27.4 (**C**H_2CH_2Br).

5-Bromopentanoic acid pentafluorophenyl ester [201]

To pentafluorophenol (600 mg, 3.26 mmol) in dry ether (60 mL) was added 5-

bromovaleryl chloride (1.05 eq., 1.00 mL, 7.47 mmol), followed by triethylamine (1.05 eq., 1.04 mL, 7.47 mmol). The reaction was stirred at ambient temperature for 1 hour, diluted with dichloromethane (50 mL) and washed with 2M HCl (1 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50:1 Petroleum ether 40-60 °C:Ether) to give the title compound as a colourless oil (2.16 g, 6.22 mmol, 88 %).

R_f 0.85 (3:1 P:Et_2O)

δ_H ($CDCl_3$, 300 MHz) 3.46 (q, *J* 4.7, 3.7, 2H, C**H_2**Br), 2.71 (q, *J* 7.5, 4.7, 2H, COC**H_2**), 2.04-1.88 (m, 4H, C**H_2**C**H_2**CH_2Br).

δ_C ($CDCl_3$, 75 MHz) 169.0 (**C**O), 142.9-136.0 (Ph**C**F), 125.0 (Ph**C**), 32.6 (**C**H_2CH_2Br), 32.3 (**C**H_2Br), 31.5 (CO**C**H_2), 23.3 ($COCH_2$**C**H_2).

3.10 Formation of PFP Phenyl Vinyl Sulfonate [190]

To triethylamine (1.5 eq., 1.02 mL, 7.33 mmol) in dichloromethane (35 mL) at 0 °C was added pentafluorophenol (1.0 eq., 899 mg, 4.88 mmol) dropwise, followed by *trans*-β-styrenesulfonyl chloride (1.0 eq., 990 mg, 4.88 mmol) in dichloromethane (5 mL) over a 15 minute period. The reaction was warmed to r.t. and stirred for 2 hours, then quenched with 1M HCl (30 mL). The mixture was extracted with dichloromethane (3 × 30 mL) then washed with water (2 × 30 mL) and brine (2 × 30 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 Hexanes:Ether) to give the title compound as a white solid (1.16 g, 3.30 mmol, 68 %).

R_f 0.50 (4:1 H:Et_2O)

δ_H ($CDCl_3$, 300 MHz) 7.70 (d, *J* 21.1, 1H, C**H**SO_2), 7.57-7.42 (m, 5H, Ph**H**), 6.94 (d, *J* 21.1, 1H, C**H**Ph).

δ_C ($CDCl_3$, 75 MHz) 147.8 (**C**HSO_2), 132.4 (Ph**C**H), 131.2 (Ph**C**), 129.4-119.6 (Ph**C**H).

LRMS (EI+) 373 (MNa^+, 35 %), 325 (M^+–C_2H, 45 %), 226 (M^+-C_4F_4, 80 %), 153 (PhC_2H_4SO, 100 %), 136 ($PhCHCH_2S$, 10 %).

3.11 Crystal Structure Data for 2-Methyl-3-(4-nitro-phenyl)-isoxazolidine-4-sulfonic acid 4-methyl-benzylamide [128]

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{18}H_{21}N_3O_5S$

Formula weight	391.44	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No.14)	
Unit cell dimensions	a= 7.8042(1) Å	α= 90°
	b= 25.7850(3) Å	β=
105.000(1)°		
	c= 9.8170(1) Å	γ= 90°
Volume	1908.17(4) $Å^3$	
Z	4	
Density (calculated)	1.36 Mg/m^3	
Absorption coefficient	0.20 mm^{-1}	
F(000)	824	
Crystal size	0.4 x 0.2 x 0.2 mm^3	
Theta range for data collection	3.81 to 27.53°.	
Index ranges	-9<=h<=10,	-33<=k<=33,
-12<=l<=12		
Reflections collected	28749	
Independent reflections	4337 [R(int) = 0.044]	
Reflections with I>2sigma(I)	3734	
Completeness to theta = 27.53°	98.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4337 / 0 / 249	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.045, wR2 = 0.111	
R indices (all data)	R1 = 0.054, wR2 = 0.116	
Largest diff. peak and hole	0.39 and -0.38 $e.Å^{-3}$	

Data collection KappaCCD, Program package WinGX, Abs correction not applied, Refinement using SHELXL-97, Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)

S	7340(1)	4760(1)	1764(1)	32(1)
O(1)	3425(2)	4213(1)	2112(1)	45(1)
O(2)	6042(2)	5162(1)	1730(1)	40(1)
O(3)	9065(2)	4813(1)	2712(1)	44(1)
O(4)	12500(2)	3266(1)	8568(2)	95(1)
O(5)	11275(3)	2564(1)	7570(2)	104(1)
N(1)	4325(2)	4011(1)	3506(2)	39(1)
N(2)	7570(2)	4717(1)	192(2)	38(1)
N(3)	11361(3)	3034(1)	7678(2)	69(1)
C(1)	6153(2)	4212(1)	3716(2)	32(1)
C(2)	6441(2)	4166(1)	2216(2)	30(1)
C(3)	4575(2)	4046(1)	1296(2)	40(1)
C(4)	3404(3)	4245(1)	4465(3)	61(1)
C(5)	7470(2)	3900(1)	4804(2)	32(1)
C(6)	8854(2)	4148(1)	5756(2)	40(1)
C(7)	10128(3)	3867(1)	6704(2)	46(1)
C(8)	9992(3)	3337(1)	6681(2)	47(1)
C(9)	8636(3)	3076(1)	5752(2)	51(1)
C(10)	7365(3)	3362(1)	4807(2)	43(1)
C(11)	8939(2)	4390(1)	-153(2)	43(1)
C(12)	8495(2)	3818(1)	-304(2)	37(1)
C(13)	6940(3)	3645(1)	-1222(2)	47(1)
C(14)	6574(3)	3120(1)	-1379(2)	53(1)
C(15)	7745(3)	2753(1)	-636(2)	50(1)
C(16)	9284(3)	2929(1)	285(2)	52(1)
C(17)	9660(3)	3453(1)	457(2)	45(1)
C(18)	7368(4)	2181(1)	-846(3)	72(1)

Table 3. Bond lengths [Å] and angles [°].

S-O(3)	1.4315(13)
S-O(2)	1.4433(12)
S-N(2)	1.6032(16)
S-C(2)	1.7879(15)
O(1)-C(3)	1.417(2)
O(1)-N(1)	1.4636(19)
O(4)-N(3)	1.227(3)

O(5)-N(3)	1.217(3)
N(1)-C(4)	1.456(3)
N(1)-C(1)	1.482(2)
N(2)-C(11)	1.469(2)
N(3)-C(8)	1.472(3)
C(1)-C(5)	1.508(2)
C(1)-C(2)	1.550(2)
C(2)-C(3)	1.533(2)
C(5)-C(6)	1.388(2)
C(5)-C(10)	1.390(2)
C(6)-C(7)	1.379(3)
C(7)-C(8)	1.370(3)
C(8)-C(9)	1.381(3)
C(9)-C(10)	1.383(3)
C(11)-C(12)	1.513(3)
C(12)-C(17)	1.383(3)
C(12)-C(13)	1.385(3)
C(13)-C(14)	1.383(3)
C(14)-C(15)	1.385(3)
C(15)-C(16)	1.380(3)
C(15)-C(18)	1.508(3)
C(16)-C(17)	1.386(3)
O(3)-S-O(2)	118.89(8)
O(3)-S-N(2)	108.18(9)
O(2)-S-N(2)	106.26(8)
O(3)-S-C(2)	106.51(8)
O(2)-S-C(2)	107.58(8)
N(2)-S-C(2)	109.18(8)
C(3)-O(1)-N(1)	101.43(12)
C(4)-N(1)-O(1)	104.96(15)
C(4)-N(1)-C(1)	112.55(15)
O(1)-N(1)-C(1)	102.51(12)
C(11)-N(2)-S	122.07(13)
O(5)-N(3)-O(4)	124.0(2)
O(5)-N(3)-C(8)	117.1(2)
O(4)-N(3)-C(8)	118.9(2)
N(1)-C(1)-C(5)	111.53(13)
N(1)-C(1)-C(2)	102.26(12)

C(5)-C(1)-C(2)	113.13(13)
C(3)-C(2)-C(1)	103.07(13)
C(3)-C(2)-S	113.69(11)
C(1)-C(2)-S	109.48(10)
O(1)-C(3)-C(2)	104.42(13)
C(6)-C(5)-C(10)	119.63(16)
C(6)-C(5)-C(1)	120.03(15)
C(10)-C(5)-C(1)	120.24(15)
C(7)-C(6)-C(5)	120.78(18)
C(8)-C(7)-C(6)	118.30(18)
C(7)-C(8)-C(9)	122.67(18)
C(7)-C(8)-N(3)	118.6(2)
C(9)-C(8)-N(3)	118.8(2)
C(8)-C(9)-C(10)	118.48(19)
C(9)-C(10)-C(5)	120.14(18)
N(2)-C(11)-C(12)	114.96(15)
C(17)-C(12)-C(13)	118.40(18)
C(17)-C(12)-C(11)	120.45(17)
C(13)-C(12)-C(11)	121.14(17)
C(14)-C(13)-C(12)	120.56(19)
C(13)-C(14)-C(15)	121.39(19)
C(16)-C(15)-C(14)	117.64(19)
C(16)-C(15)-C(18)	121.1(2)
C(14)-C(15)-C(18)	121.2(2)
C(15)-C(16)-C(17)	121.5(2)
C(12)-C(17)-C(16)	120.54(19)

Table 4. Anisotropic displacement parameters ($Å^2x10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	34(1)	26(1)	33(1)	1(1)	3(1)	-2(1)
O(1)	33(1)	53(1)	45(1)	3(1)	1(1)	0(1)
O(2)	48(1)	28(1)	42(1)	-1(1)	7(1)	5(1)
O(3)	38(1)	42(1)	45(1)	1(1)	-2(1)	-10(1)

O(4)	45(1)	157(2)	71(1)	27(1)	-4(1)	21(1)
O(5)	119(2)	104(2)	89(2)	48(1)	24(1)	57(2)
N(1)	34(1)	43(1)	40(1)	1(1)	10(1)	0(1)
N(2)	40(1)	37(1)	36(1)	6(1)	9(1)	3(1)
N(3)	58(1)	100(2)	54(1)	33(1)	25(1)	31(1)
C(1)	35(1)	27(1)	33(1)	-3(1)	7(1)	-1(1)
C(2)	35(1)	24(1)	31(1)	-1(1)	6(1)	-2(1)
C(3)	42(1)	40(1)	35(1)	-4(1)	4(1)	-11(1)
C(4)	49(1)	79(2)	62(1)	-6(1)	26(1)	8(1)
C(5)	36(1)	34(1)	28(1)	0(1)	9(1)	0(1)
C(6)	41(1)	44(1)	34(1)	-3(1)	8(1)	-5(1)
C(7)	36(1)	68(1)	34(1)	-1(1)	8(1)	-1(1)
C(8)	39(1)	72(1)	34(1)	15(1)	14(1)	16(1)
C(9)	58(1)	40(1)	57(1)	13(1)	19(1)	9(1)
C(10)	46(1)	34(1)	46(1)	1(1)	5(1)	-1(1)
C(11)	40(1)	43(1)	51(1)	2(1)	19(1)	-2(1)
C(12)	35(1)	41(1)	40(1)	-2(1)	17(1)	0(1)
C(13)	39(1)	52(1)	49(1)	-10(1)	8(1)	7(1)
C(14)	36(1)	60(1)	64(1)	-24(1)	14(1)	-5(1)
C(15)	51(1)	45(1)	62(1)	-9(1)	32(1)	-6(1)
C(16)	53(1)	45(1)	58(1)	6(1)	16(1)	6(1)
C(17)	38(1)	48(1)	48(1)	1(1)	8(1)	0(1)
C(18)	82(2)	47(1)	100(2)	-17(1)	46(2)	-14(1)

Hydrogen bonds with H..A <r(A) + 2.000 Angstroms and <DHA> 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N2-H2N	0.79	2.20	171	2.974	O2 [-x+1, -y+1, -z]

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