University College London

# Fundamental Studies on 2,4,6-Trichlorophenyl Sulfonate Esters

By

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# Declaration

The work described in this thesis is the work of the author and has not previously been submitted to this or any other university for any other degree.

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# Abstract

This thesis describes the application of 2,4,6-trichlorophenylsulfonate esters in the synthesis of sulfonamides.

The sulfonamide unit is an important structural motif due to its frequent occurrence in a range of pharmaceuticals, particularly antibiotics. Sulfonamides can be readily synthesised from pentafluorophenyl (PFP) sulfonate esters and as an expansion to this 2,4,6 trichlorophenyl (TCP) sulfonates have been developed. These have the added advantage of lower toxicity and reduced cost of trichlorophenol. TCP sulfonates can be synthesised directly from sulfonic acids via activation by triphenylphosphine ditriflate in moderate to excellent yields.

These compounds can then be utilised in the synthesis of sulfonamides and suitable conditions for reactions with both simple aliphatic amines and more challenging anilines have been found.

The differing reactivity's of the TCP and PFP sulfonate esters have been exploited in selective sulfonamide formation. The greater stability of TCP sulfonate in comparison to PFP sulfonate also means that a broader range of transformations can be achieved in its presence. This has been shown particularly in the application of palladium chemistry to synthesise more elaborate TCP sulfonates. Also, the synthesis of novel amino acids have been targeted inorder to further demonstrate the stability of the group when performing more diverse reactions on remote sites in the molecule.

# Contents

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# Abbreviations

**ACC** – Acetyl CoA carboxylase

**ATP –** Adenosine triphosphate

**AZA** – Acetazolamide

**BINOL** – 1,1'-Bi-2-naphthol

**BTCEAD** – Bis(2,2,2-trichloroethyl)azodicarboxylate

**Bu** – Butyl

**BZA** – Brinzolamide

**CA –** Carbonic anhydrase

**CAI** – Carbonic anhydrase inhibitor

**CARP –** Carbonic anhydrase related proteins

**cGMP –** Cyclic guanosine monophosphate

**CI** – Chemical ionisation

**Cy** – Cyclohexyl

**DBU –** 1,8-Diazabicyclo[5.4.0]undec-7-ene

**DCM –** Dichloromethane

**DCP** – Dichlorophenamide

**de –** Diastereomeric excess

**DKR** – Dynamic kinetic resolution

**DMF** – Dimethylformamide

**DNA –** Deoxyribonucleic acid

**DZA** – Dorzolamide

**ee –** Enantiomeric excess

**EI** – Electron ionisation

**ES** – Electrospray

**Et** – Ethyl

**EZA** – Ethoxzolamide

**HIV –** Human immunodeficiency virus

**HMPA** – Hexamethylphosphoramide

**HPLC** – High pressure liquid chromatography

**HRMS** – High resolution mass spectrometry

**ICE** – Interleukin -1β converting enzyme

**IL-1β** – Interleukin -1β

**IOP** – Intraocular pressure

**IR** – Infrared spectroscopy

**KHMDS** – Potassium hexamethyldisilazide

**LCMS** – Liquid chromatography mass spectrometry

**LiHMDS** – Lithium hexamethyldisilazide

**LRMS** – Low resolution mass spectrometry

**MP** – Melting point

**MZA** – Methazolamide

**NBS** – *N*-Bromosuccinimide

**NHMDS** – Sodium hexamethyldisilazide

**NMR** – Nuclear magnetic resonance

**PABA –** *para*-Aminobenzoic acid

**PC** – Pyruvate carboxylase

**PFP –** Pentafluorophenyl

**RNA –** Ribonucleic acid

**SYNPHOS** – [(5,6),(5',6')-bis(ethylenedioxy)biphenyl-2,2'-yl]bis(diphenylphosphine)

**TBAB –** *tetra*-Butyl-ammonium bromide

**TBAC –** *tetra*-Butyl-ammonium chloride

**TBAI –** *tetra*-Butyl-ammonium iodide

**TBS** – *tert*-Butyldimethylsilyl

**TCCA** – Trichloroisocyanuric acid

**TCP –** 2,4,6-Trichlorophenyl

**TCT** – 2,4,6-Trichloro-[1,3,5]-triazine

**TFA** – Trifluoroacetic acid

**THF** – Tetrahydrofuran

**TLC** – Thin layer chromatography

**TMGA –** Tetramethylguanidinium azide

**Troc -** 2,2,2-Trichlorethoxycarbonyl chloride

**Ts** – Tosyl

**Z** – Benzyloxycarbonyl

# Chapter One

# Introduction

## 1.1 Sulfonamides as Potent Therapies for Disease

Since the discovery of the first sulfonamide antibiotic prontosil and its active metabolite sulphanilamide (**1**) the importance and diversity of sulfonamide drugs has grown placing them at the forefront of drug design.[1] Although initially exploited as antibiotics their activity has since been demonstrated to encompass diuretic, antitumour, antithyroid, hypoglycaemic and protease inhibitory activity.[1-5]

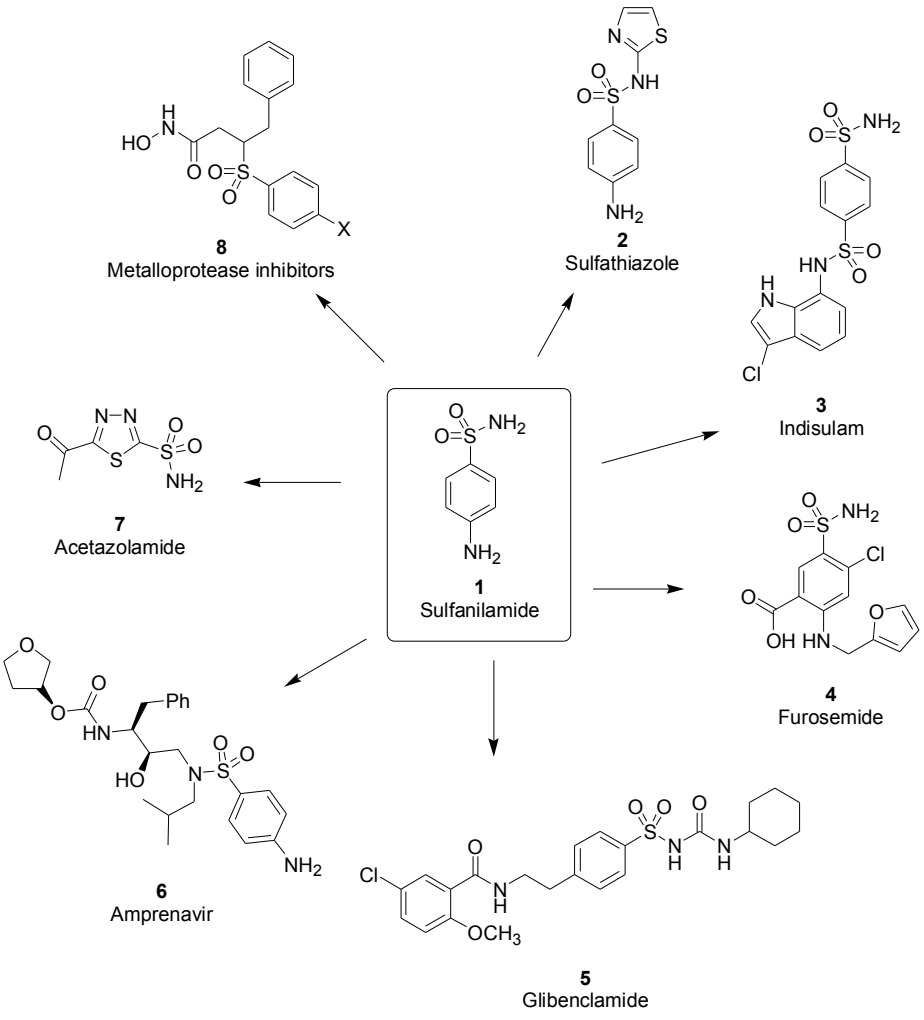



**Figure 1** The main classes of therapeutic agents developed from sulfanilamide

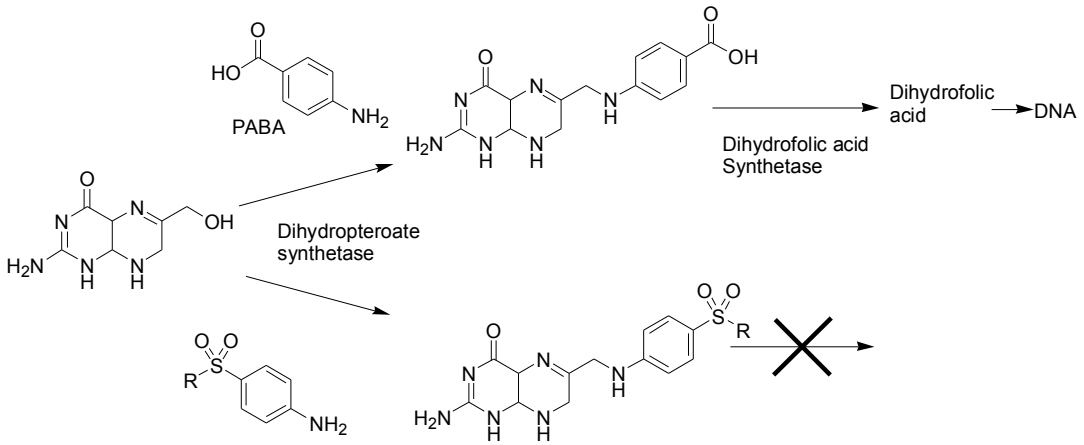
The development of many therapeutic agents has started with sulfanilamide (**1**) as the lead molecule resulting in the discovery of drugs with a varied spectrum of biological actions. This is epitomised by the antibacterial agent sulfathiazole (**2**),[1] the anticancer

sulfonamide indisulam (**3**),[6] the diuretic furosemide (**4**),[7] the hypoglycaemic agent glibenclamide (**5**),[8] the HIV protease inhibitor amprenavir (**6**),[9] the carbonic anhydrase inhibitor acetazolamide (**7**)[2] or the metalloprotease inhibitors of type **8** (Figure 1).[10]

## 1.1.2 Sulfonamides as Anti-Bacterial Agents

Starting with the first recognised sulfonamide antibacterial, sulfanilamide, in 1935 sulfonamides were initially employed as antibiotics.

Sulfonamides were shown to act as bacteriostatic agents, disrupting the synthesis of folic acid.[7] By mimicking *para*-aminobenzoic acid (PABA) they inhibit dihydropteroate synthetase, an enzyme vital in the eventual synthesis of folic acid (Scheme 1). Folic acid is essential for the synthesis of purine nucleotides for DNA and RNA and thus, sulfonamides act by preventing DNA replication and transcription and therefore cell growth.[11] Humans are unaffected as their cells do not synthesise folic acid but instead they obtain it from the diet, and it is brought through the cell membranes by a transport protein not possessed by bacteria.




**Scheme 1** Inhibition of the synthesis of folic acid

The development of bacterial resistance to some sulfonamides has seen their use as antibacterials restricted in modern therapy. Even so, it is worth highlighting some of the sulfonamide antibiotics still in clinical use. Nowadays sulfonamide antibiotics are often used in combination with other drugs, for example, sulfamethoxazole (**9**, Figure 2) and trimethoprim are used together in the treatment of urinary tract infections, acting synergistically to block sequential steps in bacterial folic acid

metabolism.[12] Sulfathiazole (**2**, Figure 2) is used in combination with sulfacetamide and sulfabenzamide in the treatment of vaginal bacterial infections.[13]

Another antibacterial used today is silver sulfadiazine (**10**, Figure 2), which has found applications as a treatment of toxoplasmic encephalitis in HIV-infected patients and as a topical treatment for severe burns, where its anti-microbial properties aid healing.[14-16]

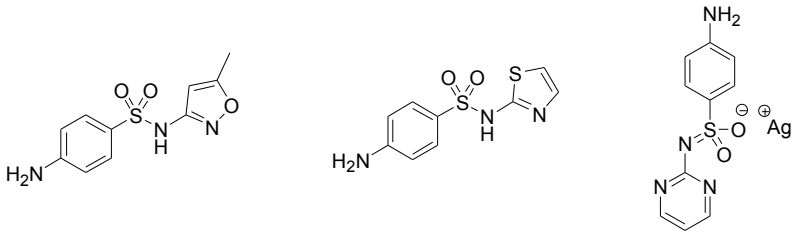
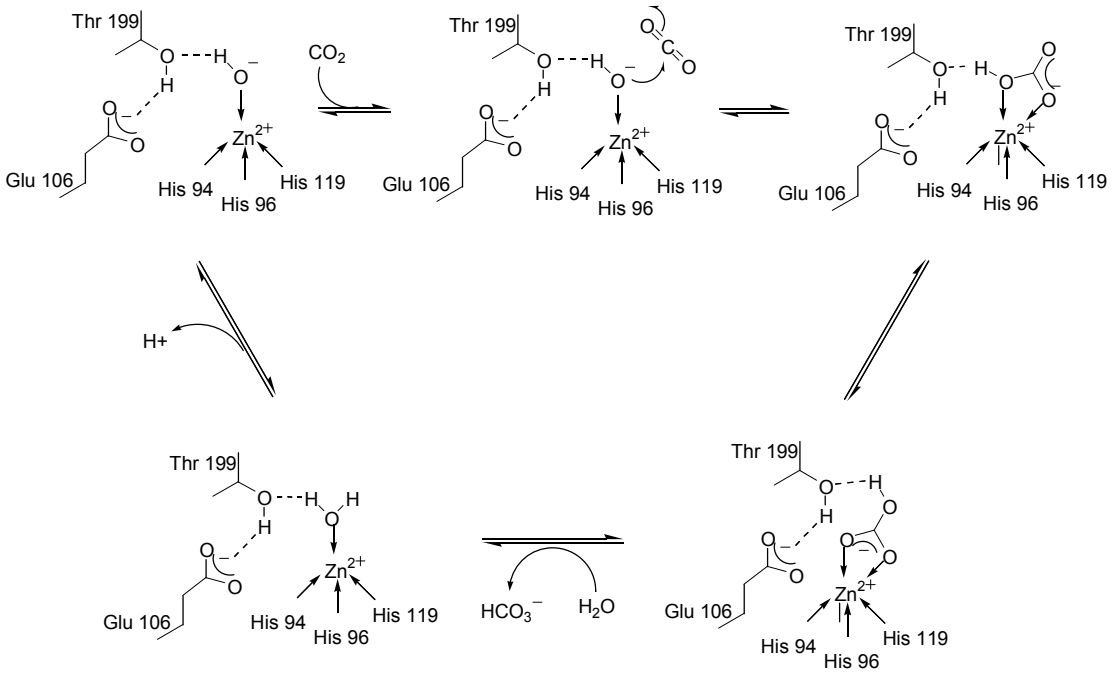



**Figure 2** Sulfonamide antibiotics

## 1.1.3 Sulfonamides as Carbonic Anhydrase Inhibitors

Carbonic anhydrases (CA) are ubiquitous metalloenzymes consisting of a single polypeptide chain co-ordinated around a zinc centre. In mammals 16 different CA isozymes or CA related proteins (CARP) have been identified and these have a broad tissue and subcellular distribution.[17] Several of these isozymes are cytosolic (CA I, CA II, CA III, CA VII, CA XIII), some are membrane bound (CA IV, CA IX, CA XII, CA XIV, CA XV), CA VA and CA VB are located in the mitochondria and CA VI is secreted in the saliva and milk.[17, 18]

Carbonic anhydrases catalyse the hydration of carbon dioxide and dehydration of bicarbonate ($CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$, Scheme 2). They are involved in many important physiological processes as bicarbonate is required for carboxylation in several fundamental metabolic pathways including lipogenesis, ureagenesis, pyrimidine synthesis, glucogenesis and biosynthesis of amino acids.[19] CAs are also implicated in physiological processes associated with respiration and transport of $CO_2$/bicarbonate between metabolising tissues and lungs, pH homeostasis and electrolyte secretion in a range of tissues/organs.[2] Their broad distribution and vital roles in many important physiological processes make CAs attractive targets in drug discovery.




**Scheme 2** Representation of catalytic mechanism for the CA catalysed $CO_2$ hydration

X-ray crystallographic structures have been elucidated for many sulfonamide inhibitors bound to isozymes CA I, II and IV.[20-22] These demonstrate that the sulfonamides bind, in deprotonated form, to the Zn(II) ion of the enzyme through the nitrogen atom of the sulfonamide moiety in a tetrahedral geometry (Figure 3). The NH moiety is also hydrogen bonded to Thr 199, which in turn participates in a hydrogen bond with the carboxylate group of Glu 106.[20-22] The backbone NH moiety of Thr 199 is involved in a hydrogen bond with one of the oxygens of the sulfonamide group. These interactions result in the sulfonamides having a strong affinity for the CA active site.

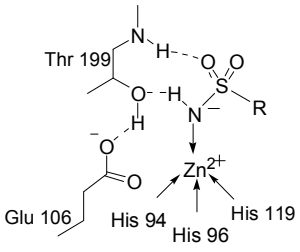



**Figure 3** Sulfonamide bound to carbonic anhydrase

The ability of sulfonamides to act as carbonic anhydrase inhibitors has lead to their application in the treatment or prevention of a variety of diseases including glaucoma, epilepsy, edema, diabetes and potentially cancer.[1, 3, 7]

### 1.1.3.1 Sulfonamides as Antiglaucoma agents

Elevated intraocular pressure (IOP) associated with this disease can be reduced by the inhibition of the CA isozymes (CA II and CA VI) present within the ciliary processes of the eye, which results in a diminished rate of bicarbonate and aqueous humor secretion.

#### *1.1.3.1.1 Systemic drugs*

Sulfonamides such as acetazolamide (AZA, **7**), methazolamide (MZA, **11**), ethoxzolamide (EZA, **12**) and dichlorophenamide (DCP, **13**) have been employed in the systemic treatment of glaucoma for over 45 years (Figure 4).[2, 23] These inhibitors indiscriminately inhibit all CA's and consequently they have many associated side effects, such as fatigue, depression, weight loss, gastrointestinal irritation, metabolic acidosis, renal calculi and transient myopia.[24] These side effects led to investigations into topical treatments for glaucoma.

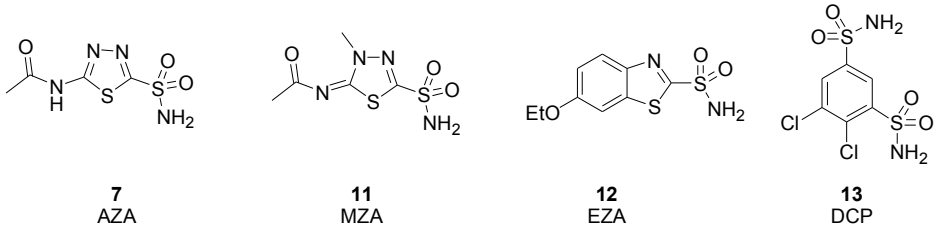



**Figure 4** Systemic anti-glaucoma drugs

#### *1.1.3.1.2 Topically acting drugs*

Initial issues in developing a topically acting drug arose due to the undesirable physicochemical properties of the existing CAIs, which proved ineffective when administered topically.[7, 25, 26] In 1995 dorzolamide (DZA, **14**) was the first drug to be clinically used as a topical treatment for ocular hypertension and glaucoma followed in 1998 by brinzolamide (BRZ, **15**) (Figure 5).[27, 28]

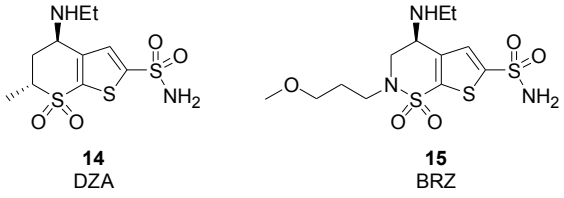



**Figure 5** Topical anti-glaucoma drugs

They show fewer side effects compared to the systemic drugs with the main observed side effects being stinging, burning or reddening of the eye, blurred vision and a bitter taste.[28] They both contain chiral centres making then more expensive to produce and there are on going investigations into alternative inhibitors.

One approach to this search is that taken by Supuran *et al.*, whereby they take aromatic/heterocyclic sulfonamide cores, which are well established inhibitiors of CA, and attach water-solubilising tails to improve their physiocochemical properties.[29-35] For example, benzolamide (BZA, **16**) is a very potent CA inhibitor but as a consequence of its polar nature and hence poor physiocochemical properties it does not show systemic efficacy against glaucoma.[36] BZA was seen as an ideal candidate for the 'tail' approach[29-35] and several ester and amide derivatives were synthesised and tested for CA inhibition and then investigated for topical efficacy. All derivatives showed low nanomolar activity against CAs I, II and IV and some were topically effective in lowering IOP in normotensive rabbits. In fact, in comparison to dorzolamide and brinzolamide, compounds **17-20** showed improved efficacy with prolonged duration of action (Figure 6).[37] Also solutions of these new CAI's had neutral pH compared to the acidic solutions of dorzolamide and brinzolamide (pH 5.5), which cause eye irritation.

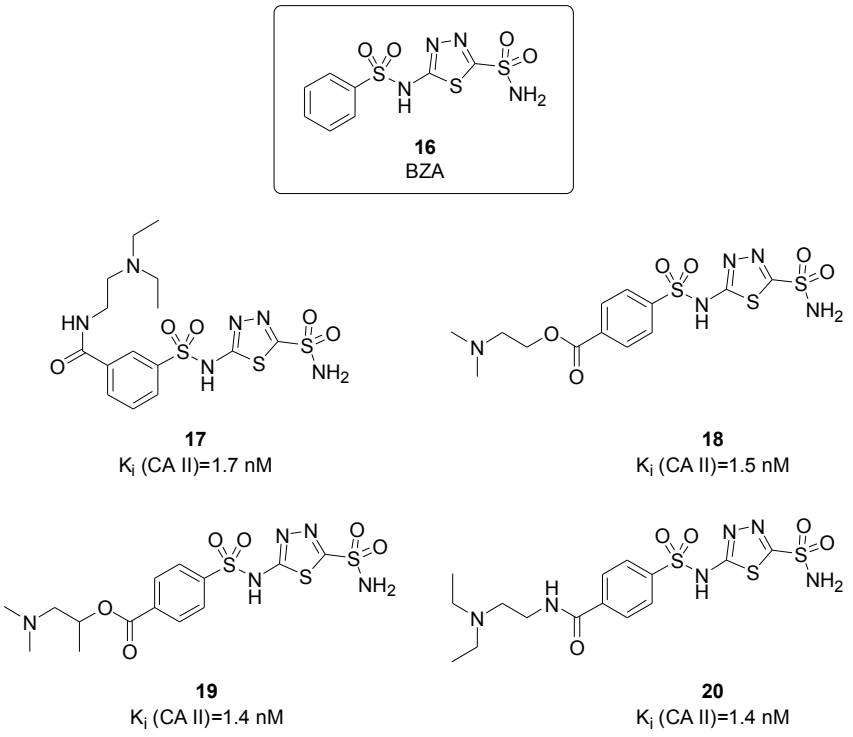


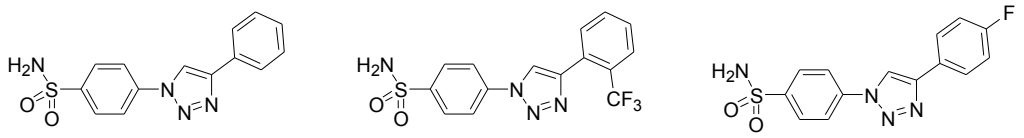

**Figure 6** CA inhibitors with potential topical anti-glaucoma properties

### 1.1.3.2 Sulfonamides as Potential Anti-Obesity Drugs

CA isozymes VA and VB are located in the mitochondria and are implicated in many physiological processes including fatty-acid biosynthesis.[38] Bicarbonate, rather than carbon dioxide, has been established to be the substrate for the carboxylating enzymes pyruvate carboxylase (PC), acetyl CoA carboxylase (ACC) and carbamoyl phosphate synthetases I and II. These enzymes are involved in many biosynthetic processes such as lipogenesis. The bicarbonate is mostly supplied by the catalytic action of the mitochondrial isozymes CA VA and VB (probably assisted by the high activity of isozyme CA II).[39] This has led to speculation about the potential of CA II, VA and VB inhibitors as therapeutic agents involved in the prevention and treatment of obesity.

This has been substantiated by evidence of weight loss in obese patients who have been administered the antiepileptic drugs zonisamide and topiramate. X-ray structures of both topiramate and zonisamide bound to CA II have been reported. These show their high affinity for this CA isozyme and further studies have demonstrated that they both inhibit CA isozymes II, VA and VB.[40, 41] Hence, it is believed that the antiobesity properties of these drugs may be due to the CA II/CA V inhibition. This has led to the synthesis of CA VA and VB inhibitors with the purpose of investigating their potential as antiobesity drugs with a novel mechanism of action.[39]

Supuran *et al.* synthesised a range of triazole sulfonamides, *via* the facile 'click chemistry', to evaluate their activity against CAs II, VA and VB and their potential as therapeutics against obesity.[42] A library of ten benzenesulfonamides containing triazole tethered phenyl tail groups was synthesised (examples shown in Figure 7). They all showed low to mid nanomolar inhibition of the relevant isozymes, as exemplified by compounds **21**-**23**.



**21**
$K_I$ (CA II) = 7.9 nM
$K_I$ (CA VA) = 17.8 nM
$K_I$ (CA VB) = 10.6 nM

**22**
$K_I$ (CA II) = 8.3 nM
$K_I$ (CA VA) = 17.1 nM
$K_I$ (CA VB) = 12.9 nM

**23**
$K_I$ (CA II) = 40.3 nM
$K_I$ (CA VA) = 14.2 nM
$K_I$ (CA VB) = 11.2 nM

**Figure 7** Novel CA inhibitors as potential anti-obesity therapeutics

### 1.1.3.3 Sulfonamides as Anticancer Agents

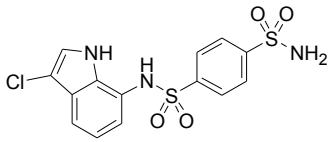
With the American Cancer Society estimating the number of cancer deaths at 7.6 million people worldwide during 2007 cancer is a major health problem.[43] New therapeutic approaches are needed to augment the existing treatments available for the prevention and treatment of cancer.

Chegwidden and Spencer reported the inhibition of growth of human lymphoma cells by CA inhibitors acetazolamide (**7**), methazolamide (**11**) and ethoxzolamide (**12**).[44] When nucleotide precursors were added the inhibition was modulated, which inferred that it was due to the lack of bicarbonate available for nucleotide synthesis.[44] Pastorek *et al.* have shown that *in vitro* acetazolamide strongly reduces the evasiveness of some renal cancer cell lines.[45] These observations have catalysed a proliferation of research into the connection between CAs and cancer, and the application of CA inhibitors in the prevention of tumour growth.

CA IX, CA XII and CA XIV have been strongly implicated in tumour growth of various cancer types with CA XII and CA XIV being appreciably overexpressed in renal carcinoma.[46] CA IX is of particular interest as a target as in healthy human it is only present in tissues of gastrointestinal tracts but is significantly overexpressed in cancer cells of various organs including oesophagus,[47] lungs,[48] kidney,[49] breast,[50] cervix,[51] head and neck,[52] and bladder.[53]

Hypoxia is a key feature of many tumours and is strongly associated with tumour propagation, malignant progression and resistance to chemotherapy and radiotherapy.[54, 55] The expression of CA IX is regulated through the hypoxia inducible factor 1 (HIF1) cascade. Hypoxic tumours have an acidic pH of 6 (normal tissue pH is 7.4), which contributes to the resistance to weakly basic anticancer drugs. On deletion of the CA IX active site and on inhibition of the isozyme by CA IX selective sulfonamides this acidification is reduced, thus implicating CA IX in this process.[56]

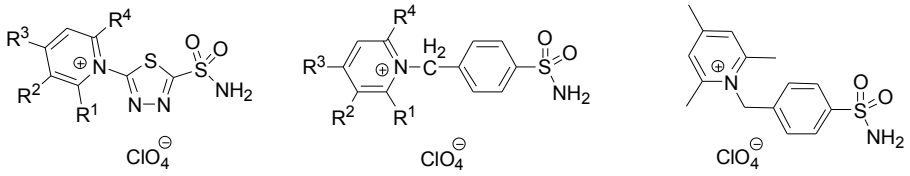
Indisulam (**3**, Figure 8) is a potent anticancer sulfonamide which is currently in phase II clinical trials in Europe and the United States. It acts as a strong CA II and CA IX inhibitor with a $K_i$ of 24 nM.[6, 57]



**3**
Indisulam

**Figure 8** Anticancer sulfonamide Indisulam

CA IX is a membrane bound isozyme which has an extracellularly exposed active site. By the synthesis of membrane impermeant inhibitors selective inhibition of the membrane bound (CA IV, IX, XII and XIV) over cystolic CA's can be achieved. This approach has been taken by Supuran *et al.* with membrane impermeability being achieved through the synthesis of highly polar salt-like compounds. Compounds of type **24** and **25** (Figure 9) were shown to discriminate for the membrane-bound versus cytosolic isozymes, selectively inhibiting only CA IV in *ex vivo* and *in vivo* studies in two model systems (human redblood cells and perfusion experiments in rats respectively).[58] They also possess good activity against isozyme CA IX and thus compounds of this type may constitute the basis for new anticancer therapies and useful probes to further investigate these targets.[59] Indeed, compound **26** was used by Svastova *et al.* to investigate the role of CA IX in the acidification of hypoxic tumours.[56]



**24** **25** **26**

**Figure 9** Selective CA inhibitors

In an effort to find potent and selective CA IX inhibitors a series of indanesulfonamides were synthesised and assessed for activity against CAI, CA II and CA IX.[60] All compounds in this series showed weak inhibition of CA I. Compounds **27**, **28** and **29** were the most potent inhibitors of CA IX with $K_i$ values between 3.4-3.7 nM and they showed good selectivity for CA IX (Figure 10).

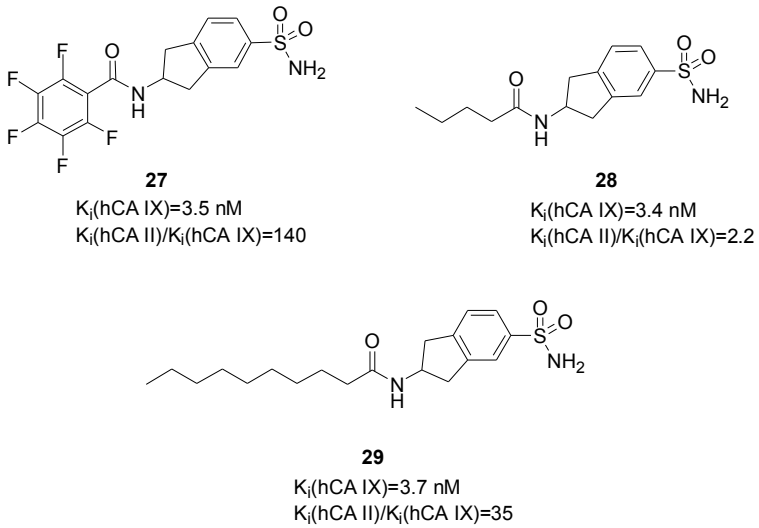


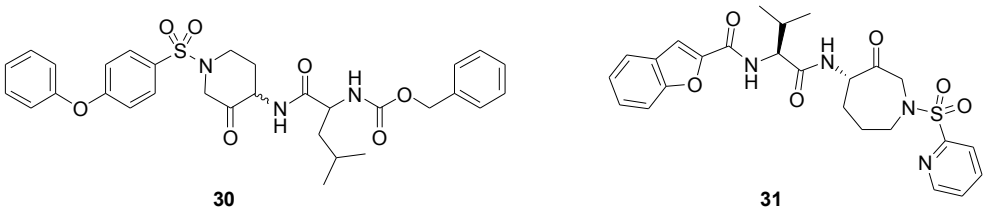

**Figure 10** CA IX inhibitors

## 1.1.4 Sulfonamides and Protease Inhibition

### 1.1.4.1 Cysteine proteases

Cysteine proteases comprise a large of group of enzymes which are involved in numerous physiological processes including osteoporosis, Alzheimer's disease and arthritis.[61, 62] They are connected with a range of pathological conditions and thus, their inhibition could potentially be an effective chemotherapy in these cases.[61-63]

Cathepsin K is selectively expressed in bone osteoclasts and has been shown to play a role in bone resorption.[64] As such inhibitiors of cathepsin K could be potential therapeutic treatments for diseases such as osteoporosis which involves excessive bone loss. Sulfonamide **30** was developed as a subnanomolar peptidomimetic inhibitor with the sulfonamide moiety being incorporated in order to remove the structural liabilities associated with an amide (Figure 11).[65] Veber *et al.* synthesised a series of azepanone based inhibitors of cathepsin K. They identified sulfonamide **31** as a potent and selective reversible inhibitor of both human and rat cathepsin K ($K_i$=0.16 nM) which displays good oral biovailability in the rat (Figure 11).[66]

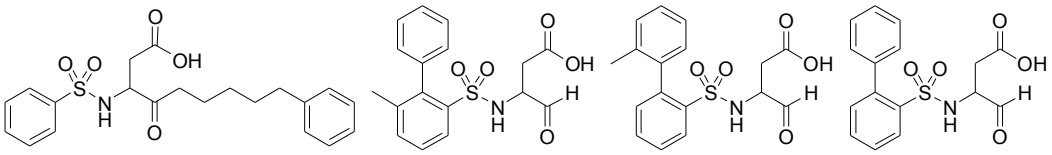


**30**
$K_i$=0.5nM

**31**
$K_i$=0.16nM

**Figure 11** Cathepsin K inhibitors

Interleukin-1β (IL-1β) is a protein which plays a key role in inflammation, brain damage and stroke. Caspase-1 (IL-1β converting enzyme, ICE) is the cysteinyl protease which catalyses the synthesis of IL-1β and as such is an attractive target in the search for new therapeutic agents for inflammatory diseases.[67, 68] Using the crystal structure of caspase-1 Sharipour *et al.* designed and synthesised a range of low molecular weight, non-peptidic, sulfonamide inhibitors of ICE.[69] Compound **35** is the most potent inhibitor of this class with a $K_i$ of 1.6 μM (Figure 12).



**32**
$K_i$ = 24 μM
$IC_{50}$ = 166 μM

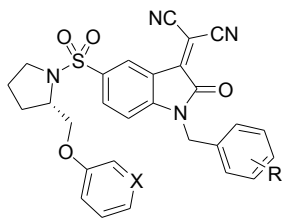
**33**
$K_i$ = 1.9 μM
$IC_{50}$ = 34.4 μM

**34**
$K_i$ = 6.8 μM
$IC_{50}$ = 34.4 μM

**35**
$K_i$ = 1.6 μM
$IC_{50}$ = 20.3 μM

**Figure 12** ICE inhibitors

Caspase-3 and -7 are involved in apoptosis (programmed cell death), which is seen in a variety of pathological conditions such as stroke and myocardial infarction, cardiomyopathy, Alzheimer's disease, sepsis, diabetes and Huntington's disease.[70] Mach *et al.* developed a series of isatin Michael acceptor caspase-3 and -7 inhibitors of the type **36**, which possessed high potency and selectivity against caspase-1, -6 and -8 (Figure 13).[71]



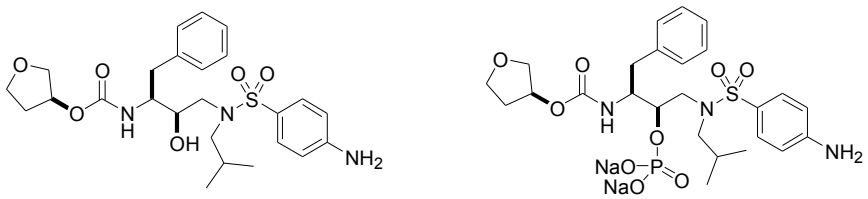
**36**
X=CH or N

**Figure 13** Caspase-3 and -7 inhibitors

### 1.1.4.2 Human immunodeficiency virus (HIV) proteases

HIV protease cleaves the viral Pr55*gag* and Pr160*gag-pol* precursor polyproteins releasing structural proteins and enzymes required for viral maturation. Its inhibition therefore renders the viral particles unable to reproduce or infect.[72] Protease inhibitors have been used clinically since 1996, usually in combination with other antiviral compounds, in the treatment of HIV infected patients.[9]

Amprenavir (**6**) is a clinically used sulfonamide HIV-1 protease inhibitor with a $K_i$ of 6 nM (Figure 14). The sulfonamide unit plays a key part in the activity of amprenivir: by increasing its water solubility, by the interaction of one of the oxygen atoms with a molecule of water present in all HIV protease complexes and by positioning the aromatic group so that it interacts with the $S_{2'}$ sub site of the enzyme.[72, 73] Due to its water solubility and its good lipophilicity it has a high oral bioavailability. It has a half life of 7-10 h which enables it to be taken less frequently than other HIV protease inhibitors and hence, has less potential for side effects. Fosamperenvir (**37**) is a prodrug of amprenevir which is a slow release version of this drug allowing for single daily dosing (Figure 14).[74]

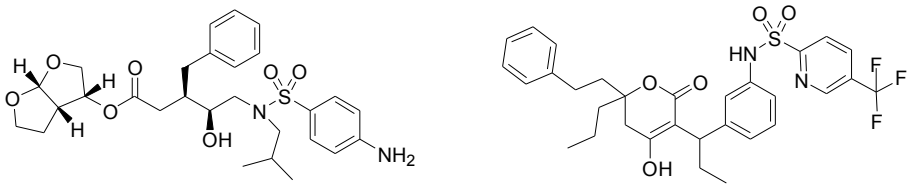



**6**
Amprenavir

**37**
Fosamprenavir

**Figure 14** HIV protease inhibitors

Mutations of the protease active site can lead to resistance to protease inhibitors, and so second generation inhibitors have been developed. These are used to treat patients who have failed in more than one anti-retrovirus treatment. Dunavir (**38**) and tipranavir (**39)** are two such drugs (Figure 15).[75]



**38**
Dunavir

**39**
Tipranavir

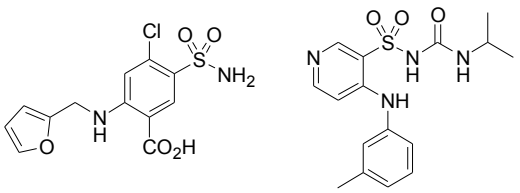
**Figure 15** Second generation HIV protease inhibitors

Dunavir (**38**) is an analogue of amprenavir (**6**) whereby the tetrahydrofuranyl group has been substituted by a bicyclic acetal.[75] The bicyclic acetal moiety not only results in increased hydrogen bonding but also results in binding orientation changes allowing dunavir to inhibit amprenivir resistant proteases.

Tipranavir (**39**) is structurally different to other protease inhibitors resulting in it having activity against protease inhibitor resistant viruses. The sulfonamide moiety hydrogen bonds to several active site residues and, along with other interactions, result in high potency with tipranavir possessing a $K_i$<1 nM against wild type and mutant proteases.[76]

## 1.1.5 Other applications for sulfonamides

Sulfonamides furosemide (**4**) and torsemide (**40**) are effective loop diuretics and as such are an essential part of the management of chronic systolic heart failure (Figure 16).[77, 78] Diuretics relieve hypertension in chronic heart failure patients by initiating the loss of water, minerals and electrolytes from the body *via* urination.



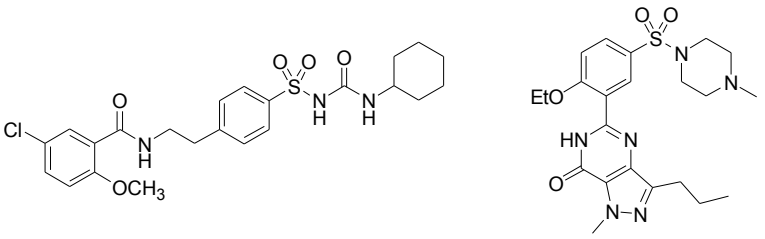
**4**
Furosemide

**40**
Torsemide

**Figure 16** Sulfonamide diuretics

Glibenclamide (**5**) is used in the treatment of type II diabetes mellitus. It a potent and selective ATP-sensitive potassium ion channel blocker, which brings about a calcium influx and then subsequent stimulation of insulin production in the β cells of the pancreas.[8]

Sildenafil (**41**) was launched in 1998 to treat erectile dysfunction and works by inhibiting the enzyme phosphodiesterase-5, which is responsible for the metabolism of cyclic guanosine monophosphate (cGMP). cGMP is responsible for the regulation of blood in the penis and therefore its inhibition results in the prolongation of penile erection.[79]




**5**
Glibenclamide

**41**
Sildenafil

**Figure 17** Other sulfonamide drugs

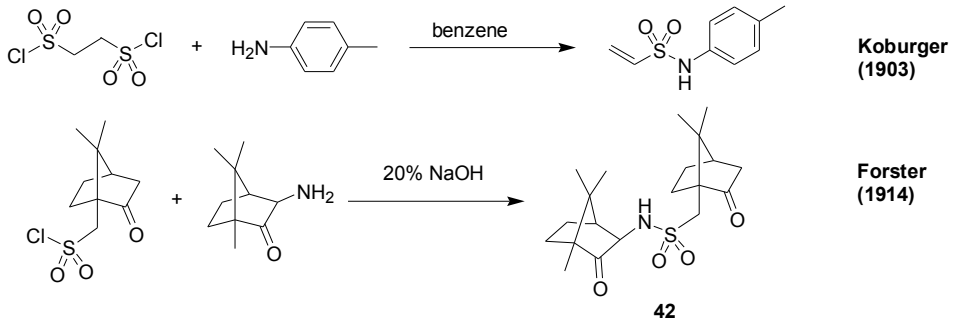
In conclusion, it has been shown that sulfonamides have a number of biological applications in the treatment of a wide range of ailments. The sulfonamide moiety can be used as bioisosteric replacements for various groups, including amides, [65] acids and alcohols, often helping to improve the metabolic stability and pharmacokinetic properties of a compound.[80] Their key importance as motifs in an array of therapeutic agents seems certain to continue.

## 1.2 Sulfonamide Synthesis

Due to the abundance and value of sulfonamides in pharmaceuticals it is vital that there are efficient and diverse ways of synthesising them.

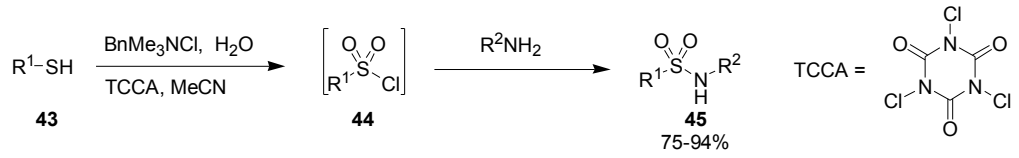
Until recently, sulfonamides have almost exclusively been synthesised from the highly reactive sulfonyl chlorides. Sulfonyl chlorides in turn are commonly synthesised from the appropriate sulfonic acid by treatment with thionyl chloride, chlorosulfonic acid, phosphorus oxychloride or phosphorus pentachloride, or by oxidation of thiols/sulfides with chlorine gas.[81]

Syntheses of sulfonamides utilising simple alkyl sulfonyl chlorides have been reported from around 1903. Koburger *et al.* showed that it was possible to obtain reactions with the normally non-nucleophilic anilines, whereas Forster *et al.* provided an interesting example in the synthesis of a camphor-derived sulfonamide (**42**) (Scheme 3).[82, 83]




**Scheme 3** Synthesis of sulfonamides from sulfonyl chlorides

In the application of chlorine gas to effect the oxidation of thiols/sulfides to sulfonyl chlorides the use of excess oxidant and/or aqueous acid can be potentially unfavourable in the case of sensitive substrates. Bonk *et al.* developed a one pot synthesis of sulfonamides in which an ice-cooled solution of thiol (**43**), $H_2O$ and $BnMe_3NCl$ was treated with trichloroisocyanuric acid (TCCA) followed by the amine (Scheme 4).[84] Key to this method is the generation of chlorine gas by mixing benzyltrimethylammonium chloride with TCCA and thus the *in situ* preparation of the sulfonyl chloride (**44**). This is a mild protocol that minimises both the amount of oxidant required and the aqueous component. A selection of alkyl and aryl thiols were subjected to these conditions and provided sulfonamides (**45**) in good yields.




**Scheme 4** Synthesis of sulfonamides from thiols using TCCA

De Luca *et al.* have developed a microwave assisted synthesis to generate sulfonamides directly from the sulfonic acid (**46**) or its sodium salt.[85] They form an acid chloride (**47**) *in situ* under microwave conditions using the mild chlorinating agent 2,4,6-trichloro-[1,3,5]-triazine (TCT) in acetone with triethylamine. After filtration NaOH and the amine were added and the reaction mixture was exposed to further microwave irradiation (Figure 18). This methodology worked well for alkyl, aryl and heteroaromatic sulfonic acids giving the sulfonamides (**48**) in good yields.

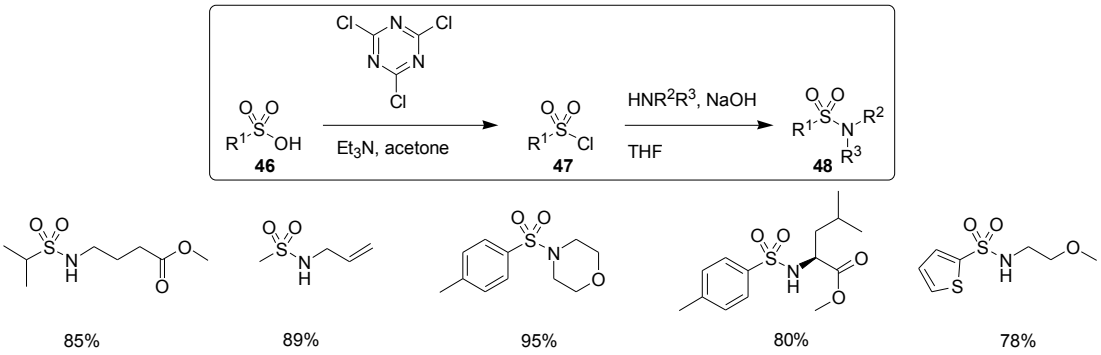



**Figure 18** Microwave assisted synthesis of sulfonamides directly from sulfonic acids

Although commonly used in the synthesis of sulfonamides sulfonyl chlorides can be difficult to prepare and handle and often are not amenable to long term storage. These issues have led to the development of alternative methods for sulfonamide synthesis.

In the preparation of Adenosine A receptor antagonists Müller *et al.* were unsuccessful in the synthesis of xanthin-8-yl benzene sulfonamides (**50**) from the corresponding sulfonic acids *via* the sulfonyl chloride. To overcome this issue the *p*-nitrobenzene sulfonates (**49**) were prepared and the sulfonamides (**50**) synthesised by displacement of the *p*-nitrophenol (Figure 19).[86]

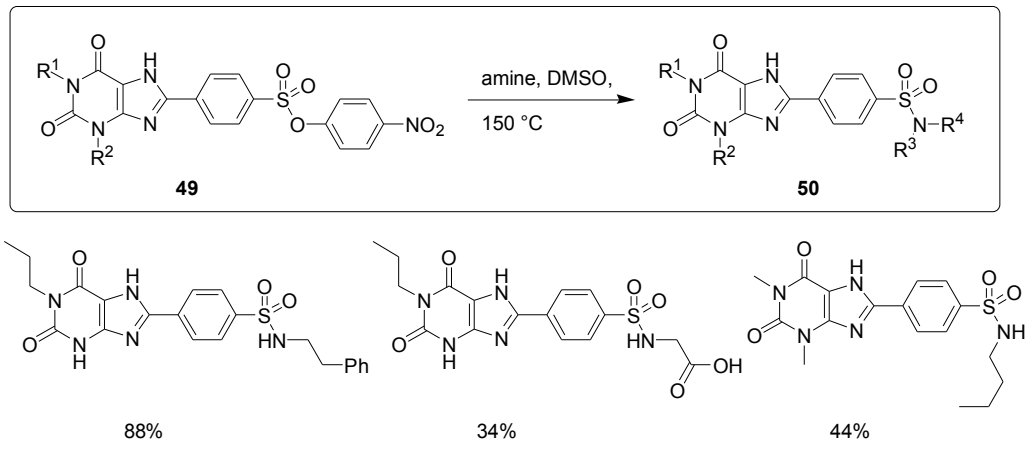
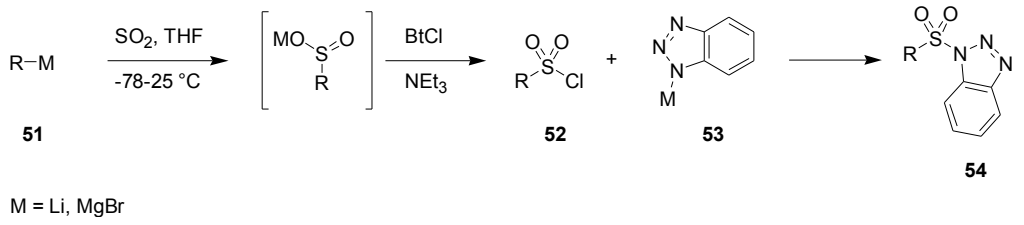



**Figure 19** Synthesis of sulfonamides from *p*-nitrophenol sulfonates

Katritzky *et al.* have utilised the sulfonylbenzotriazoyl moiety as a replacement to sulfonyl chlorides in the synthesis of sulfonamides.[87, 88] They initially synthesised the sulfonylbenzotriazoles (**54**) from the corresponding sulfonyl chlorides, but have since reported their synthesis from aryl/alkyl lithiums or Grignard reagents (**51**) by treatment with $SO_2$ and *N*-chlorobentriazole. This is believed to proceed through an intermediate sulfonyl chloride (**52**) and benzotriazoyl anion (**53**) (Scheme 5).




**Scheme 5** Synthesis of sulfonylbenzotrazoles

A variety of alkyl and aryl sulfonyl benzotriazoles were synthesised *via* this approach in good yields (41-93%) and these were used to synthesise a range of sulfonamides in good yields (Figure 20).[87]

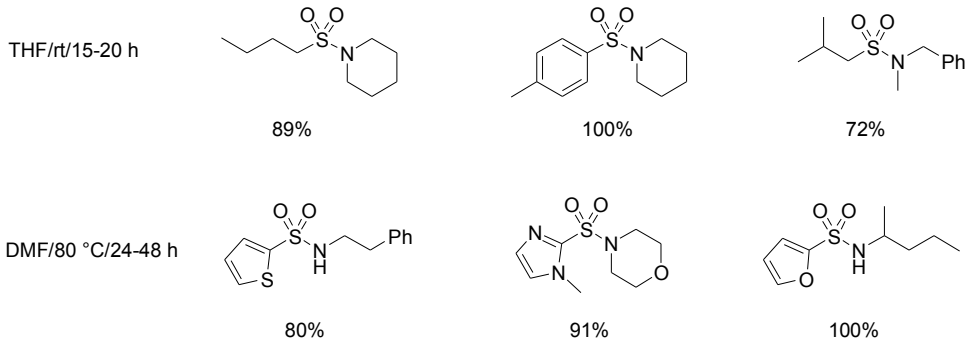
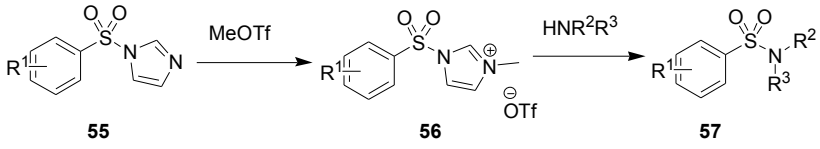



**Figure 20** Sulfnamides synthesised from sulfonylbenzotriazoles

Alkyl/aryl sulfonyl imidazoles (**55**) have also been employed in the synthesis of sulfonamides; here the imidazole needs to be activated for it to become an effective leaving group.[89] This is achieved by alkylation using methyl triflate to give the imidazolium triflate (**56**). When amines were added to these salts the desired sulfonamides (**57**) were obtained in good yield (Scheme 6).




**Scheme 6** Synthesis of sulfonamides via sulfonyl imidazolium triflates

There are few methods available for the synthesis of sulfonamides from the corresponding sulfonic acid. One such route has been developed by Shaabani *et al.* whereby the sulfonamides are formed *via* the reaction of sulfonic acids (**58**), isocyanides (**59**) and water in dichloromethane at ambient temperature.[90] The sulfonamides (**60**) were isolated in good yield (Figure 21).

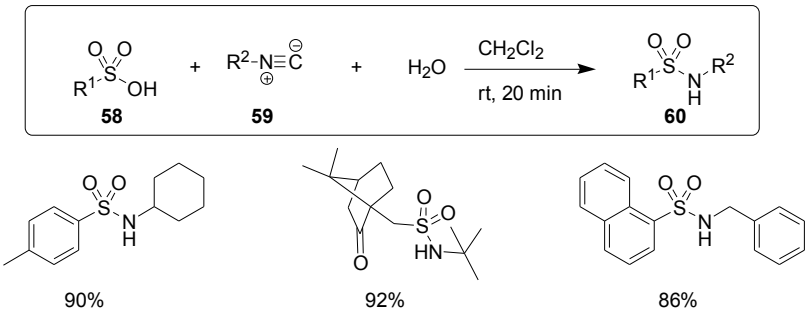
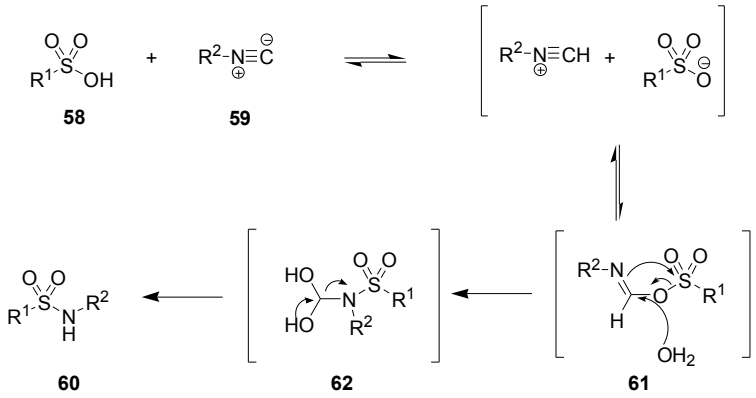


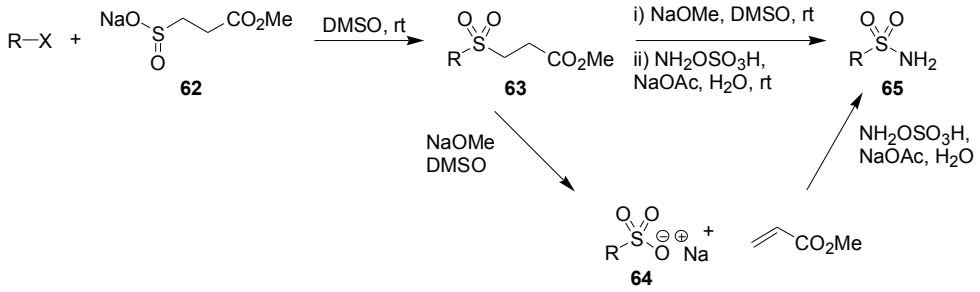

**Figure 21** Synthesis of sulfonamides from sulfonic acids and isocyanides

This reaction doesn't occur in the absence of water and they have proposed the following mechanism. It is believed that protonation of the isocyanide (**59**) by the sulfonic acid occurs to generate intermediate **61**, which on quenching with water produces intermediate **62** and thus, elimination of formic acid gives the sulfonamide (**60**) (Scheme 7). [90]



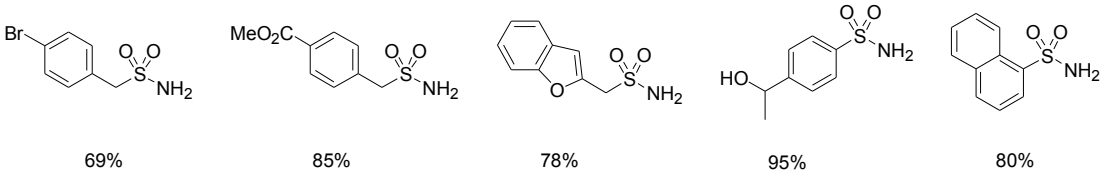

**Scheme 7** Proposed reaction mechanism between sulfonic acids and isocyanides

Sulfonamides can also be synthesised from sulfinates. Baskin *et al.* have developed a one pot process utilising sodium 3-methoxy-3-oxopropane-1-sulfinate (**62**) as a sulfinate transfer reagent.[91] Initial alkylation of sodium 3-methoxy-3-oxopropane-1-sulfinate (**62**) with the alkyl halide is followed by *β*-elimination and then sulfonamide formation (Scheme 8). It is possible to isolate the intermediate sulfones (**63**) and sodium sulfinates (**64**). This procedure can be applied to aryl halides but at a higher temperature (110 °C); the presence of CuI is required for the initial step and the sulfone needs to be isolated due to the excess of reagents used.




**Scheme 8** Synthesis of sulfonamides from alkyl and aryl halides

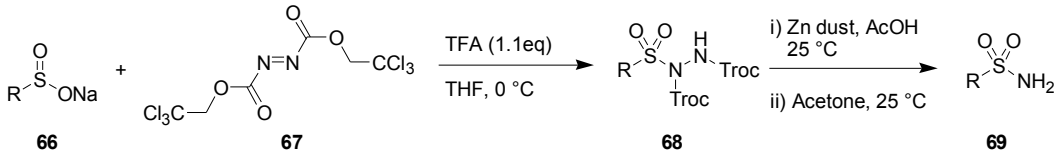
The sulfonamides **65** are isolated in reasonable yields. This method is a convenient procedure which is compatible with many functional groups (Figure 22).




69% 85% 78% 95% 80%

**Figure 22** Sulfonamides synthesis from alkyl and aryl halides

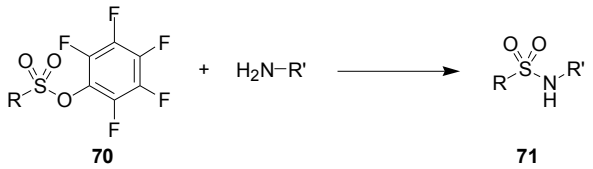
An alternative method for synthesising sulfonamide from sulfinates utilises bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD, **67**) as an electrophilic nitrogen source.[92] Treatment of the appropriate sulfinic acid sodium salt (**66**) with BTCEAD (**67**) and TFA gives the corresponding hydrazide (**68**), which on treatment with zinc dust and then acetone yields the desired sulfonamide (**69**) (Scheme 9). This is a mild two step process which has been successful for both aromatic and aliphatic sulfinates.




**Scheme 9** Synthesis of sulfonamides from sulfinates using BTCEAD

## 1.2.1 PFP sulfonate esters

Caddick *et al.* have developed pentafluorophenyl (PFP) sulfonate esters (**70)** as alternatives to sulfonyl chlorides in the synthesis of sulfonamides (Scheme 10).[93-95] The sulfur centre is susceptible to nucleophilic attack, especially by amines, to make sulfonamides (**71**) (Scheme 10).



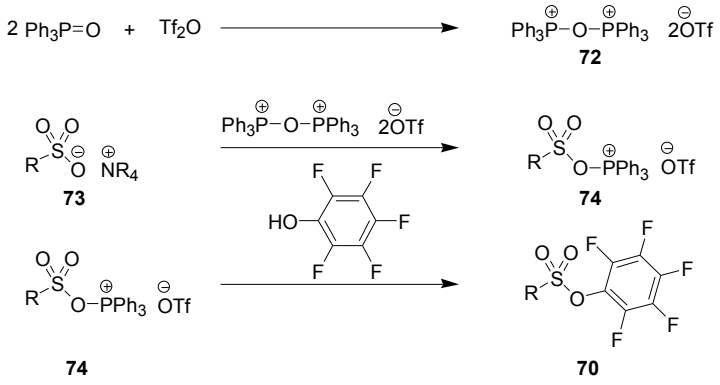

**Scheme 10** Sulfonamides from PFP sulfonate esters

PFP sulfonate esters are generally crystalline solids making them amenable to long term storage and providing ease of handling. They have also proven to be stable to acid and base work-ups and column chromatography.

Extensive investigations have been carried out into the nature of this class of compounds demonstrating their versatility in the synthesis of sulfonamides.

### 1.2.1.1 Synthesis of Pentafluorophenyl Sulfonate Esters

Despite the plethora of coupling reagents used in the synthesis of amides until recently there existed no analogous route to the synthesis of sulfonamides or sulfonate esters from sulfonic acids. Hence, initially the PFP sulfonate esters needed to be synthesised from the appropriate sulfonyl chloride. This was impractical and limited the range of esters that could be produced. A successful route to the desired sulfonate esters was found by activation of sulfonic acid salts (**73**) using triphenylphosphine ditriflate (**72**) (Scheme 11). The intermediate **74** is sufficiently activated to undergo reaction with nucleophiles such as the PFP anion, with the formation of the P=O π bond believed to be the driving force for the reaction.[96]




**Scheme 11** Activation of Sulfonic Acids by Triphenylphosphine Ditriflate

This methodology has been proven to be robust displaying high functional group tolerance and giving excellent yields and can also be applied in the direct synthesis of sulfonamides from sulfonic acid salts (Figure 23).[96]

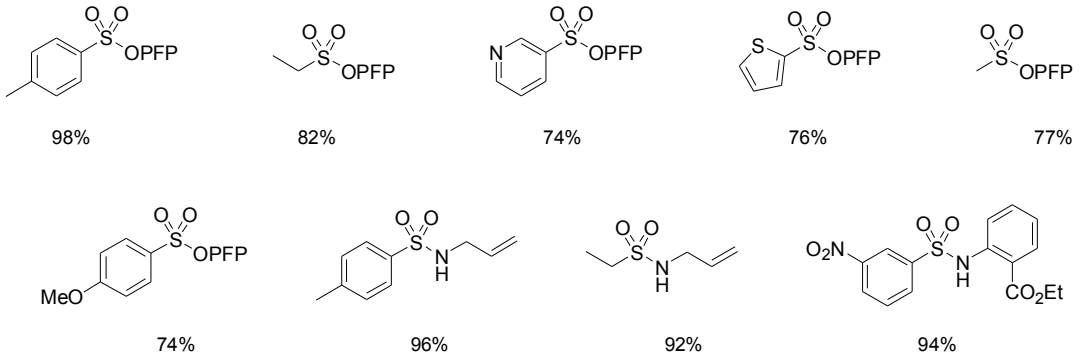
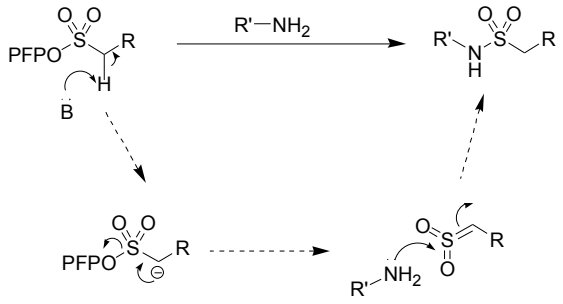



**Figure 23** Synthesis of Sulfonate esters and Sulfonamides directly from sulfonic acids

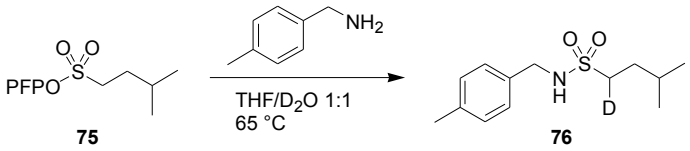
By using a solid-supported phosphine oxide the need for purification by column chromatography can be avoided and thus renders this reaction amenable to high throughput chemistry.

### 1.2.1.2 Reactivity of Pentafluorophenyl Sulfonate Esters

The reactivity of the PFP sulfonate esters falls into two main categories: i) Alkyl-PFP-esters and ii) Aryl-PFP-esters. Alkyl-PFP-esters are believed to react *via* a sulfene intermediate which is formed by deprotonation of the α-C-H (Scheme 12). This mechanism was supported by incorporation of deuterium into the product (**76**) from the reaction of PFP sulfonate **75** with 4-methylbenzylamine in the presence of $D_2O$ (Scheme 13).[94]

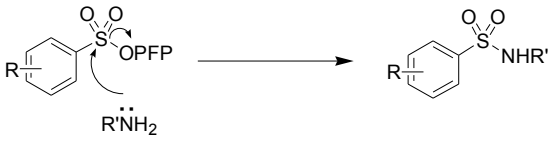



**Scheme 12** Proposed mechanism of reaction for alkyl PFP sulfonate esters



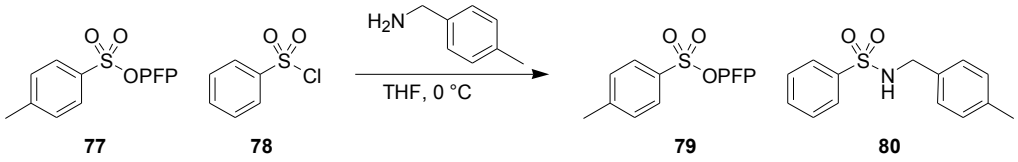

**Scheme 13** Reaction supporting the mechanism of reaction for alkyl PFP sulfonate esters

The alkyl PFP sulfonates also generally require milder conditions than the aryl PFP sulfonates, for which the reaction proceeds via the direct displacement of the PFP alcohol (Scheme 14).



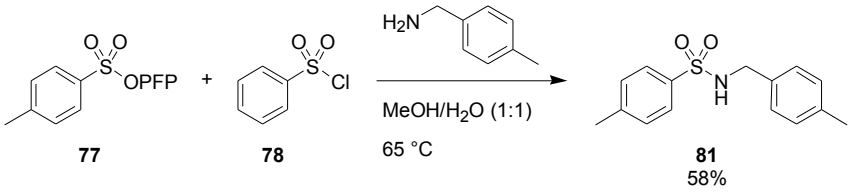

**Scheme 14** Mechanism of reaction for aryl PFP sulfonate esters

PFP sulfonates are less reactive than sulfonyl chlorides and therefore require higher temperatures and stronger bases (typically at 65 °C with DBU).[97] This observation was further supported by the preferential nucleophilic attack by an amine on a sulfonyl chloride in the presence of a PFP sulfonate. Scheme 15 shows the reaction of one equivalent of 4-methylbenzylamine with a mixture of benzenesulfonyl chloride (**78**) and PFP tosylate (**77**) which gave solely **80**, the product derived from reaction with the sulfonyl chloride (**79**).



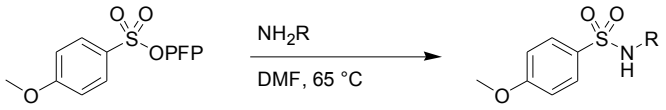

**Scheme 15** Comparison of reactivities of PFP sulfonate esters and TCP sulfonate esters

A major advantage PFP sulfonate esters have over sulfonyl chlorides is their ability to react under aqueous conditions to give the desired sulfonamide in good yields. This was demonstrated when a 1:1 mixture of benzenesulfonyl chloride (**78**) and PFP tosylate (**77**) in an aqueous medium (1:1 methanol/water) were treated with one equivalent of amine (Scheme 16). This reaction yielded only sulfonamide **84** which was derived from the PFP tosylate and the amine.[94]




**Scheme 16** Reaction under aqueous conditions

The aryl PFP sulfonates bearing electron donating groups and sterically hindered amines react more slowly and often require increased temperatures. Wilden *et al.* envisaged that a nucleophilic catalyst would increase the rate and efficacy of these reactions. Indeed when the aminolysis reaction is performed in the presence of tetrabutylammonium chloride an acceleration of the rate is observed (Table 1).[95]



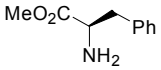
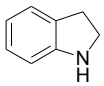
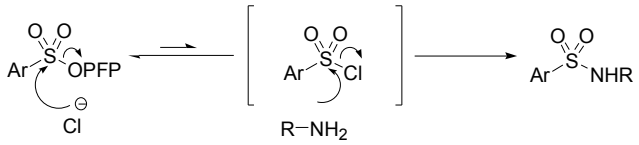

| Amine | Time No TBAC | Time TBAC (1.5 eq) | Yield (%) No TBAC | Yield (%) TBAC |
|---|---|---|---|---|
|  | >7 days | 7.5 h | 67 | 89 |
|  | 1.5 h | 25 min | 77 | 75 |
|  | >7 days | 13 h | 38 | 84 |

**Table 1** Reaction of amines with PFP *p*-methoxybenzenesulfonate in the absence and presence of TBAC

It has been postulated that this is the result of the formation of a transient sulfonyl chloride and it is this reactive species that reacts with the nucleophile (Scheme 17).[95] It is of particular note that this reaction still occurs in the presence of water.




**Scheme 17**

Overall, the PFP sulfonate ester methodology has been shown to be robust and broad in its application with alkyl, benzylic, heterocyclic and aromatic PFP sulfonate esters reacting with primary, secondary and sterically hindered amines in moderate to good yields (Figure 24).[93]

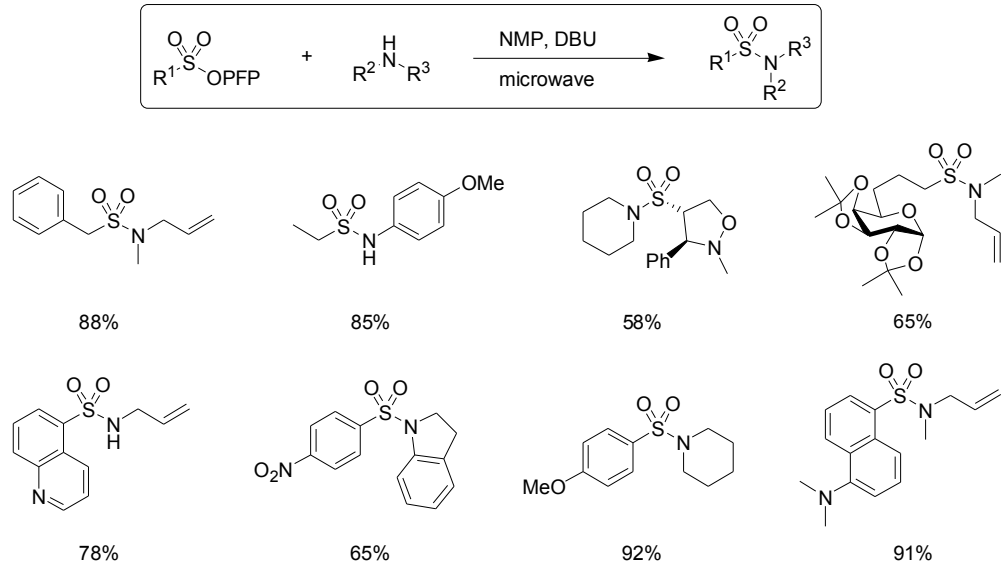
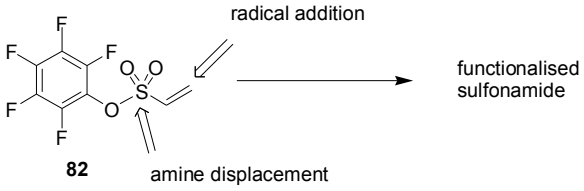



**Figure 24**

### 1.2.1.4 Elaboration of Pentafluorophenyl Sulfonate Esters

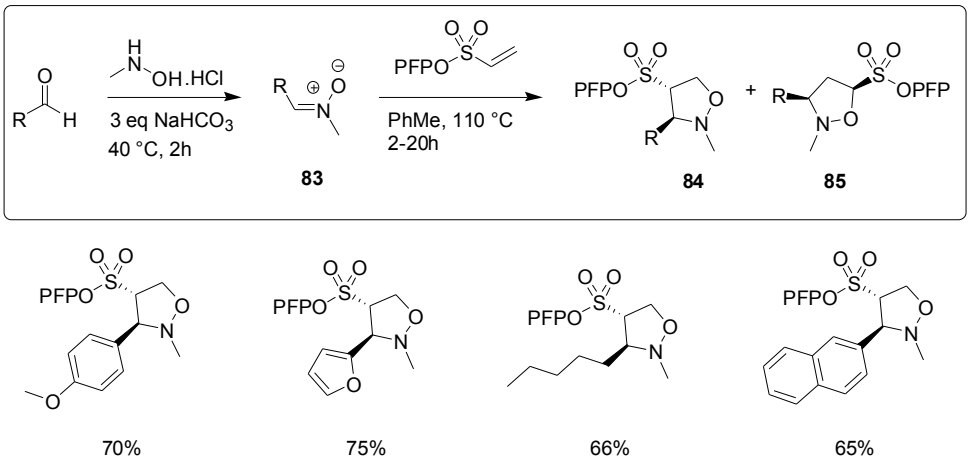
One PFP sulfonamide that has been of particular interest is PFP vinylsulfonate (**82**). This surprisingly stable compound is easily prepared from 2-chloroethane-1-sulfonyl chloride and pentafluorophenol. It is a bifunctional acceptor that reacts with both radical and nucleophilic species allowing facile access to a diverse range of sulfonamide products (Scheme 18).[97]




**Scheme 18** PFP vinylsulfonate

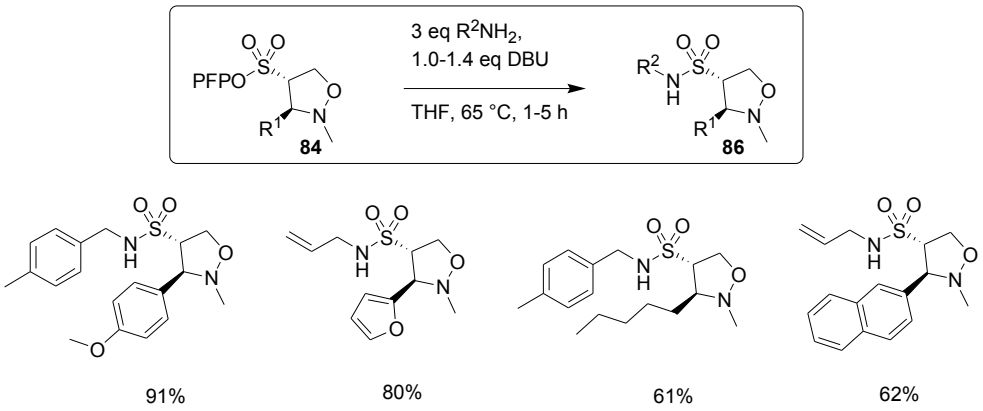
By using the PFP sulfonate moiety the radical chemistry can be optimised before the addition of functionality from the amine and thus the potential for side reactions is reduced.

The electron deficient vinyl section of PFP vinylsulfonate (**82**) can undergo cycloaddition with the 1,3-dipoles nitrones (**83**) to give isoxazolidine products **84** and **85**.[98] The 4C-substituted regioisomer (**84**) is seen as the major product and a variety of nitrones can be reacted to give access to a diverse set of highly functionalised isoxazolidines (Scheme 19).



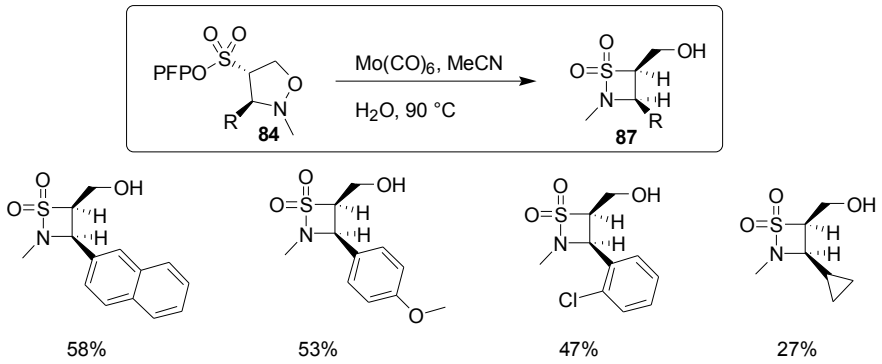

**Scheme 19** Isoxazolidine formation via 1,3-dipolar cycloaddition

The resultant PFP-substituted isoxazolidines can then be subjected to aminolysis conditions to successfully give the expected sulfonamides (Scheme 20).



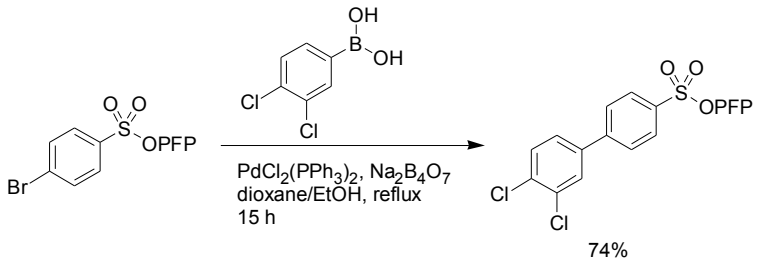

**Scheme 20** Sulfonamide formation from PFP substituted isoxazolidines

These isoxazolidines also offer an alternative route to the synthesis of *β*-sultams. When treated with $Mo(CO)_6$ the N-O bond is cleaved and subsequent displacement of the pentafluorophenol with the nitrogen gives access to the *β*-sultams (**87**) (Scheme 21).[99]




**Scheme 21** $Mo(CO)_6$ reductive cleavage of isoxazolidines to their corresponding *β*-sultams

Palladium chemistry is widely used in organic synthesis particularly in the synthesis of compounds in drug discovery. Avitabile *et al.* have demonstrated that Suzuki reactions can be performed in the presence of a PFP sulfonate ester. By using the catalyst $PdCl_2(PPh_3)_2$ and the base $Na_2B_4O_7$ in a refluxing mixture of dioxane and ethanol the Suzuki reactions proceeded in good yields (Scheme 22).[100]




**Scheme 22** Suzuki chemistry in the presence of PFP sulfonates

In conclusion, the sulfonamides are used in the treatment of a range of diseases and they continue to be of key importance in the search for new therapeutic agents. The traditional route for their synthesis can be problematic due to the difficultly in synthesising some sulfonyl chlorides, in particular heterocyclic examples, and also problems with their long term storage. Although a range of alternative methods have been developed there is still need for a straightforward and general protocol.

Caddick *et al.* have demonstrated the versatility of the PFP sulfonates but there are issues with the cost and toxicity of these compounds. With this in mind 2,4,6-trichlorophenyl (TCP) sulfonates have been put forward as less toxic and less expensive alternatives.

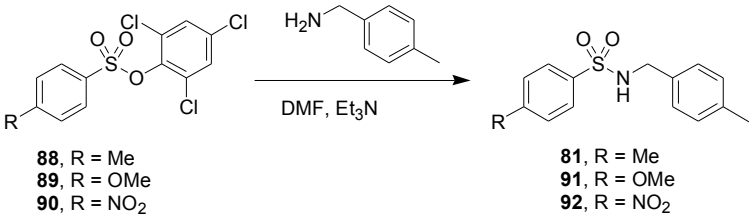
# Chapter Two

# Synthesis and Aminolysis of 2,4,6-Trichlorophenyl (TCP) Sulfonate Esters

## 2.1 Introduction

There is a degree of resistance to the use of PFP sulfonate esters on a large and general scale due to their cost and perceived toxicity. In order to address these limitations an alternative sulfonamide precursor was desired. This would require a leaving group for the aminolysis reactions, which would ideally be more stable than the PFP sulfonates. This would allow more chemistry to be carried out with the sulfonate in place, thus making them more compatible with library synthesis.

2,4,6-Trichlorophenyl sulfonates presented themselves as an ideal candidate with the parent phenol possessing a lower toxicity (currently marketed as a household antiseptic agent in the UK) and having a reduced cost. In order to establish proof of principle initial investigations were carried out within the Caddick group by C.C. Lee.[101] Three TCP sulfonate esters (**88-90**) were synthesised and then subjected to aminolysis under both thermal and microwave conditions (Scheme 23). The reactions were carried out in DMF with 1.5 eq of both 4-methylbenzylamine and triethylamine. All the desired sulfonamides (**81**, **91**, **92**) were obtained in good yield after purification by column chromatography (Table 2). These successful results showed that TCP sulfonate esters were a promising alternative to PFP sulfonate esters and that they warranted further investigations.



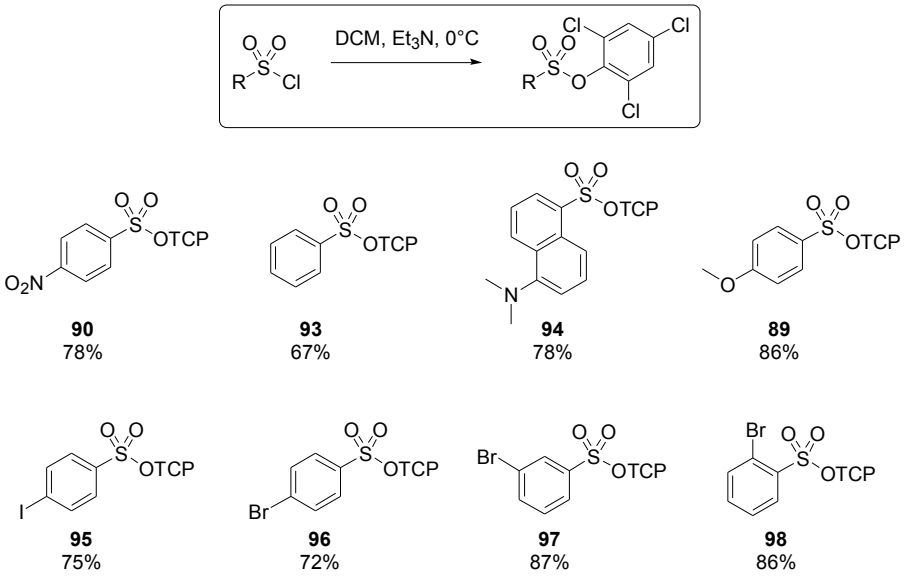

**Scheme 23**

| Entry | R | Heating | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Me | Thermal | 85 | 4.5 | 51 |
| 2 | OMe | Thermal | 85 | 6 | 66 |
| 3 | $NO_2$ | Thermal | 65 | 1.5 | 83 |
| 4 | Me | Microwave | 85 | 1 | 68 |
| 5 | OMe | Microwave | 85 | 1 | 66 |

**Table 2** Previous sulfonamide synthesis from TCP sulfonates

## 2.2 Synthesis of 2,4,6-Trichlorophenyl Sulfonate Esters

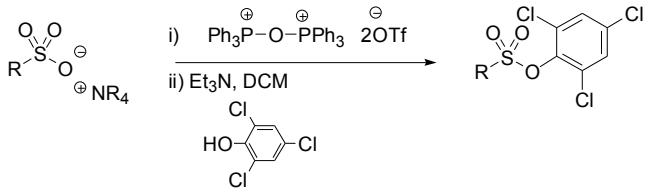
Traditionally sulfonamides and sulfonate esters are synthesised by the reaction of the appropriate amine or alcohol with a sulfonyl chloride.[102] This route was employed in the synthesis of a selection of TCP sulfonate esters required in order to explore the optimal conditions for aminolysis (Scheme 24).




**Scheme 24** Synthesis of TCP sulfonates from sulfonyl chlorides

It is counterintuitive to use sulfonyl chlorides in order to synthesise alternative sulfonamide precursors and so another route was required. The direct synthesis of PFP sulfonate esters from sulfonic acids *via* their activation by triphenylphosphine

ditriflate is now well established, and so it follows that this route should be practicable for the synthesis of TCP sulfonyl esters.[96] This procedure was successfully used in the synthesis of TCP tosylate (**88**) from the pyridinium tolyl sulfonate in a 69% yield. In order to test the generality of this route it was used to synthesise a range of sulfonate esters, and all were obtained in moderate to good yields (Scheme 25, Table 3).




**Scheme 25**

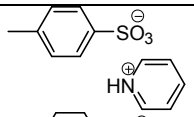
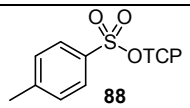
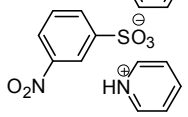
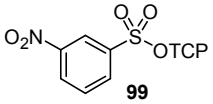
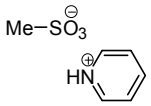
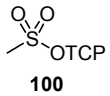
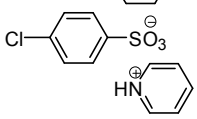
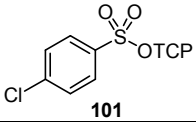
| Entry | Sulfonic acid salt | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  **88** | 69 |
| 2 |  |  **99** | 72 |
| 3 |  |  **100** | 44 |
| 4 |  |  **101** | 80 |

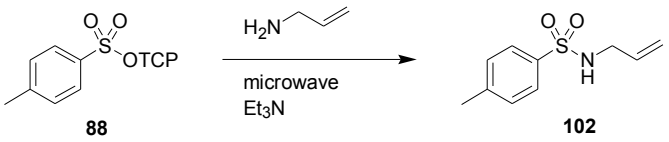
**Table 3** Synthesis of TCP sulfonate esters from sulfonic acids

# 2.3 Aminolysis of Trichlorophenyl Sulfonate Esters

## 2.3.1 Microwave Conditions

With the concept verified and a selection of TCP sulfonate esters synthesised the optimum conditions for the aminolysis reaction could be investigated. The reaction between TCP tosylate (**88**) and allylamine under microwave irradiation was selected for initial studies (Scheme 26). At first the reaction was carried out in DMF but under the microwave conditions dimethylamine was liberated and this reacted with the TCP tosylate (**88**). This resulted in a reduced yield of the desired sulfonamide **102** and *N*-dimethyl 4-methylbenzenesulfonamide was generated as a side product. It has been shown for the PFP sulfonate esters that the reaction is more efficient with increasing solvent polarity and therefore NMP was chosen as an alternative to DMF,

thus eliminating the liberation of dimethylamine but retaining a similar polarity.[93] In NMP the reaction failed to proceed to completion after 60 min at 85 °C and consequently the temperature was raised to 140 °C. At this temperature the reaction time could be reduced to 10 min and the sulfonamide **102** was obtained in the best yield (Table 4).




**88** **102**

**Scheme 26**

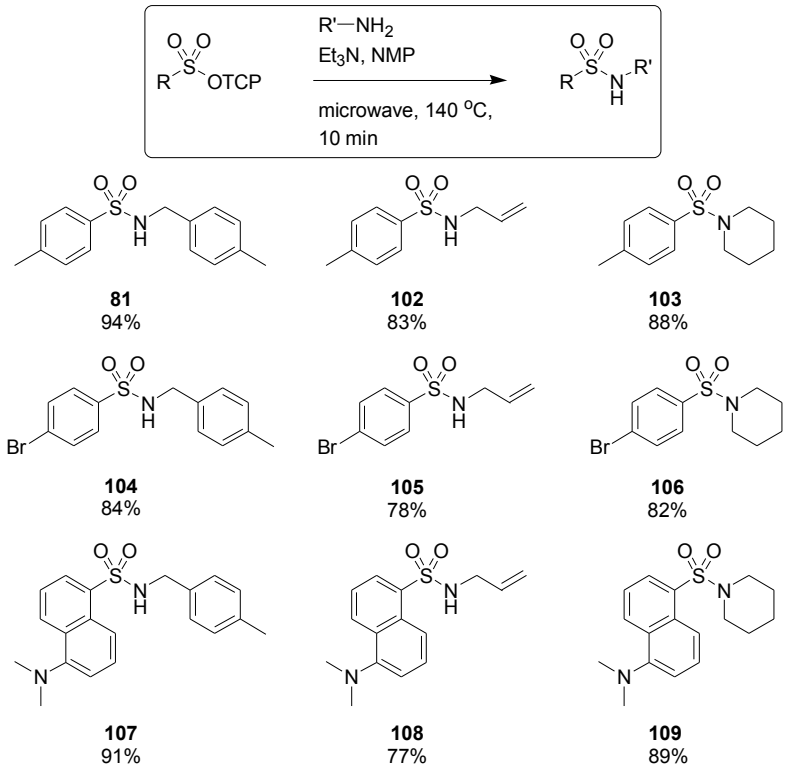
| Entry | Temperature (°C) | Solvent | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | 85 | DMF | 60 | 56 |
| 2 | 85 | NMP | 60 | 50 |
| 3 | 140 | NMP | 60 | 83 |
| 4 | 140 | NMP | 20 | 91 |
| 5 | 140 | NMP | 10 | 83 |

**Table 4** Optimisation of microwave conditions for aminolysis

With these optimised conditions the reaction of 4-methylbenzylamine with the TCP tosylate was carried out to furnish the desired sulfonamide (**81**) in a 78% yield.

The reactions were worked up by diluting with dichloromethane and washing with 2M sodium carbonate solution, 2M hydrochloric acid and water. Unfortunately, these reagents were not effective for complete removal of the trichlorophenol and NMP, and consequently column chromatography was required to purify the final compounds. However, by changing the solvent from dichloromethane to diethyl ether and using 10% aqueous lithium chloride solution instead of water the products only needed to be passed through a plug of silica. The reaction of 4-methylbenzylamine with TCP tosylate (**88**) was repeated and worked up using this improved method and gave the product (**81**) in a 94% yield (Scheme 26).

In order to test the scope of the optimised procedure the range of substrates was extended and most of the desired sulfonamides were obtained in excellent yields (Scheme 25). Unfortunately, when the less nucleophilic aniline was used no reaction occurred under these conditions.



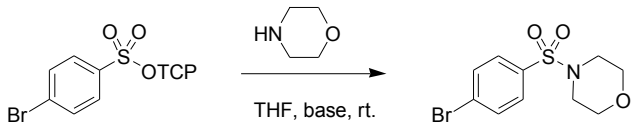

**Scheme 25** Aminolysis of TCP sulfonates

## 2.3.2 Investigation of Bases

It has so far been demonstrated that when triethylamine is used under microwave conditions the aminolysis proceeds in good yields for most amines but the reactions of the less nucleophilic amines (e.g. aniline) have been problematic. When the reaction times were increased the reaction failed to go to completion after ~4 h in the microwave, and upon increasing the temperature poor yields were obtained due to decomposition. This indicated that other bases and/or solvents should be explored.

The reaction between morpholine and 4-bromobenzene TCP sulfonate ester (**96**) was chosen to examine the use of alternative bases (Scheme 27). Morpholine is a very good nucleophile and so it was hypothesised that the reaction should proceed to completion at a reasonable rate for comparison of the various bases. The bases selected were 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), lithium hexamethyldisilazide (LiHMDS) and also DBU with the catalyst *tetra*-butyl ammonium chloride (TBAC), as used previously with PFP sulfonate esters (see section **1.2.3.2**).

The reactions were carried out at room temperature in THF using 1.1 eq of morpholine and 1.5 eq of base (Scheme 27). All reactions proceeded to completion at different rates and each gave excellent yields (Table 5).




**96** **110**

**Scheme 27**

| Entry | Base | Catalyst | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $Et_3N$ | N/A | 64 h | 90 |
| 2 | DBU | N/A | 18 h | 85 |
| 3 | DBU | TBAC | 1 h | 91 |
| 4 | LiHMDS | N/A | 15 min | 97 |

**Table 5**

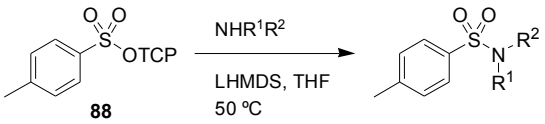
The choice of base had a marked impact on the rate of reaction, which followed the trend: $Et_3N$ < DBU < DBU + TBAC <LiHMDS. LiHMDS gave the fastest rate and the best yield.

### 2.3.2.1 Studies with Lithium Hexamethyldisilazide

Having demonstrated the reactivity of LiHMDS in the synthesis of sulfonamide **110** its general applicability and scope in the aminolysis conditions needed to be explored. Morpholine is a very good nucleophile and thus the conditions were modified so that they were appropriate for less nucleophilic amines. In order to get the reactions to proceed at a reasonable rate they were carried out at 50 ºC with 2 eq of amine and 2 eq of LiHMDS (Scheme 28). At lower temperatures and/or with reduced base the reactions did not reach completion even after 3 days.

The sulfonamides were obtained in good yield (Table 6), of particular note were the reaction rates and yields from the reactions with aniline, *N*-methylaniline and *tert*-butylamine (Table 6, Entries 4-6). Aniline had previously proven particularly problematic when reacting with TCP sulfonates using triethylamine under microwave conditions. In addition, anilines and the sterically hindered *tert*-butylamine were known to react slower and less efficiently with PFP sulfonate esters.[95, 103] For aniline the best yield achieved with triethylamine was 61% and high

temperatures (200 ºC) were required whilst with LiHMDS the reaction goes to completion at 50 ºC with a 78% yield (Table 6, Entry 5).




**Scheme 28**

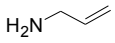
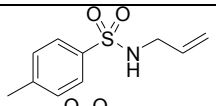
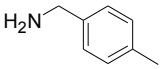
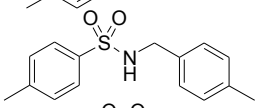
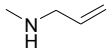
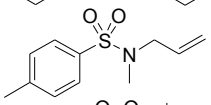
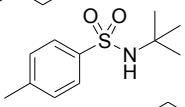
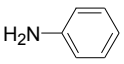
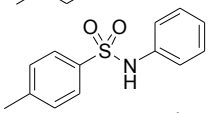
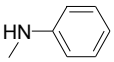
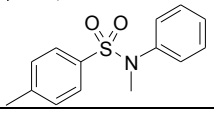
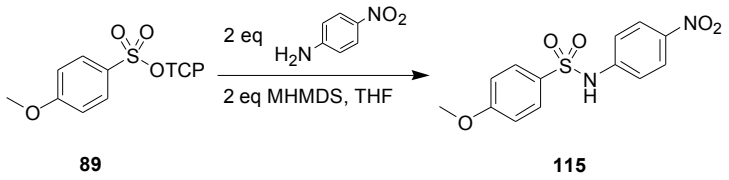
| Entry | Amine | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | 4 |  **102** | 69 |
| 2 |  | 4 |  **91** | 72 |
| 3 |  | 4 |  **111** | 51 |
| 4 |  | 18 |  **112** | 75 |
| 5 |  | 4 |  **113** | 78 |
| 6 |  | 6 |  **114** | 92 |

**Table 6**

These initial results were promising but before expanding the range of substrates the different counterions of HMDS were compared to see if any improvement on reactivity could be obtained. The reaction between 4-methoxybenzene 2,4,6-trichlorophenylsulfonate ester (**89**) and 4-nitroaniline was used to compare the reactivity of lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS) and potassium hexamethyldisilazide (KHMDS) (Scheme 29). When LiHMDS was used a homogenous solution was formed and the reaction proceeded to completion after 4 h, whilst with NaHMDS the reaction mixture was a suspension and completion was achieved after 24 h. A viscous suspension was formed with KHMDS as the base, which caused problems with stirring and the reaction remained incomplete after 28 h. The difference in the consistency of the reaction mixtures is believed to have had an influence on reactivity.



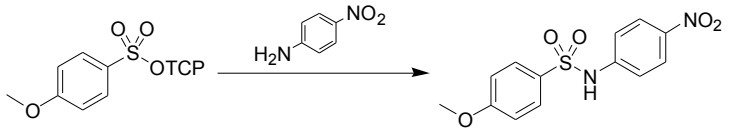

89 115

**Scheme 29**

LiHMDS had been shown to be the give the fastest rate and had the added advantage of producing a homogenous solution, which is easier to handle than a suspension.

As previously mentioned anilines have so far proven to be difficult substrates not only in the reaction with TCP sulfonate esters but also with the more reactive PFP analogues.[95] With this in mind it was considered important to fully investigate the range of anilines that could be used by synthesising a small array of sulfonamides. In order to do this three TCP sulfonate esters with differing electrophilicities: 4-nitrobenzene TCP sulfonate ester (**90**), benzene TCP sulfonate ester (**93**) and 4-methoxybenzene TCP sulfonate ester (**89**) and a range of anilines were chosen.

Before synthesising the library the reaction conditions needed to be optimised and so with this in mind the most conceptually difficult reaction, between the least electrophilic sulfonate ester, 4-methoxybenzene TCP sulfonate ester (**89**), and the least nucleophilic aniline, 4-nitroaniline, was investigated. There were initial problems with the work-up of this reaction because the basic wash (saturated sodium carbonate solution) failed to remove the trichlorophenol and additionally the aniline could not be removed by an acidic wash. Unfortunately, the aniline co-eluted with product **115** in all the TLC systems tried and so column chromatography was futile. In order to eliminate the problem of separating the excess aniline from sulfonamide **115** the number of equivalents used was reduced, initially to 1.1 eq. With 1.1 eq of aniline and 2 eq LiHMDS in THF at 50 °C the reaction took 21 h and even using this small excess of aniline there was difficulty with its removal. Therefore, microwave conditions were investigated which, would allow smaller amounts of aniline to be used without resulting in prohibitively long reaction times (Table 7). The optimal microwave conditions were found to be 120 °C for 30 min with 0.85 eq aniline and 2 eq LHMDS in THF (Table 7, Entry 7), and column chromatography was required to purify the crude products.



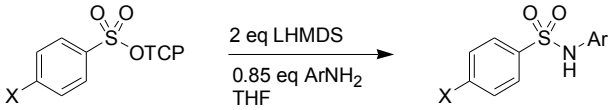

**89** **115**

**Scheme 30**

| Entry | Aniline eq | Microwave/ Thermal | Temperature (°C) | Time | LCMS result | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 2 | Thermal | 50 | 4 h | | |
| 2 | 1.1 | Thermal | 50 | 21 h | 9% aniline | 57 |
| 3 | 1.1 | *MW* | 80 | 10 min | 11% TCP sulfonate ester | |
| 4 | 1.1 | *MW* | 100 | 15 min | 6% TCP sulfonate ester | |
| 5 | 1.1 | *MW* | 100 | 30 min | 2% aniline | |
| 6 | 0.9 | *MW* | 100 | 30 min | 4% aniline | |
| 7 | 0.85 | *MW* | 120 | 30 min | 1% aniline | 47 |

**Table 7**

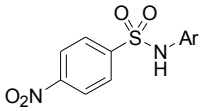
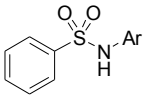
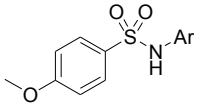
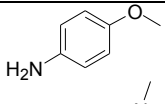
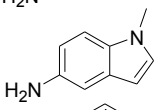
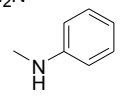
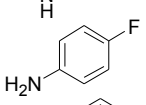
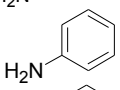
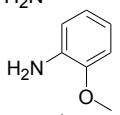
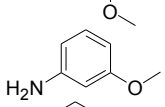
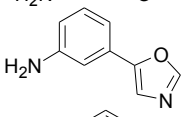
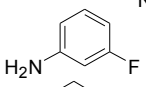
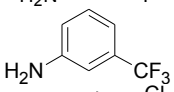
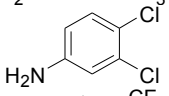
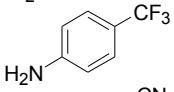
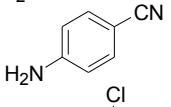
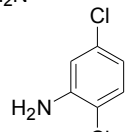
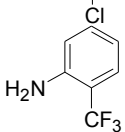
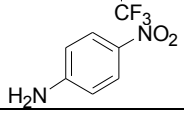
With the conditions established the arrays could be synthesised. Most reactions gave moderate to excellent yields of the desired product with the whole range of anilines reacting with generally a high level of success (Table 8).




**90**, X=$NO_2$
**93**, X=H
**89**, X=OMe

**116**, X=$NO_2$
**117**, X=H
**118**, X=OMe

**Scheme 31**

| | Aniline |  **116** |  **117** |  **118** |
|---|---|---|---|---|
| a |  | 51% | 70% | 61% |
| b |  | 31% | 85% | - |
| c |  | - | 79% | 90% |
| d |  | 75% | 80% | 89% |
| e |  | 70% | 96% | 86% |
| f |  | 70% | 89% | 72% |
| g |  | 70% | 80% | 90% |
| h |  | 64% | 35% | 66% |
| i |  | 77% | 98% | 61% |
| j |  | 74% | 88% | 89% |
| k |  | 74% | 89% | 85% |
| l |  | 27% | 41% | - |
| m |  | 62% | 85% | 84% |
| n |  | 88% | 82% | 97% |
| o |  | 70% | - | - |
| p |  | - | - | 61%[a] |

[a] compound **115**

**Table 8** Reactions of anilines with TCP sulfonates

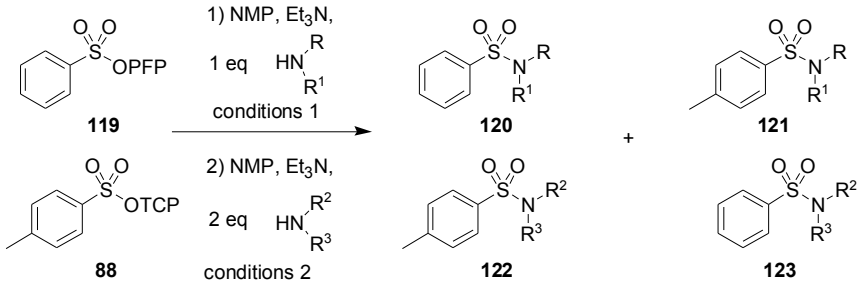
A number of reactions did not go to completion under the array conditions and for these the product was not isolated due to the difficultly in removing the unreacted

aniline. 4-Methoxybenzene TCP sulfonate (**89**) failed to react to completion with 5-amino-*N*-methylindole, 2-trifluoromethylaniline and 4-trifluoromethylaniline (Table 8, entries 118b, 118l and 118o). This is thought to be due to the electron rich nature of the TCP sulfonate ester **89**, and with 2-trifluoromethylaniline there is the added problem of possible steric hindrance of the trifluoromethyl group. In the synthesis of **116p** and **117p** all the sulfonate ester had been consumed (by LCMS) yet there was still some aniline present and this could not be removed by column chromatography due to co-elution with the product. The presence of the aniline indicated the decomposition of the starting TCP ester before the aniline had reacted completely.

One unusual result was in the reaction between 4-nitrobenzene TCP sulfonate ester (**90**) and *N*-methylaniline (Table 8, Entry 116c). Under the array conditions no product (**116c**) or starting material could be isolated and by LCMS the reaction mixture had numerous peaks present suggesting that side reactions and/or decomposition under the microwave conditions was occurring. When heating thermally at 50 °C and even performing the reaction at room temperature the starting material was consumed within two hours to give a similar LCMS trace, therefore suggesting that unwanted side reactions were occurring.

## 2.4 Selectivity

Having established the reactivity of TCP sulfonate esters the next step was to compare the reactivity and selectivity of amines towards a mixture of TCP and PFP sulfonate esters. This approach was used to ascertain whether an amine would react preferentially with the PFP sulfonate ester in the presence of a TCP sulfonate ester. This was achieved by taking an equimolar mixture of these sulfonate esters and sequentially treating them to amines under different conditions (Scheme 32). The idea was that the first amine would react with the PFP sulfonate ester and the second with the TCP sulfonate ester. Thus, with complete selectivity only products **120** and **122** would be synthesised (Scheme 32).




**Scheme 32**

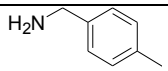
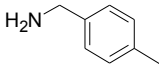
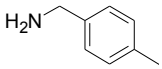
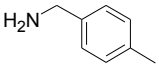
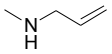
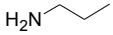
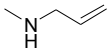
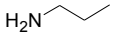
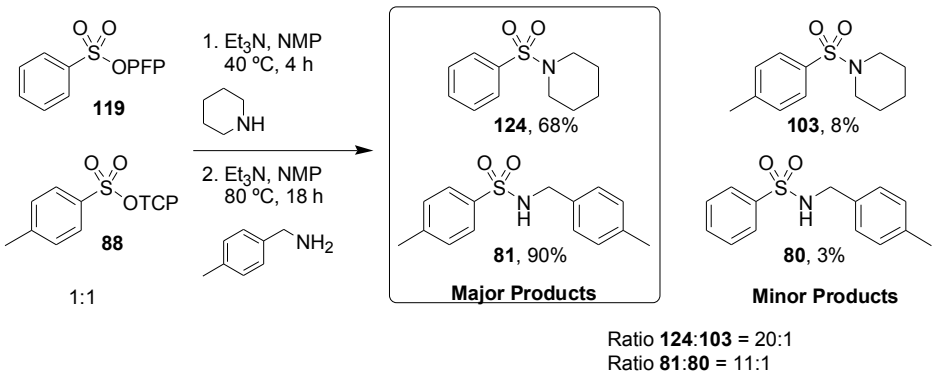
| | Amine 1 | Amine 2 | Conditions 1 | Conditions 2 | Ratio 120:121 | Ratio 122:123 |
|---|---|---|---|---|---|---|
| 1 |  |  | 50 ºC, 1 h | 100 ºC, 3 h | 30:1 | 5:1 |
| 2 |  |  | 40 ºC, 4 h | 100 ºC, 3 h | 15:1 | 15:1 |
| 3 |  |  | rt, 30 h | 80 ºC, 18 h | 20:1 | 13:1 |
| 4 |  |  | 40 ºC, 4 h | 80 ºC, 18 h | 20:1 | 11:1 |
| 5 |  |  | 50 ºC, 2 days | 80 ºC, 18 h | 9:1 | 11:1 |
| 6 |  |  | rt, 1 eq TBAC, 4 h | 70 ºC, 18 h | 10:1 | 10:1 |

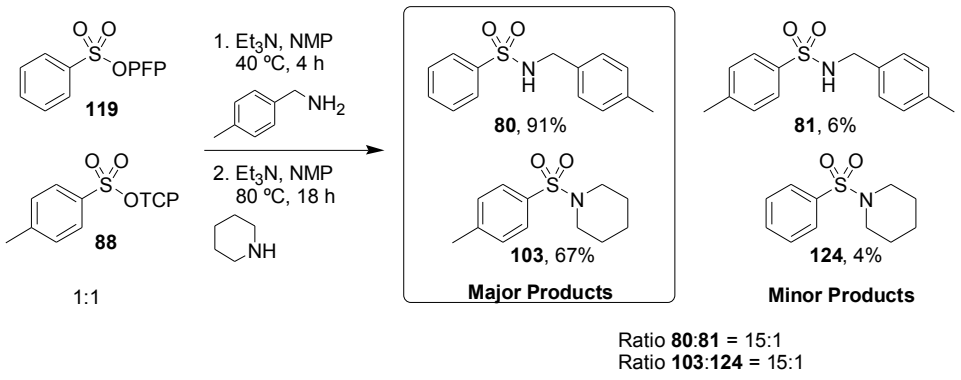
**Table 9**

A 1:1 mixture of TCP tosylate (**88**) and PFP benzene sulfonate (**119**) was initially treated with one equivalent of 4-methylbenzylamine and heated to 50 °C for 1 h and then one equivalent of piperidine was added and the mixture was heated to 100 °C for 3 h (Table 9, Entry 1). The crude $^{1}$H NMR spectrum showed that the 4-methyl benzylamine had reacted, as expected, preferentially with the benzyl PFP sulfonate to give a 30:1 mixture of **120** (R = 4-methylbenzyl, $R^1$ = H, **80**): **121** (R = 4-methylbenzyl, $R^1$ = H, **81**) and the piperidine had reacted to give a 5:1 mixture of **122** ($R^2$ = $R^3$ = cyclohexyl, **103**): **123** ($R^2$ = $R^3$ = cyclohexyl, **124**). This looked promising as it showed that the amine did react preferentially with the PFP sulfonate but the poor selectivity of the reaction with piperidine indicated that not all the PFP sulfonate ester had been fully consumed in the initial aminolysis reaction and so a longer reaction time was required.

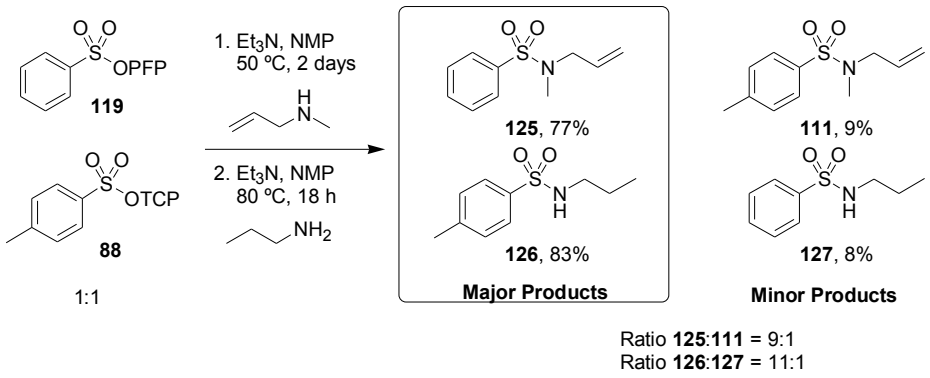
In an effort to increase the selectivity the initial temperature was reduced and 40 ºC was found to be optimal (Table 9, Entry 2). Reducing the temperature to 20 ºC gave minimal advantage in selectivity and increased the reaction time from 4 h to 30 h (Table 9, Entry 3). The addition of TBAC as a catalyst allowed the first reaction to proceed at room temperature with an increased reaction rate but gave no change to the selectivity (Table 9, Entry 6), and so gave no advantage over heating. Adding two equivalents of the second amine helped ensure the completion of the second aminolysis. When the order of amine addition was changed good selectivity was still seen (Table 9, Entry 4). With the conditions in place two different amine sequences were tried and these also gave the desired products with good selectivity and yields (Scheme 33, Scheme 34 and Scheme 35).




**Scheme 33**

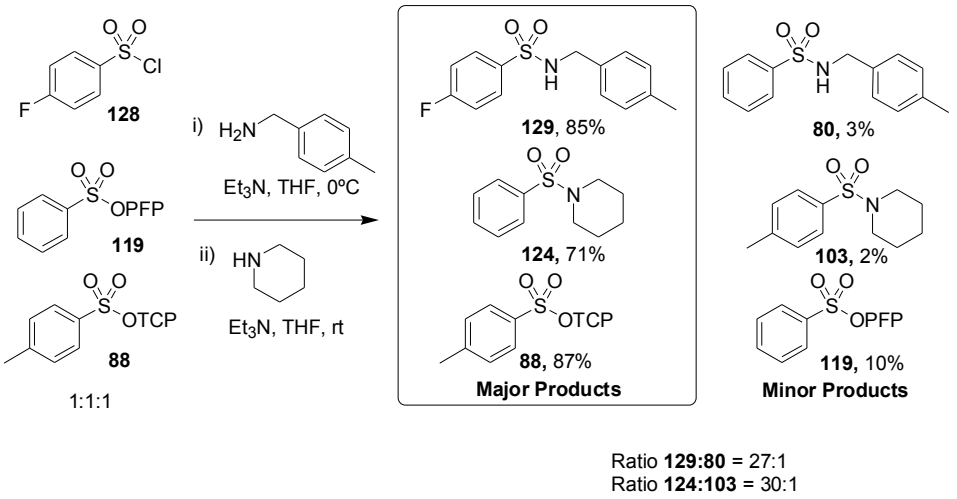



**Scheme 34**




**Scheme 35**

Having established the selectivity between the PFP sulfonate ester and TCP sulfonate ester it seemed a natural extension of this to also explore the selectivity between a sulfonyl chloride, PFP sulfonate ester and TCP sulfonate ester. The approach to this was to take an equimolar mixture of 4-fluorobenzenesulfonyl chloride (**128**), benzene PFP sulfonate ester (**119**) and 4-methylbenzene TCP sulfonate ester (**88**) and to sequentially expose this to 4-methylbenzylamine at 0°C and then piperidine at room temperature (Scheme 36). This was in the expectation that 4-fluoro-*N*-(4-methyl-benzyl)-benzenesulfonamide (**129**) and 1-benzenesulfonylpiperidine (**124**) would be formed and that 4-methylbenzene TCP sulfonate ester (**88**) would be recovered. The 4-methylbenzylamine had reacted with a small quantity of the PFP sulfonate ester (**88**) to give a 27:1 mixture of sulfonamides **129**:**80** and with the piperidine a 30:1 mixture of the PFP derived sulfonamide (**124**): TCP derived sulfonamide (**103**) was obtained. 87% of 4-methylbenzene TCP sulfonate ester (**88**) and 10% of the PFP sulfonate ester (**119**) was recovered. Overall the desired compounds were obtained as the major products in excellent selectivity and yields.




**Scheme 36**

## 2.5 Conclusions

In conclusion a new class of activated sulfonate ester has been described and it was demonstrated that they could be synthesised directly from the sulfonic acid salts using the activating agent triphenylphosphine ditriflate. This avoids the need to use sulfonyl chlorides. An efficient and high yielding method of synthesising aryl sulfonamides from these TCP sulfonates under microwave conditions has been developed, which would allow sulfonamide libraries to be rapidly synthesised. Unfortunately this protocol failed for less nucleophilic amines such as aniline and so an alternative method was established. The use of LHMDS allows anilines to react with the TCP sulfonate esters under microwave conditions to give the resultant sulfonamides in good yields. This was demonstrated by the synthesis of three small libraries of sulfonamides.

The differing reactivity of the PFP and TCP sulfonates was investigated, and amines were shown to react selectively with a PFP sulfonate ester in the presence of a TCP sulfonate ester. This idea was expanded on and the differing reactivities of a sulfonate chloride, a PFP sulfonate and a TCP sulfonate were exploited in selective sulfonamide formation.

Overall, TCP sulfonate esters have been identified as a new class of activated sulfonate ester that can be employed in the synthesis of sulfonamides utilising both simple nucleophilic amines and more challenging anilines and hindered amines. The issues of cost of pentafluorophenol have been addressed with 2,4,6-trichlorophenol

being at least ten times less expensive. Finally, the perceived problems with polyfluorinated aromatics have also been avoided by use of the TCP sulfonates.

# Chapter Three

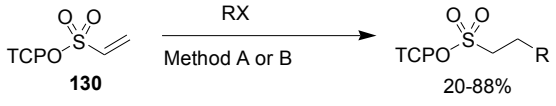
# Synthetic Manipulation of TCP Sulfonates

## 3.1 Introduction

In Chapter 2 the reactivity and selectivity of TCP sulfonates was established demonstrating the greater stability of TCP sulfonates in comparison to PFP sulfonates and sulfonyl chlorides. It is now desirable to elucidate whether this improved stability allows more diverse reactions to be performed in its presence, thus providing access to a wide range of functionalised sulfonates as intermediates for synthesis.

Section 1.2.3.4 summarised the range of reactions performed with the PFP sulfonate *in situ*, thus demonstrating the versatility of PFP sulfonates. There are those transformations which leave this moiety intact allowing for their conversion to sulfonamides, for example radical additions and isoxazolidine synthesis, or those as in the case of sultam synthesis which involve the sulfonate in the preparation of valuable highly substituted compounds.[98, 99, 104] There are limitations to their versatility as shown by the failure of cycloadditions of vinyl PFP sulfonate with azides and nitrile oxides and of the Heck and metathesis reactions of the same compound.[103]

Within the Caddick group, parallel to this project, the application of the majority of the successful reactions to the TCP sulfonates has been explored. Intermolecular radical additions to TCP vinylsulfonate (**130**) using tin mediated (Scheme 37, Method A) and tin-free conditions (Scheme 37, Method B) have been carried out to give the alkyl sulfonates in good yields.[105]




Method A = AIBN, $Bu_3SnH$, MePh, 110 °C, 2h
Method B = EPHP, $BEt_3$, air, DCM, 0 °C, 10 min
X = Br or I

**Scheme 37** Intermolecular radical addition reactions [105]

Also, the TCP vinyl sulfonates have been shown to undergo cycloaddition reactions to give isoxazolidines in good yields.[106]

This chapter describes alternative reactions that have been attempted in the preparation of novel aromatic TCP sulfonates.

## 3.2 Palladium Reactions

Palladium-catalysed cross-coupling reactions provide an efficient approach to carbon-carbon bond formation in organic chemistry.[107] They have elicited considerable attention resulting in the discovery and use of a broad variety of catalysts and ligands in the synthesis of natural products and pharmaceuticals.[108-111]

### 3.2.1 Suzuki-Miyaura Reactions

The Suzuki-Miyaura reaction is a general and powerful synthetic method for the C-C cross coupling of an aryl halide with a boronic acid and is widely used in the synthesis of compounds in drug discovery.[112-114] Sulfonyl chlorides have been reported to undergo Suzuki cross-coupling reactions with aryl boronic acids whereby the sulfonyl chloride moiety behaves as a pseudo-halide leaving group.[115] Avitabile *et al.* have shown that the PFP sulfonate group is stable to the basic conditions of the Suzuki-Miyaura reaction and that it can then be further manipulated to give the sulfonamides.[100] This led to investigations into whether Suzuki reactions can also be performed in the presence of a TCP sulfonate ester.

Considering the success of the conditions used for the PFP sulfonates by Avitabile *et al.* these were a natural starting point.[100] When this protocol was utilised for the Suzuki reaction between 4-bromobenzene TCP sulfonate ester (**96**) and 4-methoxybenzene boronic acid the desired product (**131**) was obtained as a white solid in a 87% yield. What was particularly of note was that this was an improvement on the 71% yield obtained for the analogous reaction with the 4-bromobenzene PFP sulfonate ester. Due to this excellent result these conditions were applied to other Suzuki reactions, firstly with 4-bromobenzene TCP sulfonate ester (**96**) and then with 3-bromobenzene TCP sulfonate ester (**97**) to give the products (**131**-**143**) in good yields (Figure 26). Both aromatic and heterocyclic boronic acids reacted with the only failure being 2,4-dimethylphenyl boronic acid, which was probably due to the steric hindrance imposed by the methyl groups.

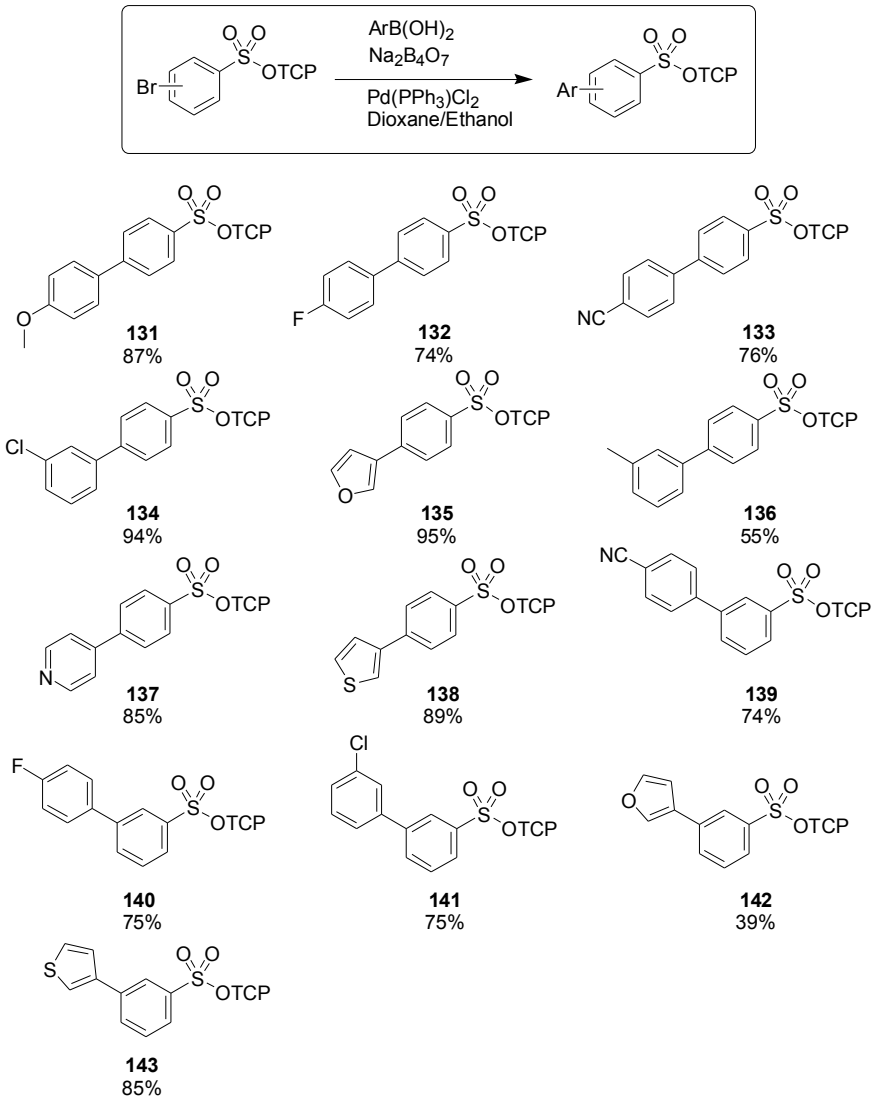
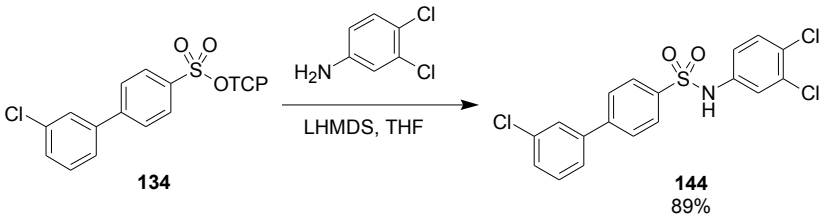


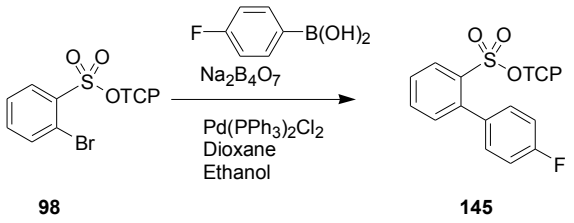

**Figure 26**

One of the Suzuki products (**134**) was selected and an aminolysis reaction was tried using the conditions developed in section 2.3.3.1. This gave the desired sulfonamide **144** in an 89% yield.




**Scheme 38**

Due to the success with 3- and 4-bromobenzene TCP sulfonate the Suzuki reactions were attempted with 2-bromobenzene TCP sulfonate (**98**) (Scheme 39).




**98** **145**

**Scheme 39**

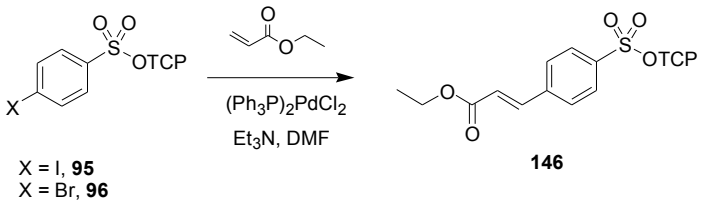
The reaction between 4-fluorobenzene boronic acid and 2-bromobenzene TCP sulfonate (**98**) was attempted. After 22 h stirring at reflux the LCMS showed the presence of bromide (**98**). The addition of another 3 mol% of catalyst and further heating did not lead to a significant progression in the reaction with the LCMS showing bromide (**98**) was still present. The reaction was worked up and purification was attempted using column chromatography, this yielded 520mg of a 3:1 inseparable mixture of the desired product (**145**) and the TCP sulfonate (**98**). At this point a different catalyst dichlorobis(tri-*o*-tolylphosphine) palladium was employed in an effort to drive the reaction to completion. Unfortunately after 14 h of heating at reflux the LCMS showed several peaks including bromide (**98**) and TCPOH. The presence of TCPOH indicated that decomposition of the bromide (**98**) or possibly the coupled product (**145**) was occurring. Bromide (**98**) is much more hindered than the 3- and 4-bromo compounds, which would explain the difficulty in getting this reaction to go to completion.

## 3.2.2 Heck Reactions

The arylation of olefins, Heck reaction, has been shown to be another powerful use of palladium catalysis with applications in many diverse areas of chemistry including natural product synthesis[116] and bioorganic chemistry.[117] With this in mind the Heck reaction seemed an ideal transformation to investigate for its utility in the presence of a TCP sulfonate ester.

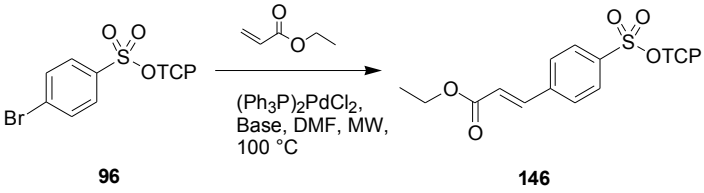
To give continuity with the Suzuki reaction the bis(triphenylphosphine) palladium dichloride catalyst was initially selected. 4-Iodobenzene TCP sulfonate (**95**) in DMF and treated with bis(triphenylphosphine) palladium dichloride (3 mol%), triethylamine (4 eq) and ethyl acrylate (3 eq) at 80 °C for 24 h to give the desired alkene (**146**) in a 74% yield (Scheme 40). Following this promising result attention was turned to the 4-bromobenzene TCP ester (**96**) and finding appropriate conditions for the reaction with ethyl acrylate. The amount of ethyl acrylate was reduced from 3

to 1.2 eq and microwave conditions were explored. The reaction proved to be very sensitive to temperature. When heating to 120 °C for 15 min the TLC showed several new spots indicating decomposition was occurring and when the temperature was reduced to 80 °C no reaction occurred. At 100 °C the reaction proceeded cleanly and was complete after 30 min to give alkene **146** in a 71% yield.




**Scheme 40**

With these encouraging results the next step was to study the effect of different bases on the rate of the reaction. As it is difficult to monitor when a microwave reaction has gone to completion all reactions were carried out for a specific time. They were then worked up to isolate the product and determine how far the reaction had proceeded. The conditions chosen for this were 100 °C for 10 min using 3 mol% bis(triphenylphosphine) palladium dichloride, 1.2 eq of ethyl acrylate and 2 eq of base in DMF.




**Scheme 41**

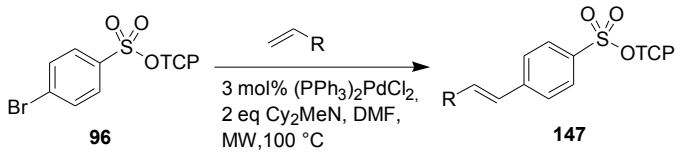
| Entry | Base | Yield (%) |
|---|---|---|
| 1 | $Et_3N$ | 22 |
| 2 | $^{n}Bu_3N$ | 8 |
| 3 | $Cy_2MeN$ | 46 |
| 4 | $Cy_2MeN$ + AgOTf | Fail |
| 5 | $K_2CO_3$ | 28 |
| 6 | $Cs_2CO_3$ | 32 |
| 7 | $K_2CO_3$ + TBAC | Fail |
| 8 | $Cs_2CO_3$ + AgOTf | 44 |

**Table 10**

The bases selected were triethylamine, tri-*n*-butylamine, methyldicyclohexylamine, potassium carbonate and caesium carbonate. Silver salts have been demonstrated to improve Heck reactions by complexing to the halide and thus facilitating oxidative

cleavage.[118] Therefore, silver triflate was tried in combination with the two best bases, methyldicyclohexylamine and caesium carbonate. Tri-*n*-butylamine (Table 10, Entry 2) was the least effective base, giving the lowest yields, whilst the reactions in which methyldicyclohexylamine (Table 10, Entry 3) were employed seemed to proceed at the fastest rate. Although similar results were seen for methyldicyclohexylamine and caesium carbonate with silver trifluoroacetate (Table 10, Entries 3 and 8 respectively) the former was chosen as the preferred base.

With the optimised conditions (Scheme 42) in place it was now suitable to expand the substrate range. Initially, the reaction with ethyl acrylate was carried out to completion to give the desired product (**146**) in a 73% yield (Table 11). The reaction with cyanoacrylate gave the product (**148**) in a 37% yield and the reaction with styrene gave the product (**149**) in a 51% yield (Table 11).




**Scheme 42**

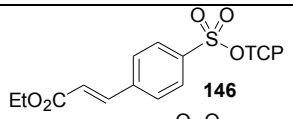
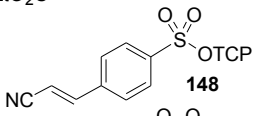
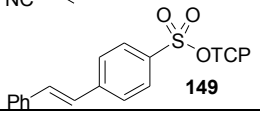
| R | Time (min) | Product | Yield (%) |
|---|---|---|---|
| EtO | 20 |  **146** | 73 |
| NC | 30 |  **148** | 37 |
| Ph | 150 |  **149** | 51 |

**Table 11**

Thus far, palladium reactions of bromoaryl TCP sulfonate esters have been investigated and the Suzuki reactions shown to proceed in good yields when using 3- and 4-bromobenzene TCP sulfonate ester. Unfortunately the coupling reactions with 2-bromobenzene TCP sulfonate ester (**98**) proved more difficult and did not proceed to completion. The Heck reactions were also explored and reactions with ethylacrylate, cyanoacrylate and styrene occurred in moderate to good yields.

In the search for alternative reactions for the preparation of novel aromatic TCP sulfonates it was considered advantageous to explore the possibility of performing an asymmetric transformation, hence incorporating a degree of chirality into these compounds. One such asymmetric reaction that has been studied previously within the Caddick group is dynamic kinetic resolution (DKR).

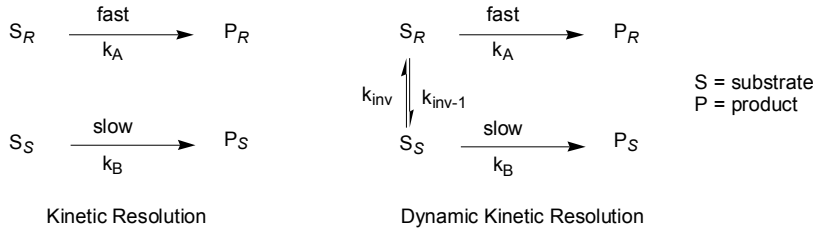
## 3.3 Dynamic Kinetic Resolution

### 3.3.1 Introduction

With the abundance of chiral natural products and biologically active compounds[119] the synthesis of chiral molecules is a significant and challenging part of organic synthesis.[120] The administration of a racemate as a pharmaceutical is undesirable as it requires higher dosing and the presence of the other enantiomer may result in adverse side effects. This has resulted in a trend towards single enantiomer drugs bringing asymmetric synthesis to the forefront of drug discovery and development.[119]

There are two major strategies in the preparation of chiral compounds: i) stereocontrolled formation of the stereogenic centre whereby the chirality is determined on formation of the chiral centre using, for example, a chiral catalyst or directed by existing chiral centres in the substrate (chiral substrate, auxiliaries); ii) resolution of a stereoisomeric mixture.

Kinetic resolution exploits the differing reactivity of the two isomers, i.e. the differing rates of formation of the two products (Scheme 43).[121, 122] If efficient one isomer will be completely converted to product whilst the other is left unchanged. This results in the maximum theoretical yield being only 50%, which limits its applications. However, dynamic kinetic resolution (DKR) overcomes this issue by combining an equilibration step of chirally labile substrates with the kinetic resolution step (Scheme 43). In order for a DKR to be effective the rate the substrates equilibrate ($k_{inv}$) must be faster than the rate of product formation ($k_A$, $k_B$), the resolution step has to be irreversible and the product should be configurationally stable under the reaction conditions.

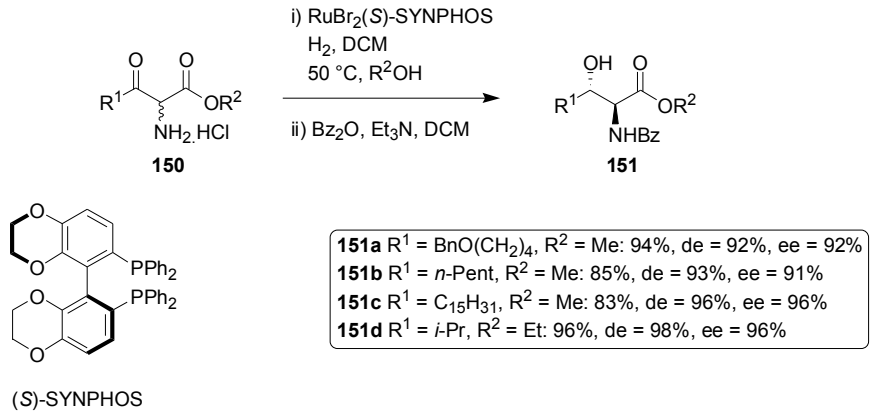



**Scheme 43** Kinetic resolution and dynamic kinetic resolution (DKR)

There are many methods of affecting DKR and these have been explored and reviewed extensively by Pellissier,[123, 124] Ward,[125] Backväll[126] and Caddick.[127] A few approaches will be highlighted herein.

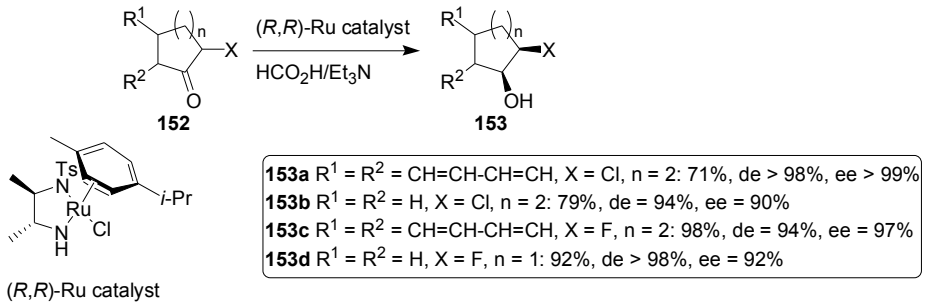
### 3.3.1.1 Chiral metal catalysts

In 1989 Noyori's group was one of the first to report the use of ruthenium-catalysed hydrogenation in the DKR of β-keto esters.[128] Since then this process has been extensively studied showing the degree of selectivity to be highly dependent upon the nature of the chiral ruthenium catalysts, reaction conditions and substrates.[129] In 2003 Genêt *et al.* developed a new atropoisomeric chiral ligand, SYNPHOS.[130] This proved effective in ruthenium-catalysed asymmetric hydrogenations and gave access to a range of optically active alcohols (**151a-d**) with ee values of up to 99% (Scheme 44).




**Scheme 44** DKR of *α*-amino-*β*-keto ester hydrochlorides

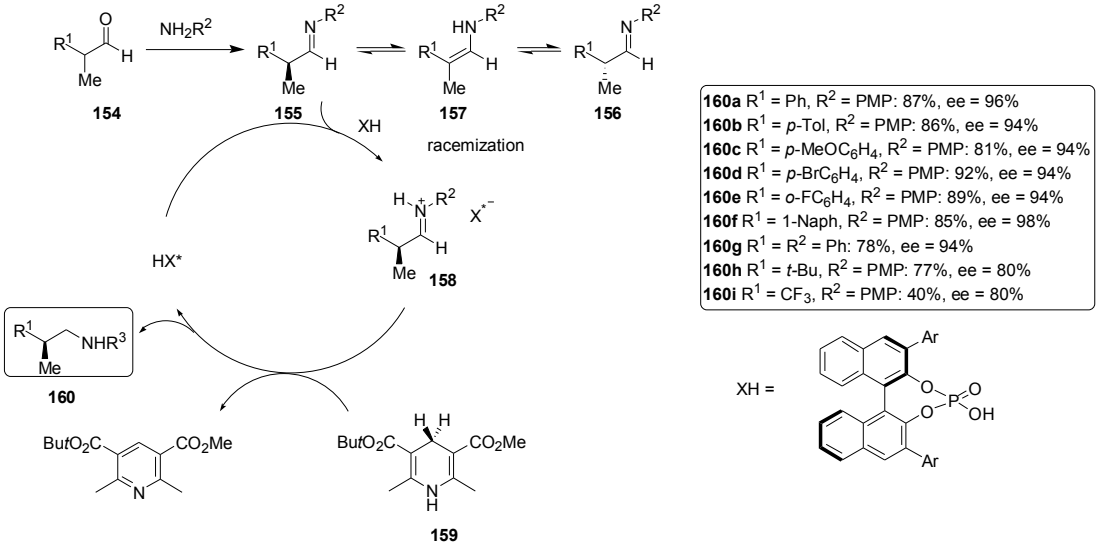
Through ruthenium-catalysed hydrogenation Lassaletta *et al.* accessed a range of chiral halohydrins (**153**) starting from the corresponding cyclic *α*-haloketones (**152**).[131] Using either $HCO_2H/Et_3N$ or $HCO_2H$/TBAB as the hydrogen source they prepared bromo-, chloro- and fluorohydrins in good yield and optical purity (Scheme 45).




**Scheme 45** Enantioselective synthesis of vicinal halohydrins *via* DKR

### 3.1.1.2 Organocatalysed DKR

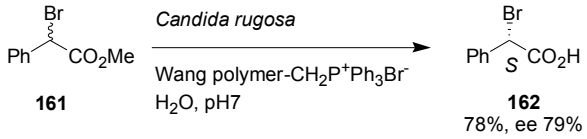
During the last few years there has been a proliferation of interest in organocatalysis and this has lead to the development of novel organocatalysed DKR processes. One such example was reported by List *et al.* whereby they developed an enantioselective reductive amination of *α*-branched aldehydes (**154**) *via* dynamic kinetic resolution. Under acidic conditions the intermediate imines (**155** and **156**) undergo facile racemisation *via* the enamine (**157**) using a BINOL phosphoric acid catalyst. The resultant iminium salt (**158**) is reduced with Hantzsch ester (**159**) to affect an overall stereoselective reduction, which thus furnishes an enantiomerically enriched product (**160**) (Scheme 46). This process was broad in scope, with both aromatic and aliphatic aldehydes being used, although the enantiomeric ratios were typically lower for simple aliphatic aldehydes (Scheme 46).[132]




**Scheme 46**

### 3.1.1.3 Enzymatic DKR

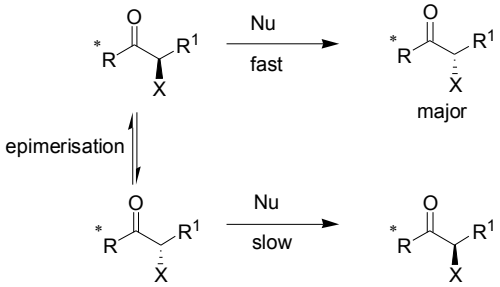
Due to the mild conditions associated with enzyme-catalysed processes enzymatic DKR is an attractive choice. Williams *et al.* have developed a DKR for the hydrolysis of $\alpha$-bromo[133] and $\alpha$-chloro esters.[134] The success of this process is due to the greater ease of racemisation of the starting ester *via* a $S_N2$ pathway than the carboxylic acid product. The resin based bromide proved to be a good bromide source and along with a commercially available enzyme, DKR was effective yielding the acid (e.g. **162**) in good yields and enantioselectivity (Scheme 47).




**Scheme 47**

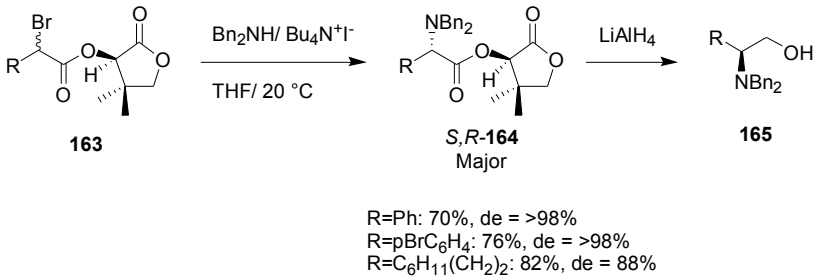
### 3.1.1.4 Configurationally labile alkyl halides

The nucleophilic displacement of the conformationally labile $\alpha$-halo carbonyl can be controlled by a chiral auxiliary adjacent to the carbonyl group (Scheme 48).[124, 135, 136] Racemisation can be induced by additives such as halide salts, bases and polar solvents. The importance of this technique is exemplified by its application in the asymmetric synthesis of a variety of $\alpha$-substituted carboxylic acid derivatives, particularly amino acids.



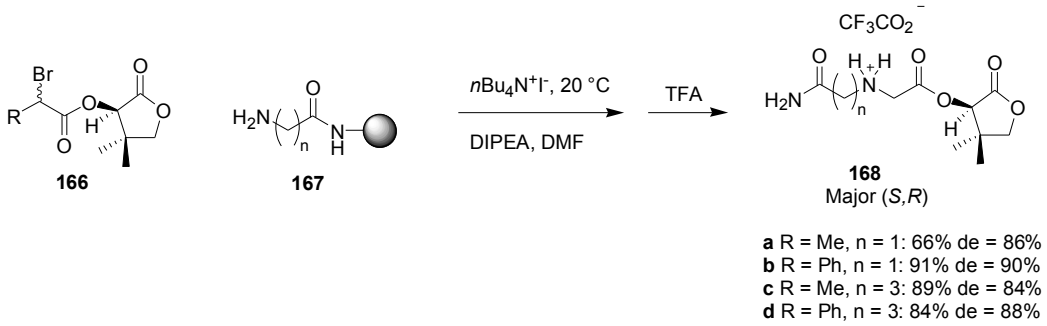

**Scheme 48** $S_N2$ reactions on configurationally labile halides

Durst *et al.* have applied this methodology in the synthesis of $\beta$-dibenzylamino alcohols (**165**) using the chiral auxiliary (*R*)-pantolactone. (*R*)-pantolactone $\alpha$-bromo esters (**163**) were treated with dibenzylamine and the epimerising agent tetrabutylammonium iodide (TBAI) to give *S,R*-**164** with good yields and selectivity (Scheme 49). [137]



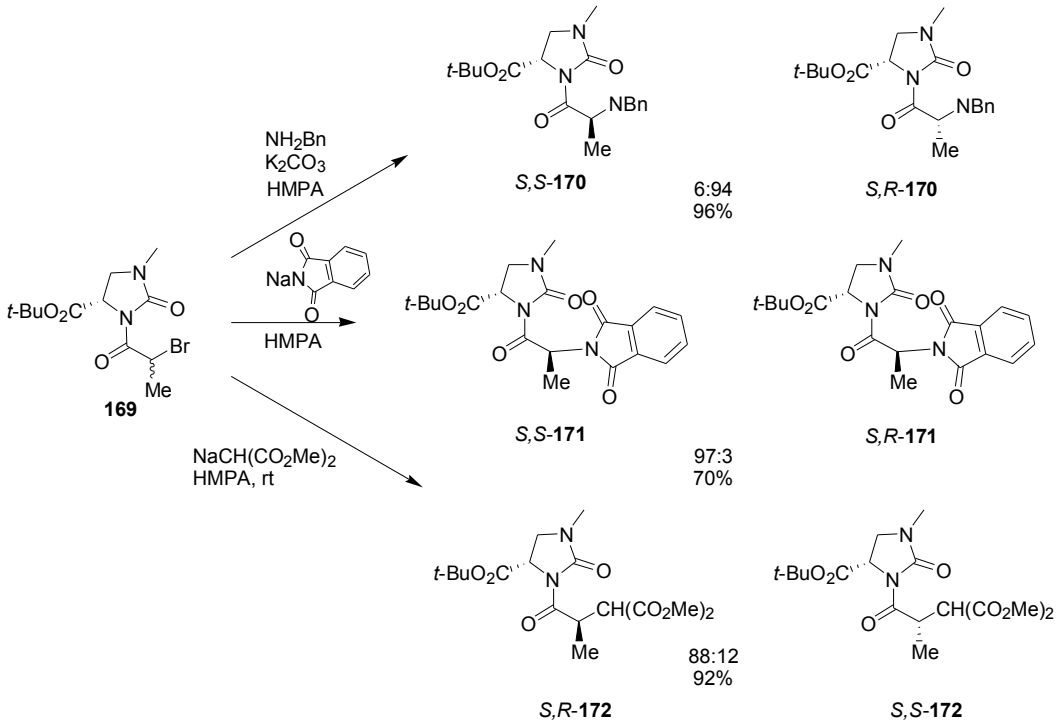

**Scheme 49** Synthesis of β-dibenzylamino alcohols using DKR

Recently Ben *et al.* have reported the first example of immobilised amine nucleophiles in DKR.[138] *α*-Bromo esters (**166**), containing (*R*)-pantolactone as the chiral auxiliary, were treated under epimerising conditions with amine nucleophiles (**167**) attached to a resin *via* an organic spacer. In comparison to the solution phase DKR superior optical purities were obtained with diastereomeric excesses ranging from 84% to 94% and yields between 66% and 98% (Scheme 50).



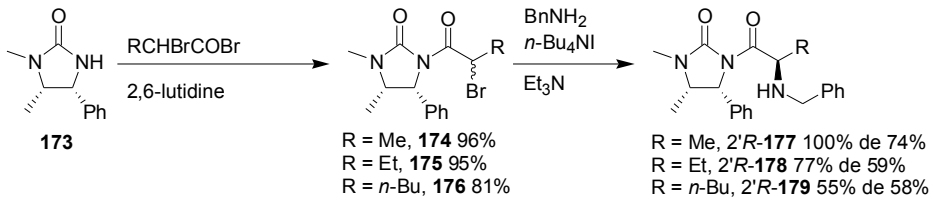

**Scheme 50** DKR using immobilised amine nucleophiles

The chiral auxiliary *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate was used by Nunami *et al.* for DKR reactions, in the stereoselective synthesis of *α*-substituted carboxylic acids. Epimerisation of the *α*-bromo substrates (**169**) was achieved under basic conditions and in the highly polar solvent HMPA. Good yields and diastereoselectivity were obtained when using both nitrogen nucleophiles, benzylamine (products *S*,*S*-**170** and *S*,*R*-**170**)[136] and sodium phthlamide (products S,S-**171** and *S*,*R*-**171**),[139] and the carbon nucleophile sodium malonate (products *S*,*S*-**172** and *S*,*R*-**170**) (Scheme 51).[140, 141] The metallated nucleophiles favour the opposite selectivity[139, 141] to the non-metallated nucleophile, benzylamine.[136] It was postulated that the attack of benzylamine was directed by hydrogen bonding to the ester group whilst the metallated nucleophiles which are unable to participate in this interaction attack from the least hindered face.[139] The products were easily converted to the corresponding *α*-amino acids and *α*-alkylsuccinic acid derivatives.




**Scheme 51**

Caddick *et al.* utilised the chiral auxiliary (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**173**) in the synthesis of amino acids *via* DKR. The imidazolidinone auxiliary **173** is readily prepared by the thermal fusion of ephedrinium chloride and urea. The required racemic $\alpha$-bromo derivatives (**174**-**176**) were synthesised by acylation of **173** with an $\alpha$-bromo acid bromide (Scheme 52).[142] Epimerisation was affected using TBAI, with THF proving to be the optimal solvent. When using benzylamine as the nucleophile the 2'*R* isomer (**177**-**179**) was obtained in good yield and selectivity.



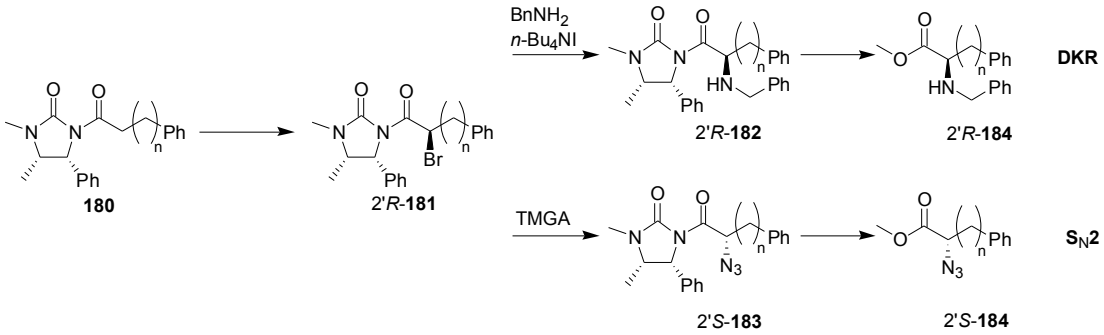

**Scheme 52**

For DKRs with the metallated nucleophile, sodium malonate, the selectivity was poor to moderate. But what was of particular note was the reversal of selectivity, in comparison to the amine nucleophile, with the major product being the 2'*R* isomer.[142]

Further exploration identified an $\alpha$-bromination protocol which allowed access to a wider range of $\alpha$-bromo substrates (Scheme 53). This enabled the DKR method to be

extended to the synthesis of a range of phenyl glycine derivatives (**184**) which were obtained in good yields and selectivity.[143]

The bromination was directed by the auxiliary to give the 2'*R*-**181** product. When this was treated with TMGA under non-epimerising conditions $S_N2$ displacement occurred to furnish 2'*S*-**183**, whilst under epimerising conditions double inversion took place and the opposite stereoselectivity was seen giving 2'*R*-**182** (Scheme 53).




**Scheme 53** Complementary DKR and substitution approach to *α*-azido/amino carboxylic acid derivatives

Using the model put forward by Durst *et al.* whereby it is proposed the substitution reactions take place *via* a dipole opposed conformation, the stereochemical outcome from the attack of sodium malonate can be explained as a result of approach of the nucleophile from the least hindered face of the chiral auxiliary (Figure 27).[144, 145]

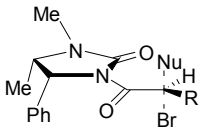
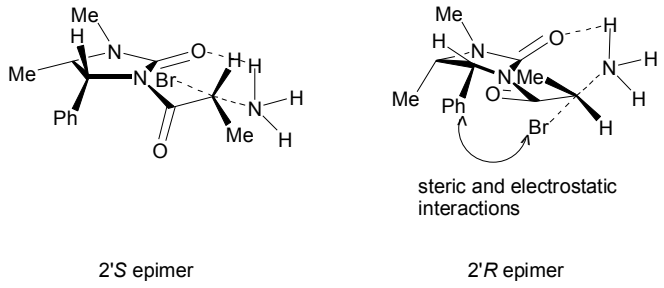



**Figure 27**

In order to rationalise the stereochemical outcome of the DKR with amine nucleophiles extensive molecular modelling experiments were carried out.[146] These indicated that the selectivity can be attributed to the ease with which the halide can leave without undesirable interactions with the bulky phenyl group (Figure 28). The steric and electrostatic interactions were shown by the molecular modelling to be much greater for the 2'*R* substrate than the 2'*S* substrate resulting in faster reaction of the latter and giving the 2'*R* isomer as the dominant product.

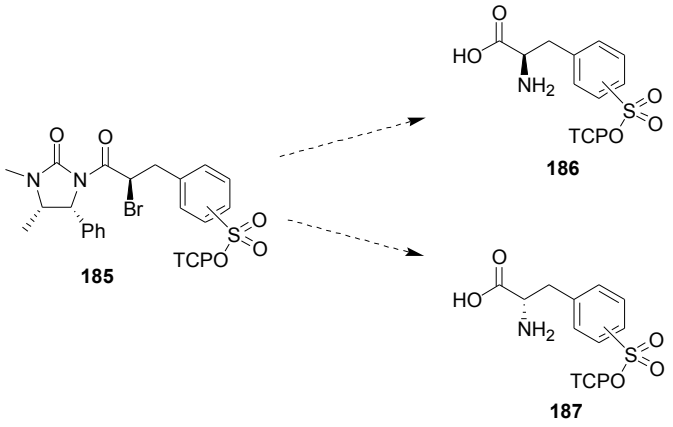



2'*S* epimer 2'*R* epimer

**Figure 28**

## 3.3.2 Towards the synthesis of TCP amino acids

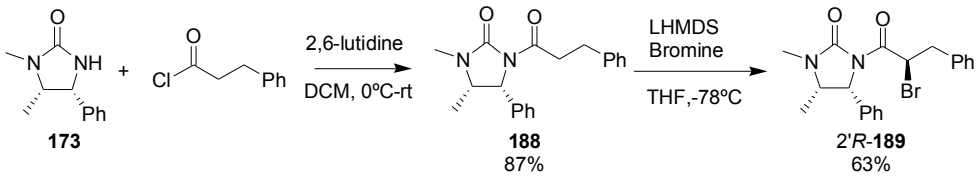
The objective was to use the imidazolidinone DKR/$S_N2$ protocol, shown in Scheme 53, for the synthesis of optically active amino acids containing a pendant TCP sulfonate on the phenyl ring. The initial targets were novel amino acids **186** and **187** (Scheme 54) as this would further probe the stability of the TCP sulfonate group when performing diverse reactions on remote sites within these molecules.




**Scheme 54**

To help establish whether this was a feasible goal the known bromide 2'*R*-**189** was synthesised. This allowed subsequent investigations into the viability of selective bromine displacement in the presence of a TCP sulfonate ester, and optimisation of the dynamic kinetic resolution procedure could also be carried out.

3-Phenylpropionyl chloride was coupled to the imidazolidinone **173** in the presence of 2,6-lutidine in DCM to give imide **188** in an 87% yield. This was treated with LHMDS in THF giving the anion to which bromine was added to produce the bromide 2'*R*-**189** in a 63% yield. The absolute configuration of **189** was confirmed by comparison to previous reported data.[147]

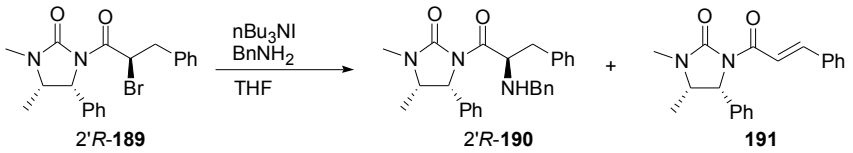



**Scheme 55**

With this compound now in place the DKR could be carried out. An issue with the nucleophilic substitution of bromide **189** is the competing elimination pathway to form the alkene **191** (Scheme 56). The elimination pathway is particularly favourable because the *β*-hydrogens are benzylic and hence, weakly acidic due to the electron withdrawing effect of the aromatic ring. Furthermore the resultant double bond is in conjugation with the aromatic ring.

The problem of elimination had been previously reduced by using the conditions benzylamine (6 eq), *tert*-butylammonium iodide (0.2 eq) at room temperature in THF.[147] The reaction was performed over 4 days under these conditions to give the DKR product (**190**) in an unsatisfactory 48% yield and 33% de (calculated by $^{1}$H NMR integration) and the elimination product (**191**) in a 15% (Table 12, Entry 1). Both the yield and the de were disappointing but these have been shown to improve on heating and so the temperature was raised in an effort to resolve these issues.[145] Performing the reaction at reflux (6 h) produced a slight increase in the yield (53%) of **190** but had a significant effect on the de resulting in a considerable improvement from 33% to 85% (Table 12, Entry 2). This thus showed that the temperature has a strong influence on the stereocontrol of the reaction.[142] To further investigate this trend the reaction was carried out in the microwave at 100 ºC. This produced **190** with a comparable yield and de but in a much shorter time (30 min) (Table 12, Entry 3). Attempts to further increase the microwave temperature resulted in a complex mixture of products and although **190** could be isolated the yield was reduced.

Under all conditions investigated the eliminated product (**191**) was isolated in a 10-15% yield. The formation of any of the alkene **191** is obviously not ideal but the complete suppression of the elimination pathway is in all probability not achievable and this amount was considered tolerable.




**Scheme 56**

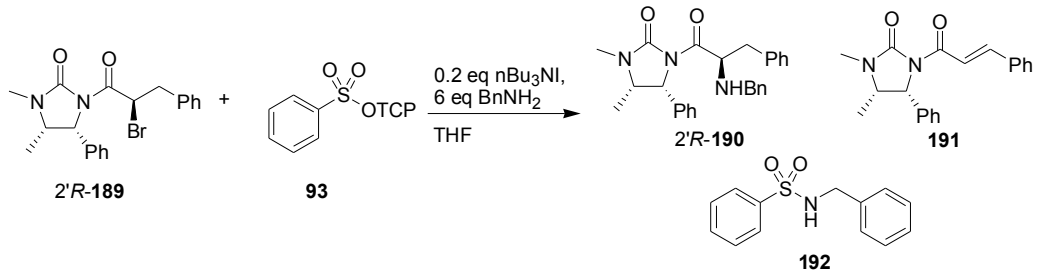
| | | Time | 2'*R*-190 | 191 |
|---|---|---|---|---|
| 1 | rt | 4 days | 48%, de 33% | 15 % |
| 2 | Reflux | 6 h | 53 %, de 85% | 10 % |
| 3 | Microwave 100 ºC | 30 min | 57%, de 85% | 13 % |
| 4 | Microwave 150 ºC | 10 min | 49%, de 77%[b] | 15 % |

**Table 12**

Having obtained the DKR product with a good de and in a reasonable yield it was now desirable to establish whether the benzylamine would react preferentially with the $\alpha$-bromo carbonyl in the presence of a TCP sulfonate. This was achieved by performing the DKR reaction in the presence of benzene TCP sulfonate (**93**) (Scheme 57).The results are shown in Table 13.

Promising results were obtained when the reaction was carried out in the microwave at 100 ºC (Table 13, entry 1). The desired DKR product (**190**) was isolated in a 68% yield with a de of 77% which are comparable values to those obtained in the absence of TCP sulfonate **93** (Table 12, Entry 3). TCP sulfonate **93** was recovered in a 61% yield and the sulfonamide **192** was obtained in a 29% yield. In an attempt to discourage this unwanted reaction the temperature was reduced and the reaction was carried out thermally at reflux (Table 13, Entry 2). This reaction again gave **190** in a comparable yield (69%) and de (69%) but there was a significant increase in the amount of sulfonamide **192** isolated (50% yield) and a lower recovery of the TCP sulfonate **93** (39%). When the temperature was reduced to room temperature (Table 13, Entry 3) a further increase in the formation of sulfonamide **192** (67%) and reduction of recovered TCP sulfonate **93** (18%) was observed.

A trend has been established whereby there is an increase in sulfonamide formation as the temperature is lowered. This trend is believed to be due to the accompanying increase in reaction times at lower temperatures resulting in a longer exposure of the TCP sulfonate to the nucleophile. Also, as 2'*R*-**189** is consumed in the reaction its concentration is, of course, reduced whilst the relative concentration of TCP sulfonate **93** increases.




**Scheme 57**

| | | | 2'*R*-190 | 191 | 192 | 93 |
|---|---|---|---|---|---|---|
| 1 | Microwave 100 ºC | 20 min | 68%, de 77% | 13% | 29% | 61% |
| 2 | Reflux | 6 h | 69%, de 69% | 16% | 50% | 39 % |
| 3 | Rt | 4 days | 63%, de 25% | 17% | 67% | 18 % |

**Table 13**

Having shown that it could be possible to achieve a degree of selectivity for amine formation over sulfonamide synthesis attention was turned to the synthesis of the desired alkyl bromides with pendant TCP sulfonates. The two initial targets were amines **193** and **194** (Figure 29).

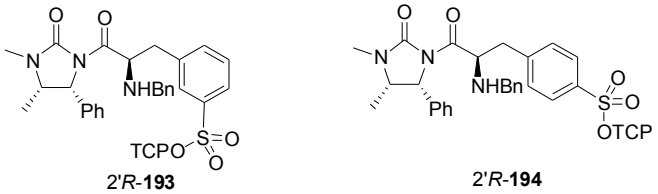
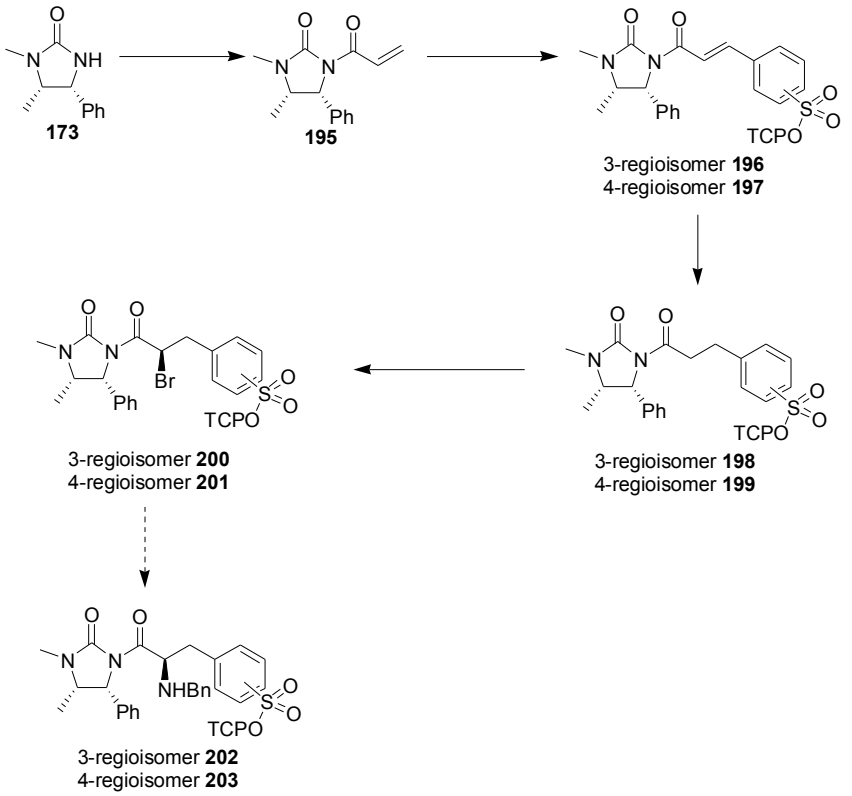


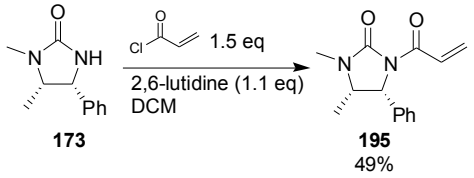

**Figure 29**

It was envisaged that the aryl TCP sulfonate could be incorporated *via* a Heck reaction with alkene **195** (Scheme 58) which could be formed by coupling the auxiliary **173** to acryloyl chloride. The resultant alkene could then be reduced to the alkane and bromination should give the required $\alpha$-bromo compounds.



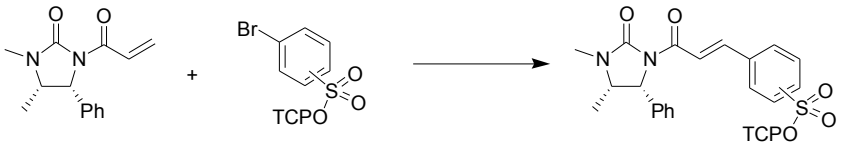

**Scheme 58**

The auxillary was coupled to acryloyl chloride to give alkene **195** in a 49% yield (Scheme 59).




**Scheme 59**

The Heck reaction conditions developed in section **3.2.2** were applied to the coupling of alkene **195** with 3- and 4-bromobenzene TCP sulfonates. The results were disappointing isolating the 3-regioisomer **196** in only a 30% yield and the 4-regioisomer **197** in a 57% yield (Table 14, Entry 1). The Heck reaction had previously been performed on alkene **195**[148] and so these conditions were employed to give an improved yield of 48% for the 3-regioisomer **196** but a reduced yield of 47% for the 4-regioisomer **197** (Table 14, Entry 2). Modification of these conditions by reduction of the mol% of catalyst and ligand gratifyingly resulted in improved yields of both the 3- and 4- isomers giving yields of 67% and 61%, respectively (Table 14, Entry 3).




**195**

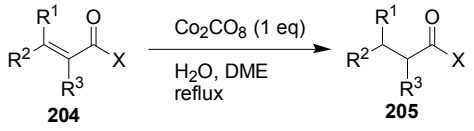
3-regioisomer **196**
4-regioisomer **197**

| | | **196** | **197** |
|---|---|---|---|
| 1 | Bromobenzene TCP sulfonate (1 eq), **195** (1.2 eq), $(PPh_3)_2PdCl_2$ (3 mol%), *N*-methyldicyclohexylamine (2 eq), DMF, *MW* | 30% | 57% |
| 2 | Bromobenzene TCP sulfonate (1 eq), **195** (1.2 eq), $(PPh_3)_2PdCl_2$ (10 mol%), P(*o*-tolyl)$_3$ (0.4 mol%), Toluene:$Et_3N$ 2:1 | 48% | 47% |
| 3 | Bromobenzene TCP sulfonate (1 eq), **195** (1.2 eq), $(PPh_3)_2PdCl_2$ (1 mol%), P(*o*-tolyl)$_3$ (2 mol%), Toluene:$Et_3N$ 2:1 | 67% | 61% |

**Table 14**

The next step was the reduction of the alkene. Hydrogenation of the 3-regioisomer **196** using 5% palladium on carbon in ethyl acetate proved to be slow and a complex mixture was obtained from which the desired product (**198**) was isolated in only a 23% yield. Changing the solvent to methanol brought no improvement.

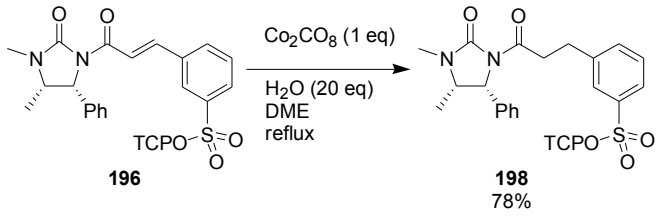
Lee *et al.* have reported the use of $Co_2(CO)_8$-$H_2O$ system for the selective reduction of α,β-unsaturated carbonyl compounds (**204**) (Scheme 60).[149] This system was successfully used in the chemoselective reduction of various *α,β*-unsaturated carbonyl compounds (**204**) including ketones, aldehydes and esters giving the desired products (**205**) in moderate to excellent yields (60-100%).




**204** **205**

**Scheme 60**

These conditions were applied to alkene **196** and initial results were promising with the alkane **198** being isolated in a 78% yield (Scheme 61).

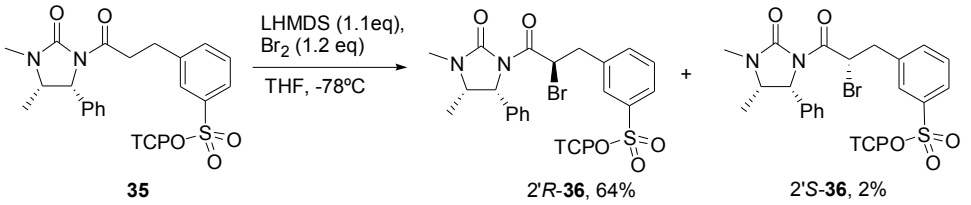



**Scheme 61**

For the 3-isomer **196** the reaction consistently proceeded with good yields but disappointingly when the conditions were applied to the 4-isomer **197** the product (**199**) was obtained in an unsatisfactory 18% yield. The reaction had gone to completion by TLC and on work up as well as isolating the alkane **199** some 2,4,6-trichlorophenol was obtained indicating that hydrolysis might have occurred.

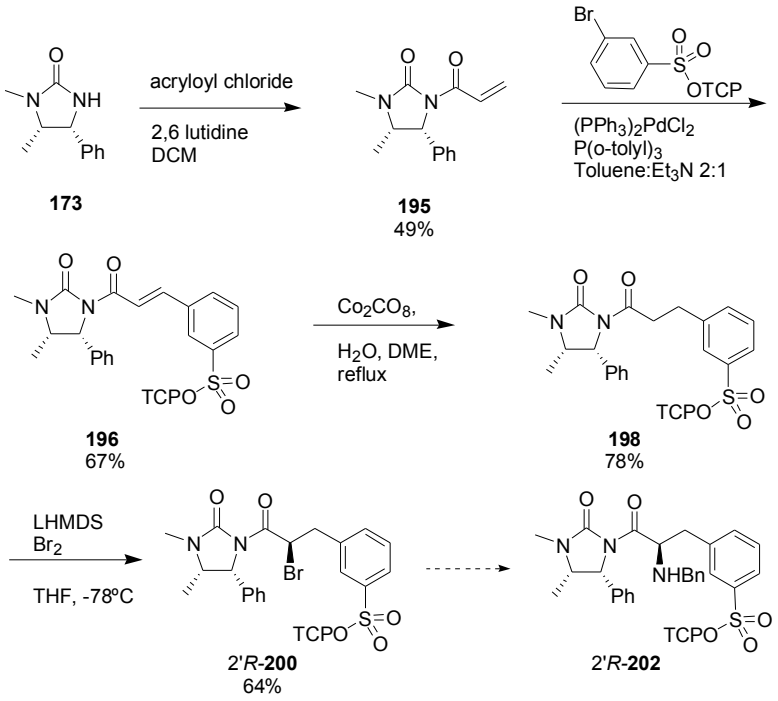
Another approach to the reduction of *α,β*-unsaturated carbonyls is using triphenylphosphine copperhydride hexamer in conjunction with water to give the carbonyl or alternatively reacting with trialkylsilylchloride to give the silyl enol ether.[150] Both these methods were applied to alkene **197** but starting material remained unreacted.

It was decided to proceed with the bromination of the alkane (**198**). Alkane **198** was subjected to the standard bromination conditions and the anticipated 2'*R* brominated product (2'*R*-**200**) was isolated in a 64% yield and only 2% of the 2'*S*-**200** was obtained (Scheme 62).




**Scheme 62**

With this route (Scheme 63) in place the synthesis of 2'R-**200** was scaled up for the subsequent DKR reaction.




**Scheme 63**

Previously DKR conditions were optimised for the model system 2'*R*-**189** (Scheme 56) in the hope that these conditions could be transferred to 2'*R*-**200**.

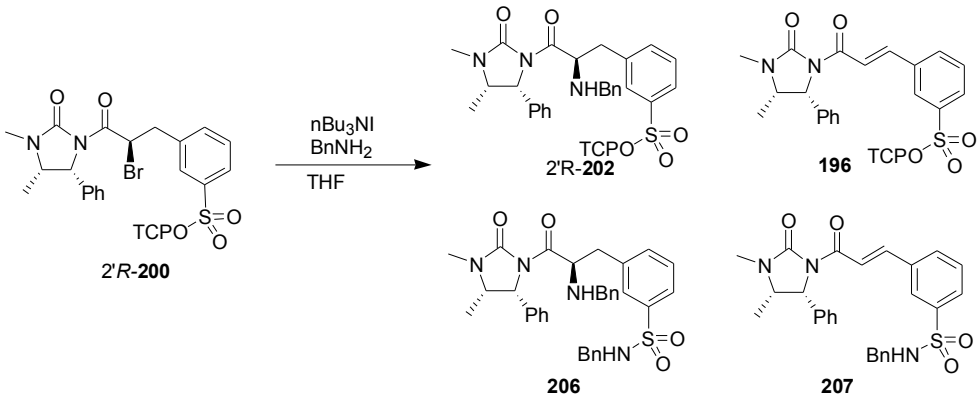
Although when using microwave conditions a degree of selectivity for substitution on the bromine over displacement of the trichlorophenol can be achieved the addition of 6 equivalents of benzylamine was deemed undesirable. Therefore before trying the DKR on 2'*R*-**200** reduction of the number equivalents of benzylamine was explored. Unfortunately, on reduction of the amount of benzylamine the reaction failed to go to completion in a reasonable timescale even when the reaction concentration was increased. In order to remedy this the addition of alternative bases was explored but for most (lutidine, sodium carbonate, sodium bicarbonate, caesium carbonate, *N*-methylmorpholine and sodium tetraborate) the reaction rate was not significantly affected. The other bases tried, *N*-methylmorpholine, potassium acetate, DMAP and DBU, promoted the unwanted elimination pathway.

These results were disappointing and it was determined that the DKR should be tried with the existing conditions to observe how the reaction preceeded.

When the existing microwave conditions (0.2 eq *n*BuNI, 6 eq benzylamine in THF in the microwave at 100 °C for 30 min) were used a complex mixture of products was obtained. The reaction was then carried out under thermal conditions at reflux and

the reaction was complete after 1.5 h. This was much quicker than for the model system **189** for which the reaction took 6 h. A mixture of products was obtained and one was identified as the undesired doubly substituted product **206,** whereby the benzylamine had displaced both the bromide and the TCP.

As the reaction had gone to completion after only 1.5 h it was believed that it might now be possible to reduce the amount of benzylamine. Therefore the reaction was carried out with only 2 equivalents of benzylamine and it proceeded to completion after 6 h in THF at reflux (Scheme 64). From LCMS and NMR data a mixture of products was identified as **202**, **196**, **206** and **207** and these could not be completely separated due to similar retention times. However a substantial amount of the elimination products **196** and **207** was observed especially compared to the anticipated 10-15% which was observed in the previous model studies. This meant that unfortunately the selectivity of the DKR reaction over the sulfonamide formation could not be properly assessed.




**Scheme 64**

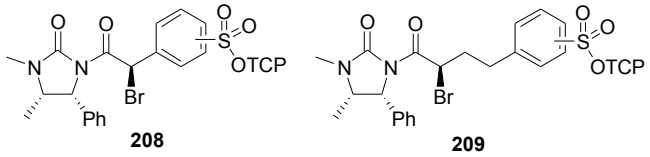
In order to establish whether DKR can be performed selectively in the presence of TCP the issue of elimination needs to be removed.

## 3.3.3 Conclusions

In conclusion the TCP sulfonate moiety of aryl TCP sulfonates has proven to be stable to the required conditions for the palladium reactions studied. The Suzuki reactions were shown to proceed in good yields when using both the 3- and 4-bromobenzene TCP sulfonate esters. Exposure of the resultant biaryl sulfonate ester to aminolysis conditions furnished the expected sulfonamide in good yield. Heck reactions with ethyl acrylate, cyanoacrylate and styrene also occurred in good yields.

In an effort to incorporate chirality, and hence more diversity, into the aryl TCP sulfonates the possibility of selectively performing DKR on the aryl TCP sulfonates was investigated. To this end a stereoselective route to give 2'*R*-**200** in good yield was established. Issues with the reduction of the alkene **196** were resolved by using $Co_2(CO)_8$-$H_2O$. The alkene of the 4-regioisomer **197** has been synthesised in good yield but problems with the reduction have not yet been resolved.

The DKR reaction on bromide 2'*R*-**200** was attempted, unfortunately despite promising results on the model system substantial elimination occurred rendering this reaction impractical. The increased amount of elimination, for the reaction of 2'*R*-**200** in comparison to 2'*R*-**189,** is most probably due to the electron deficient aromatic ring in 2'*R*-**200** increasing the acidity of the benzylic proton. To fully assess the efficacy of this DKR on an aryl TCP sulfonate the issue of elimination needs to be removed. This could be achieved by the synthesis of analogue **208** which no longer contains the benzylic proton or **209** in which the alkyl chain has been extended meaning that the resultant double bond in the elimination product would no longer be in conjugation with the aromatic ring.




**Scheme 65**

# Chapter Four

# Towards the synthesis of *β*-methoxy amino acids

## 4.1 Introduction

In recent years a diverse range of marine-derived cyclopeptides and depsipeptides have been isolated and characterised. Many of these display biological activity, which combined with unusual amino acids and complex molecular architecture make these compounds synthetically interesting.[151, 152] The callipeltins, papuamides and neamphamide A are examples of such natural products; these have been reported to display anti-HIV, antifungal, cytotoxic and sodium ionophore properties (Figure 30).[153-157] The cyclic heptapeptides cyclomarins were isolated in 1999 from a sediment sample in the vicinity of San Diego and have been shown to possess anti-inflammatory properties (Figure 30).[158] All these compounds contain a *β*-methoxy substituted amino acid: (2*S*,3*R*)-*β*-methoxytyrosine in callipeltins[159] and papuamides,[160] (2*R*,3*R*)-*β*-methoxytyrosine in neamphamide A[160] and (2*S*,3*R*)-methoxyphenylalanine in the cyclomarins.[161]

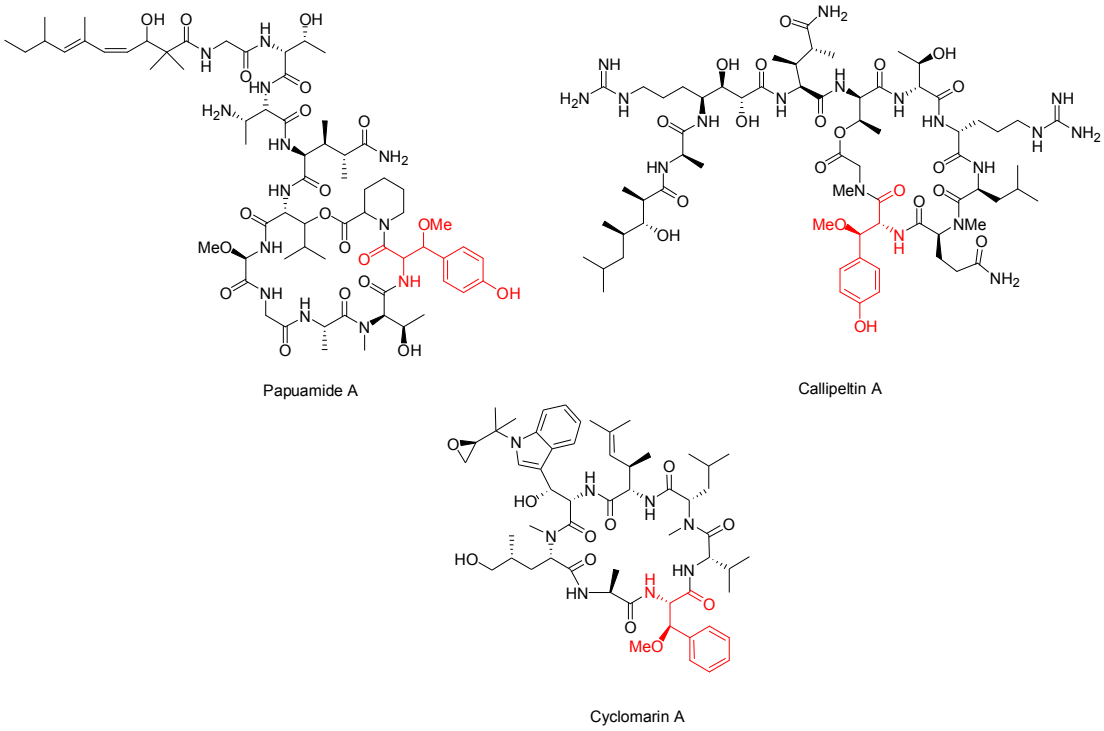
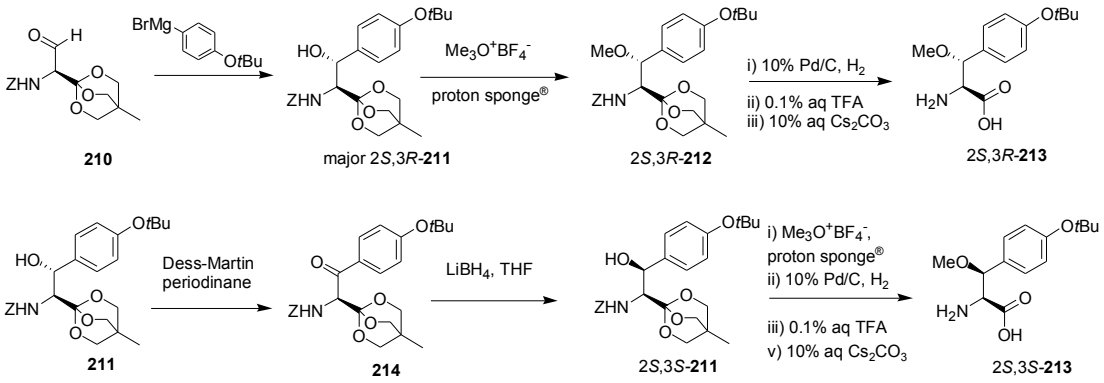



**Figure 30**

## 4.1.1 Previous syntheses of *β*-methoxy amino acids

In the initial structural studies of the callipeltins, papuamides and neamphamide A the configuration of *β*-methoxytyrosine was not established. This resulted in the majority of research focussing on synthetic strategies for the synthesis of the four possible stereoisomers. [160, 162, 163]

Using Lajoie's chiral serine aldehyde equivalent (**210**) Joullié *et al.* were able to access all four diastereomers of *β*-methoxytyrosine.[162] (*S*)-serine aldehyde (**210**) was treated with 4-*tert*-butoxyphenylmagnesium bromide to furnish the *β*-hydroxy intermediate (**211**) as a 90:10 mixture of isomers ((2*S*,3*R*):(2*S*,3*S*)) (Scheme 66). Methylation was accomplished by utilising a combination of $Me_3O^+BF_4^-$ and proton sponge, and subsequent deprotection yielded the (2*S*,3*R*)-*β*-methoxytyrosine (**213**). In order to obtain the (2*S*,3*S*)-diastereomer intermediate **211** was oxidised to give ketone **214**, which was reduced with $LiBH_4$ under Felkin-Ahn control. This gave (2*S*,3*S*)-**211** which was methylated and deprotected as with (2*S*,3*R*)-**213**. The (2*R*,3*S*) and (2*R*,3*R*) diastereomers were obtained by the same approach only starting with Lajoie's (*R*)-serine aldehyde.

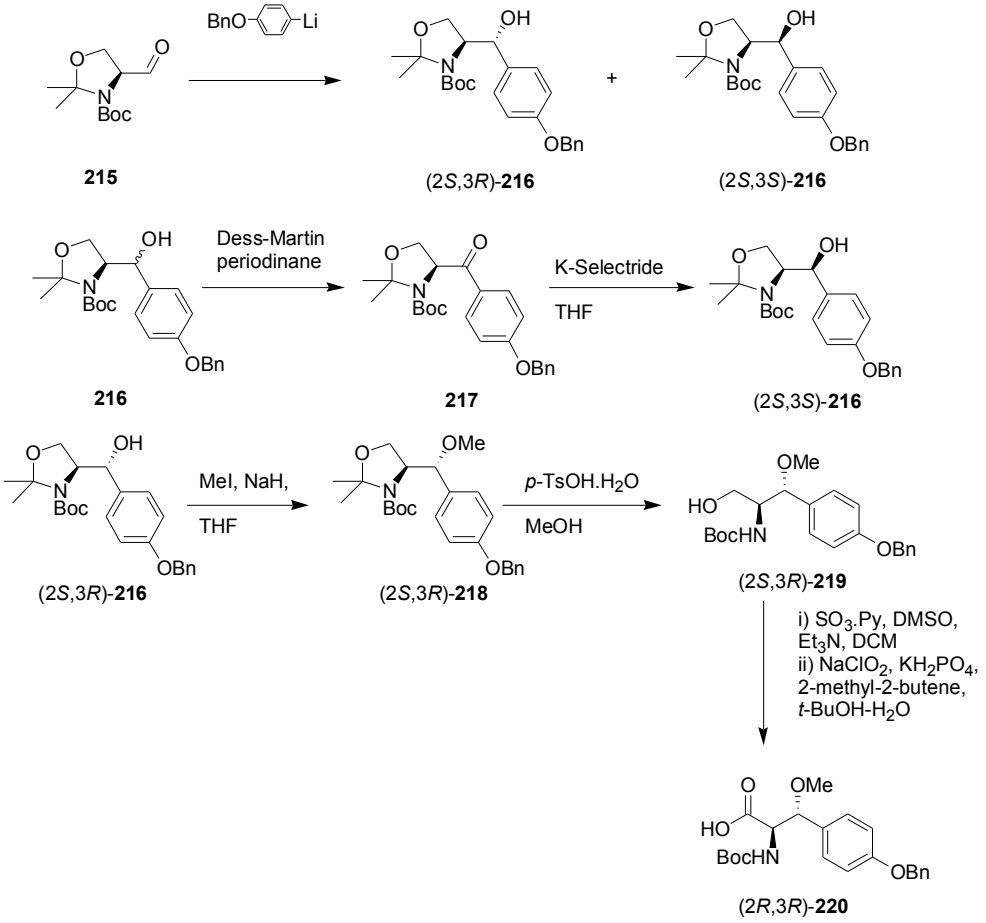



**Scheme 66**

This route was also employed in the synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-methoxyphenylalanine.[164]

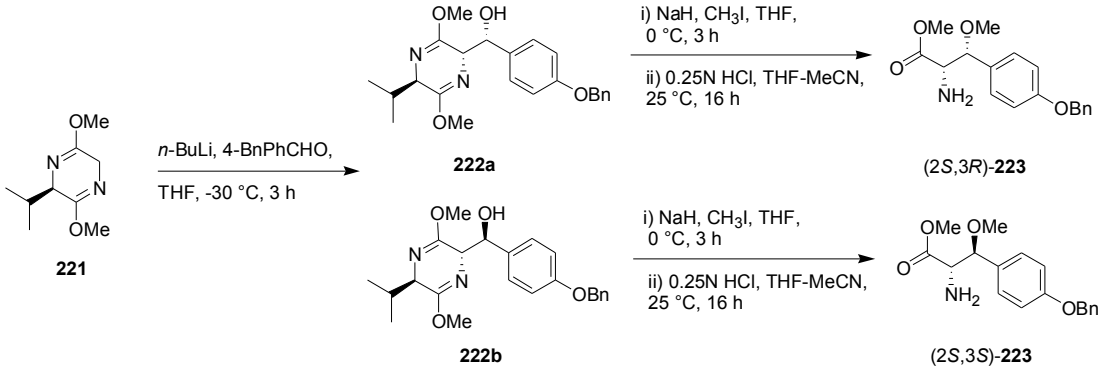
In a similar approach Hamada *et al.* synthesised the four diastereoisomers from the Garner aldehyde (**215**), which was accessed from (*S*)- and (*R*)-serine.[163] The (*S*)-Garner aldehyde, (*S*)-**215**, was treated with 4-benzyloxyphenyllithium in the presence of LiBr to give a 3:1, (2*S*,3*R*)-**216**:(2*S*,3*S*)-**216**, diastereomeric mixture (Scheme 67). Pure (2S,3*R*)-**216** was obtained by recrystallisation but unfortunately

(2*S*,3*S*)-**216** could not be separated from the mixture. Thus, (2*S*,3*S*)-**216** was synthesised from the diastereomeric mixture by DMP oxidation to give ketone **217** followed by K-Selectride reduction. Methylation was achieved using iodomethane-sodium hydride, the acetonide was removed using *p*-TsOH in methanol and the resultant amino alcohol (**219**) was oxidised to the carboxylic acid **220**. The other two diastereomers were obtained by application of this route to (*R*)-Garner aldehyde.




**Scheme 67**

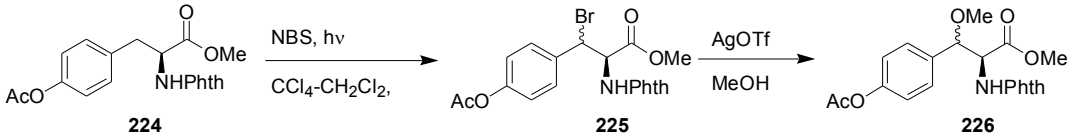
In an alternative route Gustafson *et al.* formed the two stereocentres by the addition of a metalated Schöllkopf's reagent **221** to 4-benzyloxybenzaldehyde to give a 1:1 mixture of two epimeric carbinols **222a** and **222b**.[160] These were separated chromatographically and subsequent methylation of the hydroxyl group and hydrolysis of the bis-lactam ether gave the stereochemically pure (2*S*,3*S*)- and (2*S*,3*R*)-*O*-benzyltyrosinemethyl esters **223**. The diastereomers (2*R*,3*S*)-**223** and (2*R*,3*R*)-**223** were synthesised from the other enantiomer of Schöllkopf's reagent using this route.




**Scheme 68**

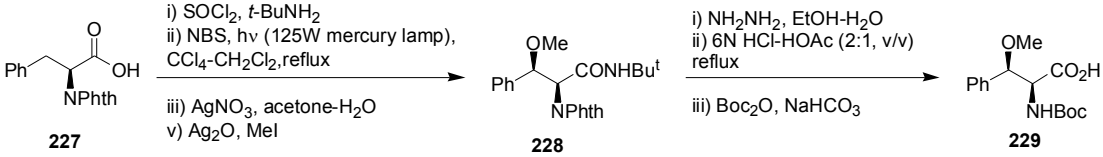
Yokokawa *et al.* synthesised (2*S*,3*R*)-*β*-methoxyphenylalanine methyl ester in high yield in four steps *via* the aldol reaction using Schöllkopf's chiral bis-lactam.[161, 165]

D'Auria *et al.* treated (2*S*)-*O*-acetyl-*N*-phthaloyltyrosine methyl ester (**224**) with *N*-bromosuccinimide to give the 3-bromo derivatives (**225**) as 1:1 mixture of diastereomers.[159] Treatment with silver triflate and methanol gave the two diastereomeric *β*-methoxytyrosine derivatives (2*S*,3*S*-**226** and 2*S*,3*R*-**226**), which were separated by HPLC and then deprotected to give the desired *β*-methoxytyrosines. The two remaining enantiomers were synthesised using the same procedure starting with (2*R*)-*O*-acetyl-*N*-phthaloyltyrosine.




**Scheme 69**

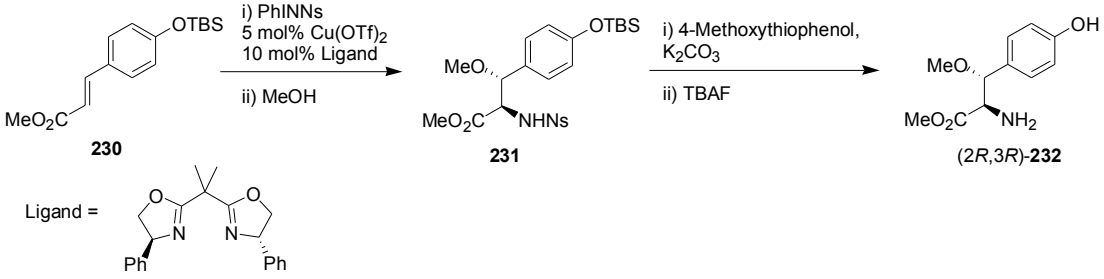
A similar route to *β*-methoxy phenylalanine started with L-phenylalanine **227** and again installed the second stereocentre using radical bromination.[166] The bromine was displaced with hydroxide and the *O*-methylation was effected with $Ag_2O$ and MeI (Scheme 70).




**Scheme 70**

Lipton *et al.* developed enantio- and diastereoselective synthesis of (2*R*,3*R*)-*β*-methoxytyrosine (**232**) (Scheme 71).[167] An asymmetric aziridination with a chiral

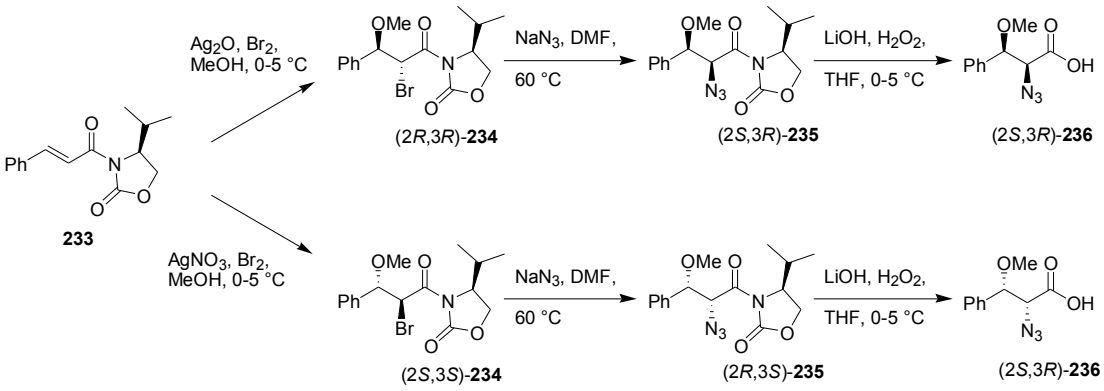
bis(oxazoline)-copper complex of *p*-coumarate TBS ether **230** followed by addition of methanol gave **231** in a greater than 19:1 dr and 28:1 er. Subsequent deprotection yielded (2*R*,3*R*)-**232**.




**Scheme 71**

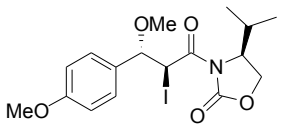
## 4.1.1 Halomethoxylation reaction

In an alternative route to the *β*-methoxyamino acids Hajra *et al.* have developed a method for asymmetric halomethoxylation using the chiral auxiliary (4*S*)-4-(1-methylethyl)-2-oxazolidinone to direct the stereochemistry.[168, 169] The reaction is carried out with halogens and promoted using silver salts to give the products with high regio- and anti-selectivity and moderate diastereoselectivity. They demonstrated this in the synthesis of both (2*S*,3*S*)- and (2*R*,3*R*)-2-azido-3-(4-benzoyloxy-phenyl)-3-methoxy-propionic acids **236**, precursors to *β*-methoxy phenylalanine (Scheme 72)**.**




**Scheme 72**

The aromatic group in the (4*S*)-*N*-cinnamoyl-4-(1-methylethyl)-2-oxazolidinones enhances the electrophilicity of the adjacent carbon, resulting in a regioselective attack of methanol on the halonium intermediate. X-ray crystal analysis of (2*S*,3*S*)-**237** confirmed this regioselectivity.[169]

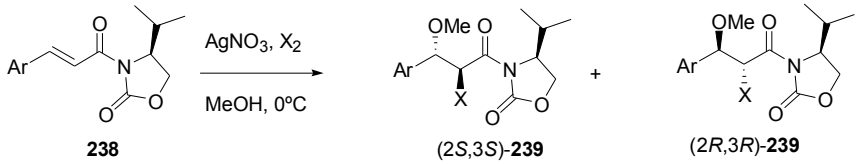



(2*S*,3S)-**237**

**Figure 31**

When alternative oxazolidinone auxiliaries, (3*S*)-3-phenyl- or (3*S*)-3-(diphenylmethyl)-2-oxazolidinones, were used complex mixtures of products were formed.[168]

Cinnamoyl and electron-deficient cinnamoyl substrates smoothly underwent bromomethoxylation, whilst for electron-rich cinnamoyl substrates better results were achieved for iodomethoxylation (Table 15). When $AgNO_3$ was used the reactions generally proceeded with a 7:3 dr in favour of (2*R*,3*S*)-**239**, similar diastereoselectivity was also seen in the presence of AgOAc. However, $Ag_2O$ was demonstrated to reverse the diastereoselectivity, especially for cinnamoyl and electron deficient cinnamoyl substrates (Table 15, compare Entries 1 and 2 and Entries 3 and 4).




**238** (2*S*,3*S*)-**239** (2*R*,3*R*)-**239**

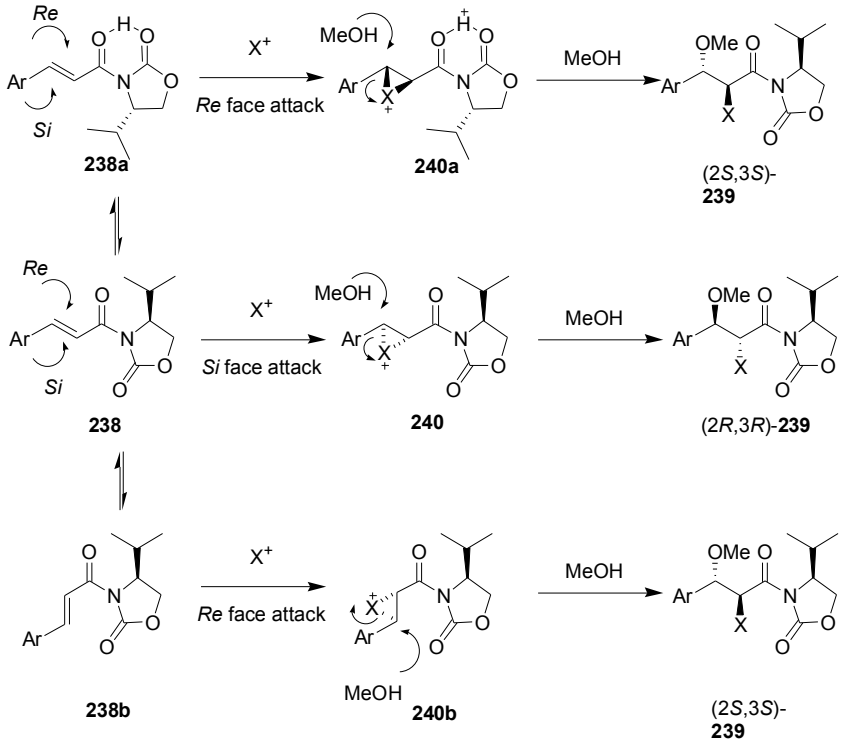
**Scheme 73**

| | Ar | AgX | X | Ratio 239 (2*S*,2*S*):(2*R*,3*R*) |
|---|---|---|---|---|
| 1 | Ph | $AgNO_3$ | Br | 71:29 |
| 2 | Ph | $Ag_2O$ | Br | 27:73 |
| 3 | 2-$NO_2C_6H_4$ | $AgNO_3$ | Br | 65:35 |
| 4 | 2-$NO_2C_6H_4$ | $Ag_2O$ | Br | 35:65 |
| 5 | 4-$MeOC_6H_4$ | $AgNO_3$ | I | 62:38 |
| 6 | 4-$MeOC_6H_4$ | $Ag_2O$ | I | 48:52 |
| 7 | 2-$ClC_6H_4$ | $AgNO_3$ | Br | 60:40 |
| 8 | 2-Naphthyl | $AgNO_3$ | I | 73:27 |

**Table 15**

Reactions of either $AgNO_3$ or AgOAc with halogens in methanol generate acid. Therefore, to explain the diastereoselectivity Hajra *et al.* have proposed that for reactions promoted by $AgNO_3$ or AgOAc the $H^+$ chelated *S-cis-syn-dipole* conformation **238a** might be involved in the reaction (Scheme 74).[168, 169] On attack of

$X^+$ from the *Re*-face and subsequent nucleophilic attack of MeOH at the *β*-position (2*S*,2*S*)-**239** is furnished as the major diastereomer. In the $Ag_2O$-promoted reaction the unchelated *S-cis-anti-dipole* conformation **238** might be involved yielding (2*R*,2*R*)-**239** as the major diastereomer. This hypothesis is supported by the $Ag_2O$-promoted reactions performed in the presence of either $HNO_3$ or AcOH for which diastereoselectivities similar to either the $AgNO_3$ or AgOAc-promoted reactions were seen. The poor diastereoselectivities of the electron rich substrates in $Ag_2O$-promoted reactions might be accounted for by the involvement of both the equilibrated *S-cis-* and *S-trans-anti-dipole* conformations **238** and **238b**, due to extensive conjugation of the electron-donating substituent at the *para*-postion with the *α*,*β*-unsaturated carbonyls.




**Scheme 74**

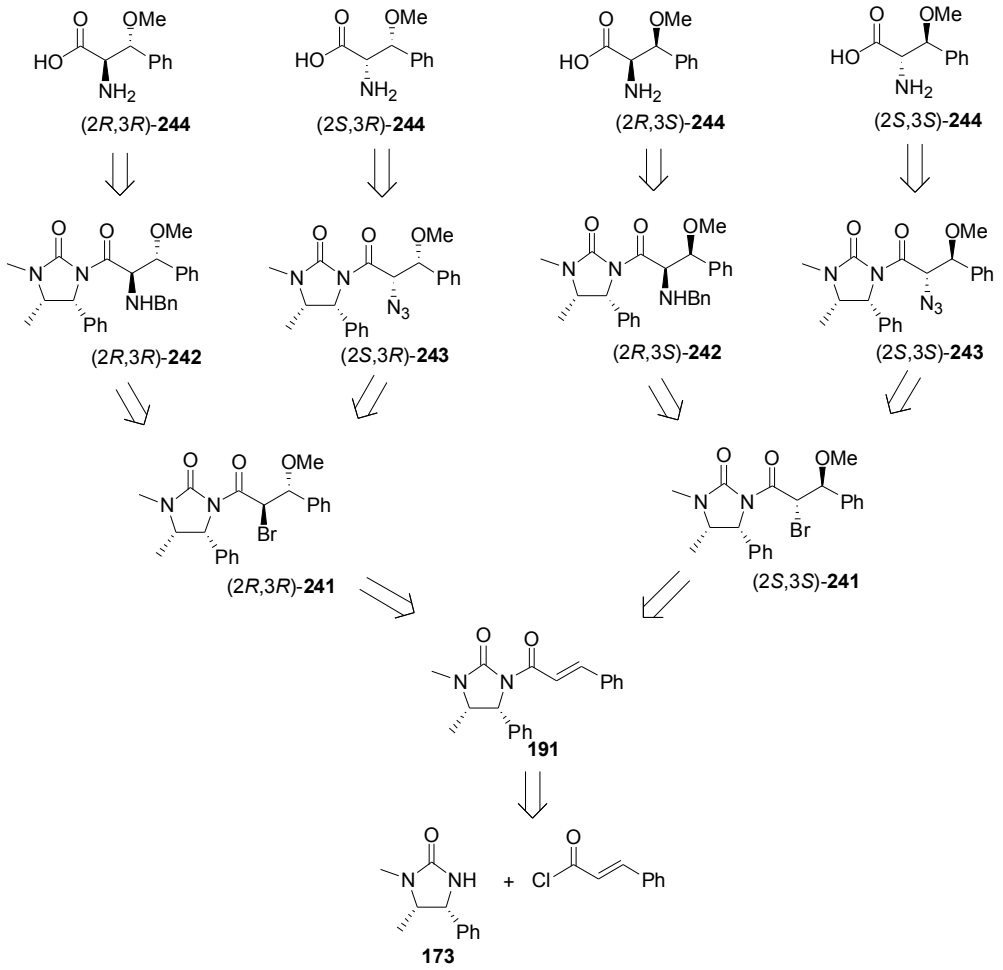
Interestingly, the work by Hajra *et al.* is the only example in which the absolute stereochemistry of the halomethoxylation *α*,*β*-unsaturated carboxylic acid derivatives is controlled, although the relative stereochemistry has been shown to be *anti* under various conditions.[170, 171] Using *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) as the bromine source Phukan *et al.* developed a regio- and stereoselective synthesis of the *anti*-alkoxybromo-carboxylic acid derivatives.[170] Whilst, Sudalai *et al.* obtained *anti*-

alkoxybromo-carboxylic acid derivatives *via* the sodium periodate mediated oxidative halogenation of alkenes with metal halides in the presence of methanol.[171]

It is noteworthy that although there is a lack of methods for the asymmetric syntheses of the *α*-halo-*β*-methoxycarboxylic acid derivatives there are a number of routes to the stereoselective synthesis of halohydrins. These include the asymmetric halohydrin reaction,[171-173] as well as reagent controlled aldol reaction of chiral *α*-halogenated imide enolates with suitable aldehydes,[174-177] catalytic asymmetric hydrogenation of *α*-chloro-*β*-ketocarboxylic acid esters and ring opening of epoxides[178-184] or cyclic sulphate.[185]

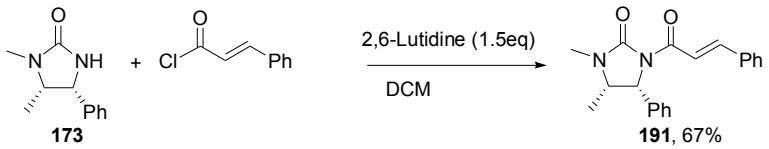
## 4.2 Towards the synthesis of *β*-methoxy amino acids

Despite the moderate diastereoselectivity of Hajra *et al*'s bromomethoxylation reaction this route was of particular interest as it was envisaged that the imidazolidinone auxiliary could be used in place of the oxazolidinone.[168, 169] The influence of *β*-substitution on the imidazolidinone DKR protocol (Section 3.1.1.4) has not been studied previously. Thus, the synthesis of these *β*-methoxy amino acids employing this DKR strategy is appealing. Furthermore, this reaction in combination with the DKR/$S_N2$ protocol could potentially provide selective routes to all four diastereomers from a common starting material **191** (Scheme 75).




**Scheme 75**

With this route in mind alkene **191** was synthesised in good yield from the auxliary **173** and trans cinnamoyl chloride (Scheme 76).




**Scheme 76**

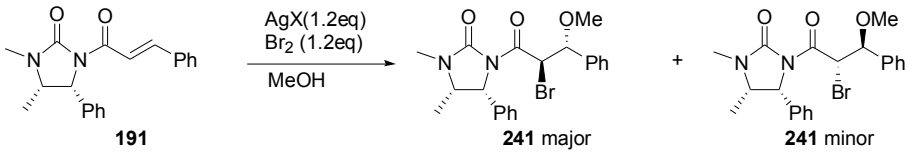
## 4.2.1 Asymmetric Halomethoxylation Reaction

Initially, the bromomethoxylation of **191** was performed at 0 ºC with silver nitrate (1.2 eq) and bromine (1.2 eq) in methanol; conditions analogous to those described by Hajra *et al*.[168, 169] The diastereomers were obtained in a 2:1 diastereomeric ratio, as calculated from the crude proton NMR spectrum (Entry 1, Table 16). The diastereomers were isolated in 88% total yield with the major isomer being obtained in a 58% yield and the minor isomer in a 30% yield. On reduction of the temperature

to –20 ºC the dr improved to 3:1 (Entry 4, Table 16) and this trend was followed at –40 ºC with an improved dr of 6:1 (Entry 5, Table 16). Unfortunately, at –60 ºC and –78 ºC dibrominated product was seen and there was no improvement in the diastereomeric ratios, which were 6:1 and 5:1 respectively (Entries 6 and 7, Table 16). Also at –78 ºC the reaction failed to go to completion. When the reaction was carried out in DCM with 20 eq MeOH only the dibrominated product was observed (Entry 2, Table 16).

In reactions where dibromination occurred the reaction mixture retained an orange colour rather than turning colourless, indicating that bromine was still present. It was hypothesised that this could be due to the lower solubility of the halide scavenger silver nitrate in MeOH. To test this theory the more soluble silver trifluoroacetate was employed in place of silver nitrate. The reaction was carried out at –78 ºC (Entry 9, Table 16) and gratifyingly no dibrominated product was seen, moreover, the dr had improved to 11:1. There was still a small amount of starting alkene present, but nevertheless this was an encouraging result.

To investigate the influence of the silver salt the reaction was carried out, at 0 ºC, in its absence and this gave the opposite selectivity with a dr of 3:5 (Entry 3, Table 16). It is also worthy to note that the reaction was much slower taking 2 h 30 min as opposed to 40 min when silver nitrate was present (Entry 3 vs Entry 1, Table 16).




**Scheme 77**

| Entry | Temp (ºC) | Time | AgX | Solvent | dr 241 major:minor |
|---|---|---|---|---|---|
| 1 | 0 | 40 min | $AgNO_3$ | MeOH | 2:1 |
| 2 | 0 | 1 h | $AgNO_3$ | DCM (20 eq MeOH) | -[a] |
| 3 | 0 | 2 h 30 | - | MeOH | 3:5 |
| 4 | -20 | 40 min | $AgNO_3$ | MeOH | 3:1 |
| 5 | -40 | 2 h | $AgNO_3$ | MeOH | 6:1 |
| 6 | -60 | 3 h | $AgNO_3$ | MeOH | 6:1[a] |
| 7 | -78 | 9 h | $AgNO_3$ | MeOH | 5:1[a, b] |
| 8 | -78 | 3 h | $AgCO_2CF_3$ | MeOH | 11:1[b] |

**Table 16** [a] dibrominated product, [b] starting material seen

All diastereomeric ratios are measured from the proton NMR spectra by comparing the $CH_ABr$ signals from the two diastereomers (Figure 32), and all product mixtures were obtained in a greater than 80 % yield.

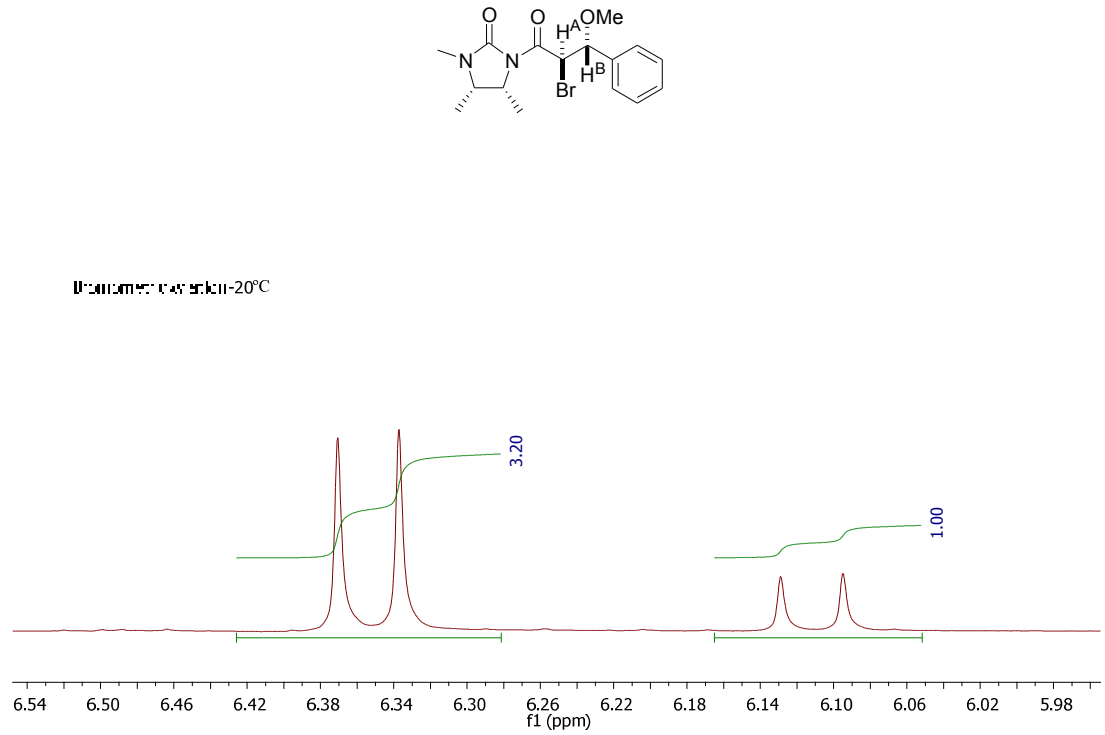
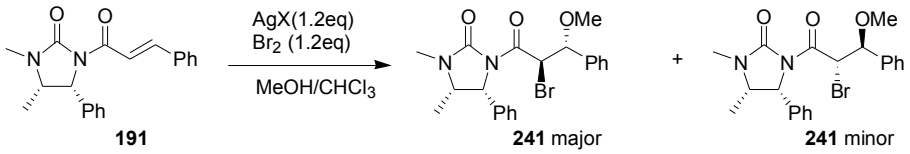



**Figure 32**

Unfortunately, repetition of the reaction at -78 °C did not give consistent results; one explanation for this is the low solubility of the starting alkene in methanol, resulting in the reaction mixture being a suspension. In order to resolve this issue the solubility of the alkene was investigated and DMF and chloroform were found to be the best solvents. Enough methanol needs to be used in order to affect the methoxylation step. Initially, a solution mixture of 2.3:1 chloroform:methanol was employed and reactions were carried out at –40 °C. On increasing the amount of silver triflate from one equivalent to two there was a complete loss of selectivity from 4:1 to 1:1 (Entries 1 and 2, Table 17). On cooling to –60 °C the starting material precipitated from solution and so to resolve this the solvent ratio was changed to 1:1 chloroform:methanol. Both the alkene and the silver triflate were soluble in this solvent mixture and on repetition the results were now consistent and so alternative silver salts could be evaluated (Scheme 78).



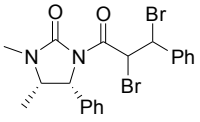

**Scheme 78**

| Entry | Temp (ºC) | AgX equivalents | AgX | $CHCl_3$:MeOH | dr 241 major:minor |
|---|---|---|---|---|---|
| 1 | -40 | 1.2 eq | $AgSO_3CF_3$ | 2.3:1 | 4:1 |
| 2 | -40 | 2.4 eq | $AgSO_3CF_3$ | 2.3:1 | 1:1 |
| 3 | -60 | 1.2 eq | $AgSO_3CF_3$ | 2.3:1 | 7:1 |
| 4 | -60 | 1.2 eq | $AgSO_3CF_3$ | 1:1 | 7:1 |
| 5 | -78 | 1.2 eq | $AgSO_3CF_3$ | 1:1 | 8:1 |
| 6 | -78 | 1.2 eq | AgOAc | 1:1 | 1:1[a] |
| 7 | -78 | 1.2 eq | $AgCO_2CF_3$ | 1:1 | 7:1 |
| 8 | -78 | 1.2 eq | $AgBF_4$ | 1:1 | 8:1 |
| 9 | -78 | 1.2 eq | $AgPF_6$ | 1:1 | 6:1 |
| 10 | -78 | 1.2 eq | $AgClO_4$ | 1:1 | 1:1 |

**Table 17** [a] dibrominated product

When the temperature was reduced from -60 to -78 °C a small improvement in selectivity was observed (Entries 4 and 5, Table 17), and therefore the lower temperature was chosen for surveying the various silver salts.

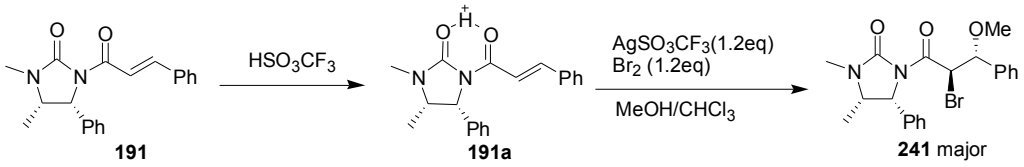
Silver triflate, silver trifluoroacetate, silver tetrafluoroborate and silver hexafluorophosphate (Entries 5, 7, 8 and 9, Table 17) all gave similar selectivity at -78 °C (dr ~7:1). Silver acetate was not soluble in the solvent mixture and this resulted in a predominance of dibrominated product **245** (Figure 33) and no selectivity in the bromomethoxylation (Entry 6, Table 17). Although silver perchlorate was in solution no selectivity was seen, with a 1:1 mixture of the two isomers being obtained (Entry 10, Table 17). Silver oxide was not soluble in the solvent mixture and the reaction didn't go to completion after 6 h. This resulted in a complex mixture of alkene **191**, dibrominated product and bromomethoxylated products.



**245**

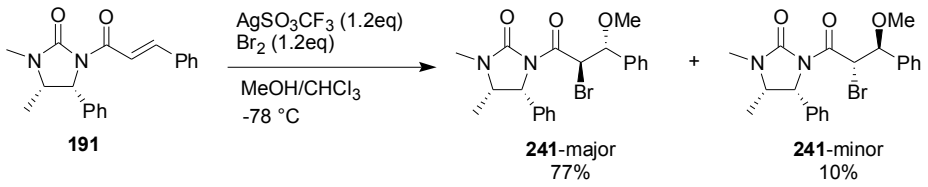
**Figure 33**

Hajra *et al.* hypothesise that the major diastereomer (2*S*,3*S*)-**29** is formed *via* the involvement of a $H^+$ chelated conformation **28a** (Scheme 74).[168, 169] The acid is formed during the reaction with $AgNO_3$ or AgOAc present. If the $H^+$ chelated conformation is involved in the bromomethoxylation of **191**, it was hypothesised that addition of an acid before addition of the silver salt and bromine could improve the diastereoselectivity (Scheme 80). Unfortunately, when this reaction was tried using triflic acid and silver triflate a disappointing dr of 5:1 was obtained, compared to 8:1 without the acid.




**Scheme 79**

As most of the dr's were calculated from the crude NMR the bromomethoxylation was carried out using silver trifluoroacetate at -78 °C and the two diastereomers were isolated; this gave the **241**-major in a 77% yield and **241**-minor isomer 10% yield (Scheme 80).




**Scheme 80**

Definitive proof of the regio- and stereochemistry of the products, **241-**major and **241**-minor, have not been determined and have, so far, been assumed based on the results of Hajra *et al.*[168, 169] Reviewing previous literature and taking electronic factors into consideration it is reasonable to assume that the methanol attacks at the benzylic position resulting in bromination of the position α to the carbonyl.[169-171] Thus, assuming this regioselectivity is correct there are four possible diastereomers (Figure 34). In order to assign the absolute stereochemistry an X-ray crystal structure is required unfortunately these products were foams and therefore, a more crystalline analogue would be required.

If, as believed, the *anti*-stereoisomers are being formed, then upon epimerisation of the *α*-position two different isomers (*syn*) will be produced. The two isolated diastereomers, **241**-major and **241**-minor, were exposed to epimerising conditions ($n$Bu$_4$NBr) and the products were isolated. Four isomers were isolated, **241**-major and **241**-minor plus their epimers. This indicates that the *α*-position is not epimerised during the bromomethoxylation reaction and thus, the products of the reaction must either be the two *anti*-isomers ((2*R*,3*R*)-**241** and (2*S*,2*S*)-**241**) or the two *syn*-isomers ((2*R*,3*S*)-**241** and (2*S*,2*R*)-**241**) (Figure 34).

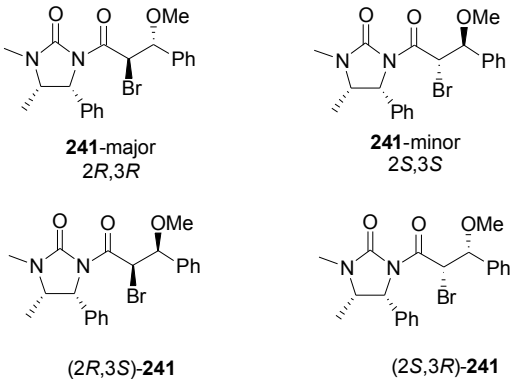
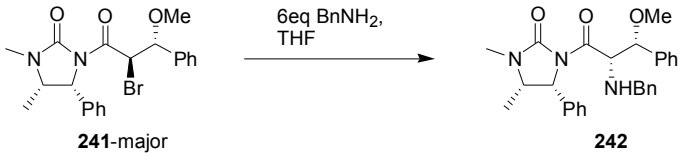


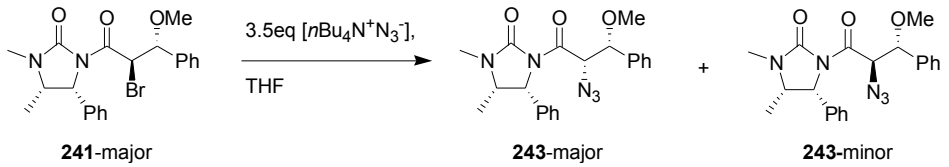

**Figure 34**

Whilst optimising the bromomethoxylation the practicality of the DKR reaction needed to be investigated. Initially the $S_N2$ displacement of the bromine with benzylamine was attempted; this would allow a quick assessment of whether elimination would be an issue. **241**-major was stirred at room temperature with 6 equivalents of benzylamine in THF (Scheme 81). After 18 h some product could be seen by TLC but it had not gone to completion and so the reaction mixture was heated to reflux for 72 h. Even then the reaction had not gone to completion but it was worked up at this point. The starting material was recovered in 23% and the desired substituted product was obtained as a single isomer in 48% yield. One other product was obtained which has been identified as the epimer of **241**-major, presumably (2*S*,3*R*)-**241**.



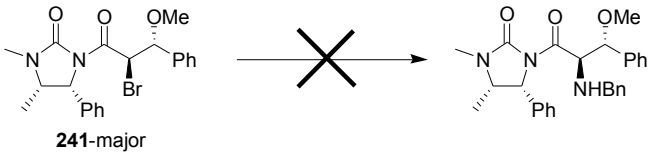

**Scheme 81**

The $S_N2$ reaction was then tried using tetrabutylammonium azide as a soluble azide source and THF as the solvent (Scheme 82). At room temperature the reaction was reluctant to go to completion but upon heating reflux completion was achieved. Two products were isolated neither of them was the starting material, **241**-major**,** or its epimer; they are believed to be the two azide diastereomers in a 6.5:1 ratio. The reaction was also carried out in NMP at 120 °C and the same two products were obtained but in a 2:1 ratio.




**Scheme 82**

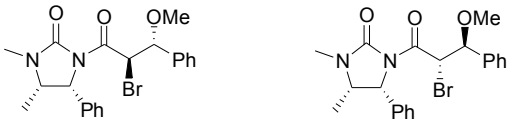
The DKR reaction was carried out with the epimerising agent tetrabutylammonium iodide in NMP at 70 °C for 24 h and a complex mixture of products was obtained containing the starting bromide, **241**-major. When it was attempted in the microwave at 100 °C the reaction was still not complete after 3 h.




**Scheme 83**

## 4.3 Conclusions and Future Work

In conclusion a bromomethoxylation reaction of chiral *α,β*-unsaturated carboxylic acid derivative **191**, which proceeds with good diastereoselectivity and yield, has been described. Through epimerisation of the products, **241**-major and **241**-minor, it was determined that these diastereomers were either the two *syn*-diastereomers or the two *anti*-diastereomers. Based on similar reactions in the literature it is feasible to conclude that **241**-major and **241**-minor are the *anti*-isomers, (2*R*,3*R*)- and (2*S*,3*S*)-**241** (Figure 35).[169-171]




(2*R*,3*R*)-**241** (2*S*,3*S*)-**241**

**Figure 35**

Under $S_N2$ conditions **241**-major did not give any eliminated product, although under the high temperatures required for it to react some epimerisation was observed. This resulted in two diastereomers being isolated. The $S_N2$ reaction was also tried but in these initial attempts the reaction did not go to completion, which resulted in a complex mixture of products.

There is opportunity to extend the substrates of the bromomethoxylation reaction by trying alternative cinnamoyl substrates; this would allow the influence of substitutents on the aromatic ring to be explored. It could also allow access to a crystalline analogue allowing the stereochemistry to be definitively assigned. Although good diastereoselectivity has been achieved there is still opportunity for improvement and there is a plethora of alternative bromine sources that could be employed.

For the $S_N2$ reaction alternative conditions, different azide sources, solvents and temperatures, need to be explored to assess whether the epimerisation can be prevented and thus, a single diastereomer obtained. Again, for the DKR reaction further conditions, alternative solvents and amines, need to be investigated.

# Experimental

## General Experimental

Solvents and reagents were commercially available and used without further purification, unless otherwise noted. Benzylamine was distilled from potassium hydroxide and tetrabutylammonium iodide was recrystallised from ethanol and dried over $P_2O_5$.

Analytical thin layer chromatography (TLC) was performed on SIL G/$UV_{254}$ silica plates and visualisation was achieved by use of UV light and potassium permanganate solution. Flash chromatography was carried out using BDH silica gel (particle size 33 micron–70 micron) and medium pressure chromatography was carried out on prepacked Isco RediSep silica cartridges, using the ISCO SQ 16X instrument.

$^{1}H$ NMR spectra were recorded on a Bruker AMX 300 (300 MHz), Bruker Avance III 400 (400 MHz), Bruker Avance 500 (500 MHz) or Bruker Avance III 600 (600 MHz) spectrometer. Chemical shifts (δ) are reported in units parts per million (ppm) relative to residual protiated signals of the solvent or to tetramethylsilane. Spin multiplicities were reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and coupling constants (J) are given in Hertz (Hz).

$^{13}C$ NMR spectra and $^{13}C$ DEPT 135 NMR spectra were recorded on a Bruker AMX 300 (75 MHz), Bruker Avance III 400 (101 MHz), Bruker Avance 500 (126 MHz) or Bruker Avance III AMX 600 (151 MHz) and standard abbreviations were used (singlet (s), doublet (d), triplet (t), quartet (q)).

Mass spectra were performed at the EPRSC National Mass Spectrometry Service Centre, University of Wales, Swansea obtained on a Quattro II or a MAT900 XLT spectrometer, at University College London on a VG70-SE or a MAT 900 XP spectrometer or at GlaxoSmithKline, Harlow on an Apex spectrometer.

Infra red spectra were run on a Shimadzu FTIR 8700 spectrometer or PerkinElmer Spectrum 100 FT-IR spectrometer operating in ATR mode with frequencies given in reciprocal centimetres ($cm^{-1}$).

All melting points were recorded on a Gallenkamp heating block and are uncorrected.

Optical rotation measurements were carried out using a PerkinElmer 343 polarimeter with a cell length of 10 cm.

Microwave reactions utilized a CEM Explorer instrument.

# Experimental for Chapter 2

## Synthesis of 2,4,6 Trichlorophenyl Sulfonyl Esters

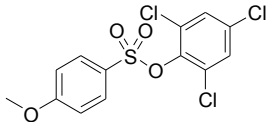
### General Procedure A

To a solution of the sulfonyl chloride (19.6 mmol) in dichloromethane (50 mL) at 0 °C was added a pre-mixed solution of 2,4,6-trichlorophenol (4.6 g, 23.4 mmol) and triethylamine (6.8 mL, 48.9 mmol) in dichloromethane (10 mL) dropwise. The reaction was stirred at 0 °C for a further 15 min and allowed to warm to room temperature over 1 h. The reaction mixture was diluted with dichloromethane (30 mL), washed with 2 M sodium carbonate solution (2 x 30 mL), 2 M hydrochloric acid (2 x 30 mL) and water (30 mL), separated, dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* to yield the crude product, which was purified as described in the individual entries below.

### General Procedure B

To a solution of triphenylphosphine oxide (1.1 g, 4 mmol) in anhydrous dichloromethane (20 mL) at 0 °C under nitrogen was added trifluoromethanesulfonic anhydride (350 mg, 2 mmol) and the mixture was stirred for 20 min. The pyridinium sulfonate salt (2 mmol) was added and the mixture was stirred for a further 20 minutes. A pre-mixed solution of 2,4,6-trichlorophenol (390 mg ,2 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (5 mL) was added dropwise over a period of 10 min. The reaction was allowed to warm to room temperature. It was then diluted with dichloromethane (30 mL) and washed with 2 M sodium carbonate solution (2 x 30 mL), 2 M hydrochloric acid (2 x 30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified as described in the individual entries below.

**4-Methoxybenzene sulfonic acid 2,4,6-trichlorophenyl ester (89)**



Synthesised using general procedure A. Purified by recrystallisation from acetone to yield white crystals (19.0 g, 52 mmol, 86%).

MP 116-120 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H, Ar*H*), 7.35 (s, 2H, Ar*H*), 7.05-7.01 (m, 2H, Ar*H*), 3.92 (s, 3H, OC*H*$_3$)

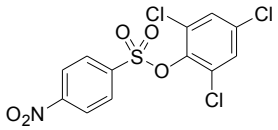
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 164.54 (s), 142.42 (s), 132.74 (s), 130.95 (d), 129.16 (d), 128.20 (s), 114.42 (d), 55.82 (q) 1 x s not observed

IR (thin film) $\nu_{max}$ 1592, 1576, 1495, 1439, 1380, 1267, 1166, 1093 cm$^{-1}$

LRMS (EI) 370 (20%), 368 (48%), 366 ($M^+$, 46%), 330 (75%), 251 (70%), 223 (100%)

HRMS (CI) calcd for $C_{13}H_{13}Cl_3NO_4S$ ($[M + NH_4]^+$): 383.9625 found 383.9629

**4-Nitrobenzene sulfonic acid 2,4,6-trichlorophenyl ester (90)**



Synthesised using general procedure A. Purified by recrystallisation from hexane/ dichloromethane to yield yellow crystals (17.9 g, 47 mmol, 78%).

MP 126-128 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.46-8.43 (m, 2H, Ar*H*), 8.26-8.22 (m, 2H, Ar*H*), 7.41 (s, 2H, Ar*H*)

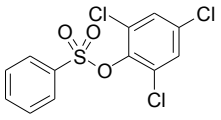
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.18 (s), 142.46 (s), 141.95 (s), 133.57 (s), 130.63 (s), 129.89 (d), 129.35 (d), 124.43 (d)

IR (thin film) $\nu_{max}$ 3055, 1562, 1537, 1393, 1265, 1194, 1136, 1092 cm$^{-1}$

LRMS (EI) 385 (4%), 383 ($[M+H]^+$, 10%), 381 (8%), 199 (25%), 197 (100%), 195 (92%)

HRMS (EI) calcd for $C_{12}H_6Cl_3NO_5S$ ($M^+$): 380.9027 found 380.9026

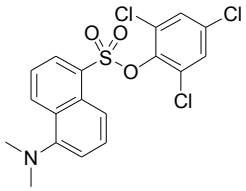
**Benzene sulfonic acid 2,4,6-trichlorophenyl ester (93)**



Synthesised using general procedure A. Purified by recrystallisation from dichloromethane/hexane to yield pale brown crystals (13.7 g, 41 mmol, 67%).

| | |
|---|---|
| MP | 62-63 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H, Ar*H*), 7.75-7.71 (m, 1H, Ar*H*), 7.62-7.58 (m, 2H, Ar*H*), 7.36 (s, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 142.31 (s), 136.97 (s), 134.66 (d), 132.91 (s), 130.90 (s), 129.24 (d), 129.18 (d), 128.53 (d) |
| IR (thin film) | $\nu_{max}$ 1562, 1443, 1387, 1265, 1190, 1092 cm$^{-1}$ |
| LRMS (EI) | 338 (2%), 336 ($M^+$, 1%), 141 (20%), 77 (100%) |
| HRMS (EI) | calcd for $C_{12}H_7Cl_3O_3S$ ($M^+$): 335.9176 found 335.9177 |

**5-Dimethylaminonaphthalene 2,4,6-trichlorophenylsulfonyl ester (94)**



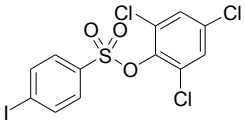
Synthesised using general procedure A. Purification by column chromatography (petroleum ether/diethyl ether) gave the product as a white solid (2.7 g, 6.3 mmol, 65%).

| | |
|---|---|
| MP | 130-132 °C |
| $^1$H NMR | (600 MHz, $CDCl_3$) δ 8.66 (d, 1H, *J* = 8.5 Hz, Ar*H*), 8.49 (d, 1H, *J* = 8.6 Hz, Ar*H*), 8.22 (dd, 1H, *J* = 1.2, 7.4 Hz, Ar*H*), 7.68 (dd, 1H, *J* = 7.6, 8.6 Hz, Ar*H*), 7.55 (dd, 1H, *J* = 7.4, 8.5 Hz, Ar*H*), 7.32 (s, 2H, Ar*H*), 7.26 (d, 1H, *J* = 7.6 Hz, Ar*H*), 2.91 (s, 6H, C*H*$_3$) |
| $^{13}$C NMR | (151 MHz, $CDCl_3$) δ 151.76 (s), 142.62 (s), 133.69 (s), 132.80 (s), 132.22 (d), 131.01 (s), 130.28 (s), 129.77 (d), 129.73 (s), 129.04 (d), 129.01 (d), 122.96 (d), 119.67 (d), 115.7 (d), 45.47 (q) |
| IR (thin film) | $\nu_{max}$ 3055, 2986, 2835, 1568, 1441, 1379, 1265, 1184 cm$^{-1}$ |

LRMS (EI) 431 (15%), 429 ($M^+$, 15%), 170 (100%), 149 (30%)

HRMS (EI) calcd for $C_{18}H_{14}Cl_3NO_3S$ ($M^+$): 428.9755 found 428.9743

**4-Iodobenzene sulfonic acid 2,4,6-trichlorophenyl ester (95)**




Synthesised using general procedure A. Purified by recrystallisation from hexane/dichloromethane to yield the product as white solid (20.9 g, 45 mmol 62%).

MP 124-126 °C

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.98-7.93 (m, 2H, Ar*H*), 7.74-7.69 (m, 2H, Ar*H*), 7.36 (s, 2H, Ar*H*)

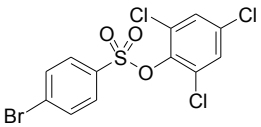
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.1 (s), 138.6 (d), 136.6 (s), 133.1 (s), 130.8 (s), 129.7 (d), 129.2 (d), 102.8 (s)

IR (thin film) $\nu_{max}$ 3053, 2986, 1570, 1445, 1391, 1265, 1055 $cm^{-1}$

LRMS (CI) 484 (25%), 482 (70%), 480 ($[M+NH_4]^+$, 68%), 358 (35%), 356 (100%), 354 (98%)

HRMS (EI) calcd for $C_{12}H_6Cl_3IO_3S$ ($M^+$): 461.8142 found 461.8146

**4-Bromobenzene sulfonic acid 2,4,6-trichlorophenyl ester (96)**




Synthesised using general procedure A. Purified by recrystallisation from dichloromethane/hexane to yield a white solid (18.1 g, 44 mmol, 72%).

MP 109-111 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H, Ar*H*), 7.76-7.72 (m, 2H, Ar*H*), 7.36 (s, 2H, Ar*H*)

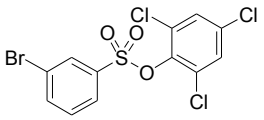
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.16 (s), 135.95 (s), 133.14 (s), 132.61 (d), 130.80 (s), 130.12 (s), 129.95 (d), 129.24 (d)

IR (thin film) $\nu_{max}$ 3053, 1576, 1445, 1394, 1265, 1194, 1069 $cm^{-1}$

LRMS (EI) 418 (7%), 416 (10%), 414 ($M^+$, 5%), 219 (65%), 217 (65%), 155 (100%), 157 (100%)

HRMS (EI) calcd for $C_{12}H_6BrCl_3O_3S$ ($M^+$): 413.8281 found 413.8281

**3-Bromobenzene sulfonic acid 2,4,6-trichlorophenyl ester (97)**



Synthesised using general procedure A. Purified by trituration with hexane to yield a white solid (14.1 g, 34 mmol, 87%).

MP 119-121 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.17 (app. t, 1H, *J* = 1.8 Hz, Ar*H*), 7.97 (ddd, 1H, *J* = 1.0, 1.6, 7.9 Hz, Ar*H*), 7.86 (ddd, 1H, J = 0.9, 1.8, 8.0 Hz, Ar*H*), 7.48 (app. t, 1H, *J* = 8.0 Hz, Ar*H*), 7.38 (s, 2H, Ar*H*),

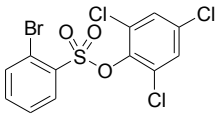
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.15 (s), 138.63 (s), 137.69 (d), 133.20 (s), 131.32 (d), 130.77 (s), 130.68 (d), 129.26 (d), 127.03 (d), 123.06 (s)

IR (thin film) $\nu_{max}$ 3055, 1562, 1443, 1391, 1265, 1190 $cm^{-1}$

LRMS (CI) 421 (20%), 419 (65%), 417 (100%), 415 ($[M+H]^+$, 50%), 221 (38%), 219 (36%), 199 (40%), 197 (62%), 195 (30%)

HRMS (CI) calcd for $C_{12}H_7BrCl_3O_3S$ ($[M + H]^+$): 414.8359 found 414.8348

**2-Bromobenzene sulfonic acid 2,4,6-trichlorophenyl ester (98)**



Synthesised using general procedure A. Purified by trituration with hexane to yield a white solid (14.0 g, 34 mmol, 86%).

MP 139 - 141 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, 1H, *J* = 2.1, 7.5 Hz, Ar*H*), 7.85 (dd, 1H, *J* = 1.6, 7.6 Hz, Ar*H*), 7.55-7.46 (m, 2H, Ar*H*), 7.35 (s, 2H, Ar*H*)

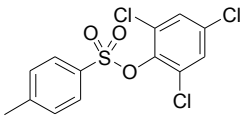
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.49 (s), 138.09 (s), 135.71 (d), 135.11 (d), 133.10 (s), 131.38 (d), 130.85 (s), 129.10 (d), 127.59 (d), 121.55 (s)

IR (thin film) $\nu_{max}$ 1568, 1443, 1387, 1265, 1192, 1128 $cm^{-1}$

LRMS 421 (20%), 419 (62%), 417 (100%), 415 ($[M+H]^+$, 45%), 221 (58%), 219 (54%), 199 (40%), 197 (75%), 195 (40%)

HRMS (CI) calcd for $C_{12}H_7BrCl_3O_3S$ ([M + H]$^+$): 414.8359 found 414.8348

**Toluene-4-sulfonic acid 2,4,6-trichlorophenyl ester (88)**



Synthesised using general procedure B. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (495 mg, 1.4 mmol, 69%).

MP 84-87 ºC

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.39 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.35 (s, 2H, Ar*H*), 2.48 (s, 3H, C*H*$_3$)

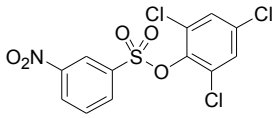
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 145.93 (s), 142.41 (s), 134.02 (s), 132.81 (s), 130.48 (s), 129.85 (d), 129.16 (d), 128.61 (d), 21.83 (q)

IR (thin film) $\nu_{max}$ 3055, 2988, 1562, 1439, 1387, 1265, 1192, 1180 cm$^{-1}$

LRMS (EI) 352 (8%), 350 (M$^+$, 10%), 200 (30%), 155 (45%), 91 (100%)

HRMS (EI) calcd for $C_{13}H_9Cl_3O_3S$ (M$^+$): 349.9338 found 349.9342

**3-Nitrophenyl 2,4,6-trichlorophenyl sulfonyl ester (99)**



Synthesised using general procedure B. The product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (689 mg, 1.8 mmol, 72 %).

MP 129-130 ºC

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.88 (app. t, 1H, J = 1.9 Hz, Ar*H*), 8.59 (ddd, 1H, J = 1.0, 2.2, 8.2 Hz, Ar*H*), 8.37 (ddd, 1H, J = 1.1, 1.7, 7.9 Hz, Ar*H*), 7.85 (app.t, 1H, J = 8.1 Hz, Ar*H*), 7.39 (s, 2H, Ar*H*)

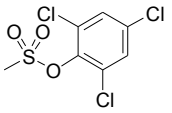
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 148.23 (s), 141.98 (s), 139.01 (s), 133.88 (d), 133.61 (s), 130.76 (d), 130.60 (s), 129.41 (d), 129.03 (d), 123.86 (d)

IR (thin film) $\nu_{max}$ 3053, 1541, 1396, 1354, 1265, 1196 cm$^{-1}$

LRMS (EI) 381 ($M^+$, 8%) 323 (82%), 313 (35%), 135 (35%) 81 (100%), 79 (58%)

HRMS (EI) calcd for $C_{12}H_6Cl_3NO_5S$ ($M^+$): 380.9027 found 380.8905

**Methyl 2,4,6-trichlorophenylsulfonyl ester (100)**



Synthesised using general procedure B. The product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (629 mg, 2.3 mmol, 44 %).

MP 63-66 ºC

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 2H, Ar*H*), 3.46 (s, 3H, C*H*$_3$)

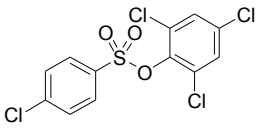
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.06 (s), 133.14 (s), 130.65 (s), 129.24 (d), 41.10 (q)

IR (thin film) $\nu_{max}$ 3055, 1562, 1447, 1379, 1184 $cm^{-1}$

LRMS (CI) 277 (80%), 275 ($M^+$, 80%), 199 (100%), 197 (100%), 167 (80%), 165 (85%), 97 (72%)

HRMS (CI) calcd for $C_7H_6Cl_3O_3S$ ($[M+H]^+$): 274.9103 found 274.9110

**4-Chlorobenzenesulfonic acid 2,4,6-trichlorophenyl ester (101)**



Synthesised using general procedure B. The product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (555 mg, 1.5 mmol, 80%).

MP 100-103 ºC

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H, Ar*H*), 7.58-7.56 (m, 2H, Ar*H*), 7.37 (s, 2H, Ar*H*)

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.26 (s), 141.60 (s), 135.49 (s), 133.20 (s), 130.88 (s), 130.02 (d), 129.69 (d), 129.32 (d)

IR (thin film) $\nu_{max}$ 3055, 1558, 1435, 1391, 1192, 1088 $cm^{-1}$

LRMS 375 (55%), 373 (100%), 371 ($M^+$, 75%), 197 (20%), 195 (18%), 177 (15%), 175 (35%)

HRMS (CI) calcd for $C_{12}H_7Cl_4O_3S$ ($[M+H]^+$): 370.8870 found 370.8881

# Aminolysis

### General Procedure C

To a solution of the TCP sulfonate (0.28 mmol) in NMP (1 mL) was added the amine (0.56 mmol) and triethylamine (0.31 mmol). The resultant mixture was heated in the microwave for 10 minutes at 140 ºC. The reaction mixture was diluted with $Et_2O$ (20 mL) and washed with 10% lithium chloride solution (2 x 10 mL), 2 M sodium carbonate solution (2 x 10 mL), 2 M hydrochloric acid (2 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*.

### General Procedure D

To a solution of the TCP sulfonate (0.28 mmol) in anhydrous THF (2 mL) under nitrogen was added the amine (0.56 mmol) and LHMDS (1M solution in THF) (0.56 mmol). The mixture was stirred for 4 h at 50 ºC. The reaction mixture was diluted with $Et_2O$ (20 mL) and washed with 2 M sodium carbonate solution (2 x 10 mL), 2 M hydrochloric acid (2 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*.

### General Procedure E

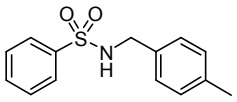
To a solution of the TCP sulfonate (0.62 mmol) in THF (3.5 mL) was added the amine (0.53 mmol) and a 1 M solution of LHMDS in THF (1.24 mmol). The mixture was heated in the microwave at 120ºC for 30 minutes. The reaction mixture was concentrated *in vacuo* and then partitioned between ethyl acetate (20 mL) and 1 M hydrochloric acid (10 mL). The organic layer was washed with water (10 mL x 2), dried ($Na_2SO_4$) and concentrated *in vacuo*.

### General Procedure F

To a solution of the PFP sulfonate (0.31 mmol) in anhydrous THF (2 mL) under nitrogen was added the amine (0.46 mmol) and triethylamine (0.93 mmol). The mixture was stirred for 6 h at reflux. The reaction mixture was diluted with $Et_2O$ (20

mL) and washed with saturated sodium hydrogencarbonate solution (2 x 10 mL), 2M hydrochloric acid (2 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*.

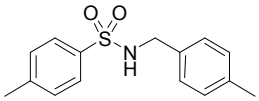
**_N_-(4-Methyl-benzyl)-benzenesulfonamide (80)**



Synthesised using general procedure F. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a pale yellow solid (56 mg, 0.21 mmol, 69%).

| | |
|---|---|
| MP | 84-86 °C, Lit.[186] 85-87 °C (hexane/ethyl acetate) |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H, Ar*H*), 7.61-7.58 (m, 1H, Ar*H*), 7.54-7.51 (m, 2H, Ar*H*), 7.09-7.05 (m, 4H, Ar*H*), 4.57 (t, 1H, *J* = 5.0 Hz, N*H*), 4.11 (d, 2H, *J* = 5.9 Hz, C$H_2$), 2.31 (s, 3H, C$H_3$) |
| $^{13}$C NMR | (126 MHz, $CDCl_3$) δ 139.98 (s), 137.89 (s), 133.14 (s), 132.77 (d), 129.48 (d), 129.22 (d), 127.93 (d), 127.21 (d), 47.19 (t), 21.15 (q) |
| IR (thin film) | $\nu_{max}$ 3265, 1446, 1420, 1320, 1157 cm$^{-1}$ |
| LRMS (CI) | 279 ($[M + NH_4]^+$, 100%), 262 (50%) |
| HRMS (ES) | calcd for $C_{14}H_{19}N_2O_2S$ ($[M + NH_4]^+$): 279.1162 found 279.1168 |

**4-Methyl-_N_-(4-methylbenzyl)benzenesulfonamide (81)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (73 mg, 94 %).

| | |
|---|---|
| MP | 93-96 ºC, Lit.[187] 86.7 ºC |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.77-7.75 (m, 2H, Ar*H*), 7.32-7.30 (m, 2H, Ar*H*), 7.10-7.06 (m, 4H, Ar*H*), 4.53 (br t, 1H, *J* = 5.6 Hz, N*H*), 4.08 (d, 2H, *J* = 6.0 Hz, C$H_2$), 2.44 (s, 3H, C$H_3$), 2.31 (s, 3H, C$H_3$) |

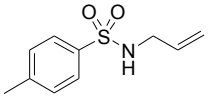
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.59 (s), 137.84 (s), 136.93 (s), 133.24 (s), 129.81 (d), 129.43 (d), 127.94 (d), 127.28 (d), 47.16 (t), 21.62 (q), 21.15 (q)

IR (thin film) $\nu_{max}$ 3053, 2986, 1421, 1331, 1265, 1161, 1094, 1057 $cm^{-1}$

LRMS (EI): 275 ($M^+$, 5%), 139 (40%), 120 (100%), 105 (70%), 91 (85%)

HRMS (EI): calcd for $C_{15}H_{17}NO_2S$ ($M^+$): 275.0980 found 275.0981

**_N_-Allyl 4-methylbenzenesulfonamide (102)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield a yellow solid (50 mg, 0.24 mmol, 83%).

MP 63-64 ºC, Lit.[188] 63-65 ºC (aq. MeOH)

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H, Ar*H*), 7.31-7.29 (m, 2H, Ar*H*), 5.71 (ddt, 1H, *J* = 17.0, 10.2, 5.8 Hz, $CH_2HC{=}CH_2$), 5.15 (app. dq, 1H, *J* = 17.1, 1.6 Hz, CH=C*H*H), 5.08 (app. dq, 1H, *J* = 10.2, 1.3 Hz, CH=C*H*H), 4.77 (t, 1H, *J* = 6.0, N*H*), 3.57 (app. tt, 2H, *J* = 1.5, 7.5 Hz , $CH_2$-CH=$CH_2$), 2.42 (s, 3H, $CH_3$)

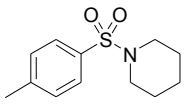
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.52 (s), 136.98 (s), 133.02 (d), 129.75 (d), 127.18 (d), 117.68 (t), 45.79 (t), 21.55 (q)

IR (thin film) $\nu_{max}$ 3055, 2987, 1421, 1333, 1265, 1163, 1094 $cm^{-1}$

LRMS (EI) 211 ($M^+$, 8%) 155 (25%), 91 (100%)

HRMS (EI) calcd for $C_{10}H_{13}NO_2S$ ($M^+$): 211.0667 found 211.0664

**1-(Toluene-4-sulfonyl)-piperidine (103)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give the product as a white solid (60 mg, 88 %).

MP 92-95 ºC, Lit.[87] 93 ºC (ethyl acetate)

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.64-7.62 (m, 2H, Ar*H*), 7.32-7.30 (m, 2H, Ar*H*), 2.96 (t, 4H, *J* = 5.5 Hz, C$H_2$), 2.42 (s, 3H, C$H_3$), 1.65-1.61 (m, 4H, C$H_2$), 1.43–1.38 (m, 2H, C$H_2$)

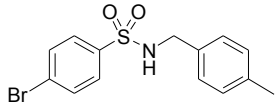
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.35 (s), 133.35 (s), 129.60 (d), 127.79 (d), 47.01 (t), 25.24 (t), 23.60 (t), 21.59 (q)

IR (thin film) $\nu_{max}$ 3055, 2928, 1339, 1165 cm$^{-1}$

LRMS (EI) 239 ($M^+$, 80%), 238 (90%), 155 (100%), 91 (98%)

HRMS (EI) calcd for $C_{12}H_{17}NO_2S$ ($M^+$): 239.0980 found 239.0973

**4-Bromo-*N*-(4-methylbenzyl)benzenesulfonamide (104)**




Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give the product as a yellow solid (69 mg, 0.25 mmol, 84%).

MP 124-128 ºC

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.72-7.70 (m, 2H, Ar*H*), 7.64-7.61 (m, 2H, Ar*H*), 7.09-7.04 (m, 4H, Ar*H*), 4.68 (br t, 1H, *J* = 5.6 Hz, N*H*), 4.09 (d, 2H, *J* = 6.0 Hz, C$H_2$), 2.31 (s, 3H, C$H_3$)

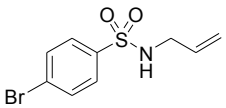
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 139.04 (s), 137.99 (s), 132.75 (s), 132.38 (d), 129.46 (d), 128.71 (d), 127.88 (d), 127.65 (s), 47.12 (t), 21.11 (q)

IR (thin film) $\nu_{max}$ 3053, 1575, 1421, 1335, 1265, 1165 cm$^{-1}$

LRMS (EI) 221 (16%), 219 (14%), 120 (24%), 86 (64%), 84 (100%)

HRMS (EI) calcd for $C_{14}H_{14}BrNO_2S$ ($M^+$): 338.9923 found 338.9910

***N*-Allyl 4-bromobenzenesulfonamide (105)**

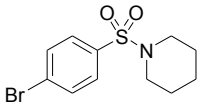



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a brown solid (57 mg, 0.21 mmol, 78%).

MP 62-64 ºC, Lit.[189] 60-61 ºC

| | |
|---|---|
| $^1$H NMR | (300 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H, Ar*H*), 7.67-7.63 (m, 2H, Ar*H*), 5.71 (ddt, 1H, *J* = 16.0, 10.2, 5.8 Hz, $CH_2HC{=}CH_2$), 5.17 (app. dq, 1H, *J* = 17.1, 1.6 Hz, CH=C*H*H), 5.10 (app. dq, 1H, *J* = 10.2, 1.3 Hz, CH=C*H*H), 4.83 (t, 1H, *J* = 6.0 Hz, N*H*), 3.60 (app. tt, 2H, *J* = 1.5, 6.0 Hz , $CH_2$-CH=$CH_2$) |
| $^{13}$C NMR | (75 MHz, $CDCl_3$) δ 139.1 (s), 132.7 (d), 132.4 (d), 128.7 (d), 127.7 (s), 118.0 (t), 45.8 (t) |
| IR (thin film) | $\nu_{max}$ 3055, 1578, 1421, 1339, 1265, 1167 cm$^{-1}$ |
| LRMS (EI) | 278 (10%), 276 ([M + H]$^+$, 10%), 221 (50%), 219 (46%), 157 (95%), 155 (100%) |
| HRMS (EI) | calcd for $C_9H_{10}BrNO_2S$ ($M^+$): 274.9610 found 274.9607 |

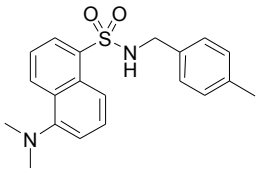
**1-(4-Bromobenzenesulfonyl)piperidine (106)**




Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (60 mg, 0.20 mmol, 82%).

| | |
|---|---|
| MP | 87-90 ºC, Lit.[190] 90-91 ºC |
| $^1$H NMR | (300 MHz, $CDCl_3$) δ 7.67-7.58 (m, 4H, Ar*H*), 2.97 (t, 4H, *J* = 5.3 Hz, C$H_2$), 1.62 (app. quintet, 4H, *J* = 5.7 Hz, C$H_2$), 1.37-1.45 (m, 2H, C$H_2$) |
| $^{13}$C NMR | (75 MHz, $CDCl_3$) δ 135.5 (s), 132.3 (d), 129.2 (d), 127.6 (s), 46.9 (t), 25.1 (t), 23.5 (t) |
| IR (thin film) | $\nu_{max}$ 3055, 2945, 2854, 1576, 1467, 1342, 1265, 1171 cm$^{-1}$ |
| LRMS (EI) | 305 (72%), 304 (100%), 303 ($M^+$, 72%), 302 (86%), 223 (47%), 221 (48%), 155 (46%), 157 (45%) |
| HRMS (EI) | calcd for $C_{11}H_{14}BrNO_2S$ ($M^+$): 302.9923 found 302.9928 |

**5-Dimethylaminonaphthalene 1-sulfonic acid 4-methylbenzylamide (107)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield a yellow oil (74 mg, 0.21 mmol, 91%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, 1H, *J* = 8.5 Hz, Ar*H*), 8.28 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.57-7.50 (m, 2H, Ar*H*), 7.20 (d, 1H, *J* = 7.5 Hz, Ar*H*), 6.99-6.94 (m, 4H, Ar*H*), 4.97 (t, 1H, *J* = 6.0 Hz, N*H*), 4.02 (d, 2H, *J* = 6.0 Hz, C$H_2$), 2.90 (s, 6H, C$H_3$), 2.25 (s, 3H, C$H_3$)

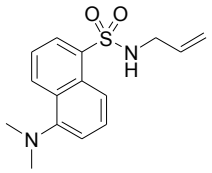
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 152.05 (s), 137.59 (s), 134.44 (s), 133.06 (s), 130.54 (d), 129.97 (d), 129.87 (s), 129.61 (s), 129.20 (d), 128.47 (d), 127.82 (d), 123.22 (d), 118.61 (d), 115.18 (d), 47.17 (t), 45.45 (q), 21.06 (q)

IR (thin film) $\nu_{max}$ 3055, 2986, 1574, 1421, 1331, 1146 cm$^{-1}$

LRMS (EI) 354 ($M^+$, 15%), 171 (100%)

HRMS (EI) calcd for $C_{20}H_{22}N_2O_2S$ ($M^+$): 354.1397 found 354.1388

**5-Dimethylaminonaphthalene 1-sulfonic acid allylamide (108)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a yellow oil (51 mg, 0.18 mmol, 77 %).

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, 1H, *J* = 8.5 Hz, Ar*H*), 8.31 (d, 1H, *J* = 8.6 Hz, Ar***H***), 8.26 (dd, 1H, *J* = 1.2, 7.3 Hz, Ar*H*), 7.49-7.59 (m, 2H, Ar*H*), 7.20 (d, 1H, *J* = 7.5 Hz, Ar*H*), 5.62 (ddt, 1H, *J* = 16.1, 10.2, 5.9 Hz, C*H*=$CH_2$), 5.08 (app. dq, 1H, *J* = 17.1, 1.6 Hz, CH=C(*H*)H), 5.00

(app. dq, 1H, *J* = 10.2, 1.2 Hz, CH=C(*H*)H), 4.80 (br. s, 1H, N*H*), 3.53 (app. tt, 2H, *J* = 1.4, 6.0 Hz, C$H_2$), 2.89 (s, 6H, C$H_3$)

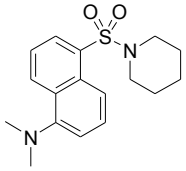
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 152.0 (s), 134.7 (s), 133.1 (d), 130.6 (d), 129.9 (s), 129.8 (d), 129.7 (s), 128.5 (d), 123.3 (d), 118.8 (d), 117.7 (t), 115.3 (d), 45.9 (t), 45.5 (q)

IR (thin film) $\nu_{max}$ 1576, 1456, 1412, 1327, 1265, 1163, 1146, 1063 cm$^{-1}$

LRMS (EI) 290 ($M^+$, 20%), 171 (100%), 170 (45%)

HRMS (EI) calcd for $C_{15}H_{18}N_2O_2S$ ($M^+$): 290.1084 found 290.1070

**Dimethyl [5-(piperidine 1-sulfonyl)napthalen-1-yl]amine (109)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a yellow oil (65 mg, 0.20 mmol, 89 %).

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.54 (app. dt, 1H, *J* = 1.0, 8.5 Hz, Ar*H*), 8.42 (m, 1H, Ar*H*), 8.20 (dd, 1H, *J* = 1.3, 7.3 Hz, Ar*H*), 7.55-7.50 (m, 2H, Ar*H*), 7.18 (dd, 1H, *J* = 0.7, 7.5 Hz, Ar*H*), 3.18 (t, 4H, *J* = 5.5 Hz, C$H_2$), 2.88 (s, 6H, C$H_3$), 1.62-1.56 (m, 4H, C$H_2$), 1.46-1.42 (m, 2H, C$H_2$)

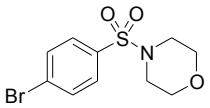
$^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.70 (s), 135.56 (s), 130.52 (s), 130.44 (d), 130.38 (d), 130.10 (s), 127.87 (d), 123.22 (d), 120.02 (d), 115.19 (d), 46.40 (t), 45.51 (q), 25.48 (t), 23.76 (t)

IR (thin film) $\nu_{max}$ 3055, 2945, 1574, 1456, 1335, 1163, 1140, 1061, 932 cm$^{-1}$

LRMS (EI) 318 ($M^+$, 25%), 171 (100%)

HRMS (EI) calcd for $C_{17}H_{22}N_2O_2S$ ($M^+$): 318.1397 found 318.1379

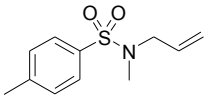
**4-(4-Bromobenzenesulfonyl)morpholine (110)**



To a solution of 4-bromobenzene TCP sulfonate (100 mg, 0.26 mmol) in THF (1 mL) was added morpholine (55 µl, 0.36 mmol) and LHMDS (1M solution in THF) (360 µl, 0.36 mmol). The mixture was stirred for 30min at rt. The reaction mixture was diluted with $Et_2O$ (20 mL) and washed with 2M sodium carbonate solution (2 x 10 mL), 2M hydrochloric acid (2 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (Petroleum ether/diethyl ether) to yield a white solid (71 mg, 0.23 mmol, 97%).

| | |
|---|---|
| MP | 147-149 °C, Lit.[191] 151-155 °C |
| $^1$H NMR | (300 MHz, $CDCl_3$) δ 7.72-7.59 (m, 4H, Ar*H*), 3.72–3.75 (m, 4H, C$H_2$), 2.98-3.01 (m, 4H, C$H_2$) |
| $^{13}$C NMR | (75 MHz, $CDCl_3$) δ 134.3 (s), 132.5 (d), 129.3 (d), 128.3 (s), 66.1 (t), 46.0 (t) |
| IR (thin film) | $\nu_{max}$ 3055, 2886, 1576, 1354, 1171 cm$^{-1}$ |
| LRMS (EI) | 307 (30%), 305 ($M^+$, 30%), 221 (20%), 219 (20%), 157 (20%), 155 (22%), 86 (100%) |
| HRMS (EI) | calcd for $C_{10}H_{12}BrNO_2S$ ($M^+$): 304.9716 found 304.9710 |

***N*-Allyl-4,*N*-dimethylbenzenesulfonamide (111)**



Synthesised using general method D. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield a yellow solid (32 mg, 0.14 mmol, 51%).

| | |
|---|---|
| $^1$H NMR | (300 MHz, $CDCl_3$) δ 7.67 (d, 2H, *J* = 8.2 Hz, Ar*H*), 7.32 (d, 2H, *J* = 7.9 Hz, Ar*H*), 5.71 (ddt, 1H, *J* = 16.2, 9.8, 6.3 Hz, $CH_2HC{=}CH_2$), 5.21-5.15 (m, 2H, $CH_2HC{=}CH_2$), 3.62 (d, 2H, *J* = 6.2 Hz , $CH_2CH{=}CH_2$), 2.65 (s, 3H, C$H_3$), 2.43 (s, 3H, C$H_3$) |

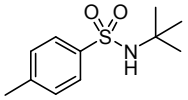
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.4 (s), 134.5 (s), 132.6 (d), 129.7 (d), 127.5 (d), 119.1 (t), 53.1 (t), 34.2 (q), 21.6 (q)

IR (thin film) $\nu_{max}$ 3055, 2986, 1421, 1339, 1265, 1163 $cm^{-1}$

LRMS (ES) 226 ($[M + H]^+$, 100), 473 (10%)

HRMS (ES) calcd for $C_{11}H_{16}NO_2S$ ($[M + H]^+$): 226.0896 found 226.0901

**_N_-tert-Butyl-4-methyl-benzenesulfonamide (112)**



Synthesised using general method D. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a brown solid (49 mg, 0.22 mmol, 75%).

MP 111-114 ºC, Lit.[192] 115-115.5 (ethanol)

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.8 Hz, Ar*H*), 7.26 (d, 2H, *J*= 7.3 Hz, Ar*H*), 4.70 (br. s, 1H, N*H*), 2.45 (3H, s, Ar$CH_3$), 1.24 (s, 9H, $C(CH_3)_3$)

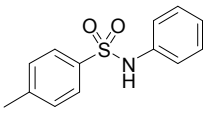
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.8 (s), 140.5 (s), 129.5 (d), 127.0 (d), 54.6 (s), 30.2 (q), 21.5 (q)

IR (thin film) $\nu_{max}$ 3055, 2984, 1421, 1323, 1151 $cm^{-1}$

LRMS (CI) 228 ($[M+H]^+$, 38%), 172 (100%)

HRMS (CI) calcd for $C_{11}H_{17}NO_2S$ ($[M+H]^+$): 228.1058 found 228.1055

**4-Methyl-_N_-phenylbenzenesulfonamide (113)**



Synthesised using general method D. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield a white solid (54 mg, 0.22 mmol, 78%).

MP 93 – 96 ºC, Lit.[193] 102 ºC

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H, Ar*H*), 7.26-7.23 (m, 4H, Ar*H*), 7.15-7.06 (m, 3H, Ar*H*), 6.47 (br s, 1H, N*H*), 2.39 (s, 3H, $CH_3$)

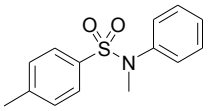
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.95 (s), 136.50 (s), 136.18 (s), 129.70 (d), 129.40 (d), 127.33 (d), 125.53 (d), 121.82 (d), 21.61 (q)

IR (thin film) $\nu_{max}$ 3234, 2918, 1597, 1482, 1415, 1335, 1294, 1154 $cm^{-1}$

LRMS (EI): 247 ($M^+$, 20%), 99 (58%), 86 (100%)

HRMS (EI): calcd for $C_{13}H_{13}NO_2S$ ($M^+$): 247.0662 found 247.0673

**4,*N*-Dimethyl-*N*-phenyl-benzenesulfonamide (114)**



Synthesised using general method D. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to yield the product as a white solid (68 mg, 0.26 mmol, 92 %).

MP 92-94 ºC, Lit.[194] 95-97 ºC

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.30-7.22 (m, 5H, Ar*H*), 7.08-7.11 (m, 2H, Ar*H*), 3.16 (s, 3H, C*H*$_3$), 2.41 (s, 3H, C*H*$_3$).

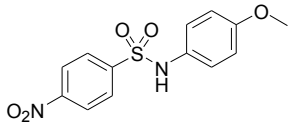
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.5 (s), 141.6 (s), 133.6 (s), 129.3 (d), 128.8 (d), 127.9 (d), 127.3 (d), 126.6 (d), 38.1 (q), 21.6 (q)

IR (thin film) $\nu_{max}$ 2924, 1598, 1455, 1336, 1156, 1088 $cm^{-1}$

LRMS (ES) 262 ($[M + H]^+$, 100%), 540 (20%)

HRMS (ES) calcd for $C_{14}H_{16}NO_2S$ ($[M + H]^+$): 262.0896 found 262.0897

***N*-(4-Methoxyphenyl) 4-nitrobenzenesulfonamide (116a)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a pale brown solid (84 mg, 0.27 mmol, 51%).

MP 183-185 °C, Lit.[195] 187-189 °C

$^1$H NMR (400 MHz, DMSO) δ 10.24 (s, 1H, N*H*), 8.38-8.35 (m, 2H, Ar*H*), 7.93-7.89 (m, 2H, Ar*H*), 7.00-6.96 (m, 2H, Ar*H*), 6.84-6.80 (m, 2H, Ar*H*), 3.67 (s, 3H, C*H*$_3$)

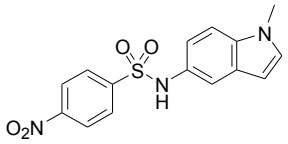
$^{13}$C NMR (101 MHz, DMSO) δ 156.88 (s), 149.62 (s), 144.76 (s), 120.04 (s), 128.20 (d), 124.45 (d), 124.00 (d), 114.37 (d), 55.07 (q)

IR (thin film) $\nu_{max}$ 3277, 1524, 1507, 1347, 1243, 1158 cm$^{-1}$

LRMS (ES) 307 (([M– H]$^-$, 100%)

HRMS (ES) calcd for $C_{13}H_{11}N_2O_5S$ ([M– H]$^-$) : 307.0383 found 307.0392

**_N_-(1-Methyl-1H-indol-5-yl) 4-nitrobenzenesulfonamide (116b)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (55 mg, 0.17 mmol, 31%).

MP 159-161 °C

$^1$H NMR (400 MHz, DMSO) δ 10.19 (s, 1H, N*H*), 8.35-8.31 (m, 2H, Ar*H*), 7.92-7.88 (m, 2H, Ar*H*), 7.30 (d, 1H, *J* = 8.7 Hz, Ar*H*), 7.30 (d, 1H, *J* = 3.0 Hz, Ar*H*), 7.24 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.85 (dd, 1H, *J* = 2.0, 8.7 Hz, Ar*H*), 6.34 (dd, 1H, *J* = 0.7, 3.0 Hz, Ar*H*), 3.72 (s, 3H, C*H*$_3$)

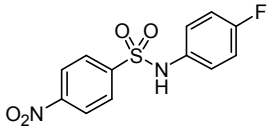
$^{13}$C NMR (101 MHz, DMSO) δ 149.50 (s), 145.02 (s), 134.32 (s), 130.62 (d), 128.23 (d), 128.03 (s), 127.91 (s), 124.33 (d), 117.21 (d), 114.63 (d), 110.06 (d), 100.26 (d), 32.44 (q)

IR (thin film) $\nu_{max}$ 3255, 1530, 1347, 1310, 1166 cm$^{-1}$

LRMS (CI) 332 ([M + H]$^+$, 32%), 145 (100%)

HRMS (CI) calcd for $C_{15}H_{14}N_3O_4S$ ([M + H]$^+$): 332.0705 found 332.0720

**_N_-(4-Fluorophenyl) 4-nitrobenzenesulfonamide (116d)**

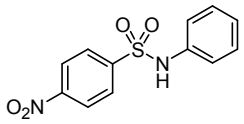


Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (118 mg, 0.40 mmol, 75%).

MP 181-184 °C, Lit.[196] 189.5-190 °C

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 10.56 (s, 1H, N*H*), 8.39-8.36 (m, 2H, Ar*H*), 7.96-7.93 (m, 2H, Ar*H*), 7.15-7.07 (m, 4H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 159.37 (d, $^1J_{CF}$ = 241.9 Hz), 149.76 (s), 144.43 (s), 132.92 (d, $^4J_{CF}$ = 2.7 Hz), 128.19 (d), 124.6 (d), 123.58 (dd, $^3J_{CF}$ = 8.5 Hz), 116.05 (dd, $^2J_{CF}$ = 22.7 Hz) |
| IR (thin film) | $\nu_{max}$ 3055, 1526, 1504, 1421, 1350, 1265, 1167 cm$^{-1}$ |
| LRMS (ES) | 295 ([M - H]$^-$, 100%) |
| HRMS (ES) | calcd for $C_{12}H_8FN_2O_4S$ ([M - H]$^-$): 295.0183 found 295.0188 |

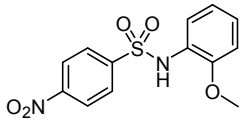
**4-Nitro-*N*-phenylbenzenesulfonamide (116e)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (104 mg, 0.37 mmol, 70%). Data in agreement with literature.[196]

| | |
|---|---|
| MP | 170-173 °C, Lit.[196] 172.5-173 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.30-8.26 (m, 2H, Ar*H*), 7.94-7.91 (m, 2H, Ar*H*), 7.29-7.26 (2H, m, Ar*H*), 7.21-7.18 (1H, m, Ar*H*), 7.09-7.06 (2H, m, Ar*H*), 6.79 (br s, 1H, N*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 150.26 (s), 144.62 (s), 125.27 (s), 129.71 (d), 128.53 (d), 126.56 (d), 124.30 (d), 122.47 (d) |
| IR (thin film) | $\nu_{max}$ 2852, 1522, 1464, 1377, 1337, 1313, 1159 cm$^{-1}$ |
| LRMS (ES) | 277 ([M - H]$^-$, 100%) |
| HRMS (ES) | calcd for $C_{12}H_9N_2O_4S$ ([M - H]$^-$): 277.0278 found 277.0276 |

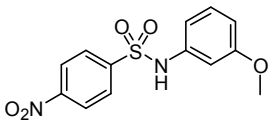
***N*-(2-Methoxyphenyl)4-nitrobenzenesulfonamide (116f)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (124 mg, 0.40 mmol, 76%).

| | |
|---|---|
| MP | 155-158 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.25-8.22 (m, 2H, Ar*H*), 7.93-7.90 (m, 2H, Ar*H*), 7.56 (dd, 1H, *J* = 1.6, 7.9 Hz, Ar*H*), 7.11 (ddd, 1H, *J* = 1.6, 7.6, 8.2 Hz, Ar*H*), 7.08 (br. s, 1H, N*H*), 6.94 (app. dt, 1H, *J* = 1.2, 7.7 Hz, Ar*H*), 6.75 (dd, 1H, *J* = 1.3, 7.7 Hz, Ar*H*), 3.62 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 150.11 (s), 149.89 (s), 144.84 (s), 128.53 (d), 126.62 (d), 124.63 (s), 123.92 (d), 122.25 (d), 121.32 (d), 110.75 (d), 55.60 (q) |
| IR (thin film) | $\nu_{max}$ 3277, 1608. 1525, 1507, 1347, 1243, 1158 cm$^{-1}$ |
| LRMS (ES) | 331 ($[M + Na]^+$, 100%), 262 (85%) |
| HRMS (ES) | calcd for $C_{13}H_{16}N_3O_5S$ ($[M + NH_4]^+$): 326.0805 found 326.0803 |

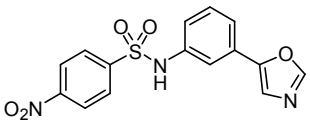
**_N_-(3-Methoxyphenyl)4-nitrobenzenesulfonamide (116g)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (115 mg, 0.37 mmol, 70%).

| | |
|---|---|
| MP | 118-121 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.30-8.26 (m, 2H, Ar*H*), 7.99-7.96 (m, 2H, Ar*H*), 7.18-7.13 (m, 1H, Ar*H*), 7.11 (br. s, 1H, N*H*), 6.71-6.69 (m, 2H, Ar*H*), 6.64-6.61 (m, 1H, Ar*H*), 3.75 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 160.48 (s), 150.26 (s), 144.50 (s), 136.55 (s), 130.44 (d), 128.57 (d), 124.34 (d), 113.88 (d), 111.55 (d), 107.97 (d), 55.41 (q) |
| IR (thin film) | $\nu_{max}$ 3246, 1606, 1593, 1529, 1348, 1261, 1155 cm$^{-1}$ |
| LRMS (ES) | 307 ($[M – H]^-$, 100%) |
| HRMS (ES) | calcd for $C_{13}H_{11}N_2O_5S$ ($[M – H]^-$): 307.0383 found 307.0371 |

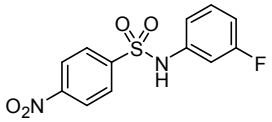
***N*-[3-(2-Amino-1-hydroxyvinyl)-phenyl]4-nitrobenzenesulfonamide (116h)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow oil (116 mg, 0.34 mmol, 64%).

| | |
|---|---|
| MP | 177-180 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 10.83 (s, 1H, N*H*), 8.45 (s, 1H, Ar*H*), 8.38 (d, 2H, *J* = 8.9 Hz, Ar*H*), 8.03 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.66 (s, 1H, Ar*H*), 7.48-7.46 (m, 2H, Ar*H*), 7.36 (app. t, 1H, *J* = 8.2 Hz, Ar*H*), 7.10-7.08 (m, 1H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 152.47 (d), 150.31 (s), 150.06 (s), 144.98 (s), 138.14 (s), 130.71 (d), 128.81 (d), 128.67(s), 125.15 (d), 123.00 (d), 120.95 (d), 120.95 (d), 115.91 (d) |
| IR (thin film) | $\nu_{max}$ 3141, 1609, 1516, 1494, 1347, 1158 cm$^{-1}$ |
| LRMS (ES) | 344 ([M – H]$^-$, 100%) |
| HRMS (ES) | calcd for $C_{15}H_{10}N_3O_5S$ ([M – H]$^-$): 344.0336 found 344.0329 |

***N*-(3-Fluorophenyl)4-nitrobenzenesulfonamide (116i)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (122 mg, 0.41 mmol, 77%).

| | |
|---|---|
| MP | 136-138 °C, Lit.[197] 131-132 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 10.92 (s, 1H, N*H*), 8.40-8.38 (m, 2H, Ar*H*), 8.05-8.02 (m, 2H, Ar*H*), 7.33-7.27 (m, 1H, Ar*H*), 6.96-6.89 (m, 3H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.13 (d, $^1J_{CF}$ = 241.1), 149.90 (s), 144.33 (s), 138.65 (d, $^3J_{CF}$ = 10.3 Hz), 131.13 (dd, $^3J_{CF}$ = 9.5 Hz), 128.19 (d), |

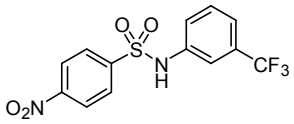
124.71 (d), 115.78 (dd, $^4J_{CF}$ = 2.8 Hz), 111.18 (dd, $^2J_{CF}$ = 21.0 Hz), 106.79 (dd, $^2J_{CF}$ = 25.3 Hz)

IR (thin film) $\nu_{max}$ 3262, 1600, 1522, 1485, 1332, 1306, 1156, 1132 $cm^{-1}$

LRMS (ES) 295 ($[M - H]^-$, 100%), 231 (15%)

HRMS (ES) calcd for $C_{12}H_8FN_2O_4S$ ($[M - H]^-$): 295.0183 found 295.0178

**4-Nitro-*N*-(3-trifluoromethylphenyl)benzenesulfonamide (116j)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (135 mg, 0.39 mmol, 74%).

MP 148-150 °C, Lit.[197] 148-149 °C

$^1$H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, N*H*), 8.41-8.38 (m, 2H, Ar*H*), 8.05-8.02 (m, 2H, Ar*H*), 7.55-7.40 (m, 4H, Ar*H*)

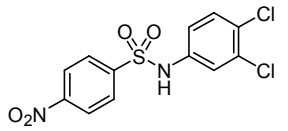
$^{13}$C NMR (101 MHz, DMSO) δ 149.96 (s), 144.21 (s), 137.76 (s), 130.78 (d), 129.92 (q, $^2J_{CF}$ = 37.0 Hz), 128.20 (d), 124.78 (d), 123.64 (d), 123.57 (q, $^1J_{CF}$ = 272.5 Hz), 121.06 (dq, $^3J_{CF}$ = 3.8 Hz), 116.1 (dq, $^3J_{CF}$ = 4.0 Hz)

IR (thin film) $\nu_{max}$ 3267, 3055, 1533, 1331, 1265, 1171 $cm^{-1}$

LRMS (ES) 345 ($[M - H]^-$, 100%),

HRMS (ES) calcd for $C_{13}H_8F_3N_2O_4S$ ($[M - H]^-$): 345.0151 found 345.0145

***N*-(3,4-Dichlorophenyl)-4-nitrobenzenesulfonamide (116k)**

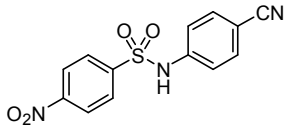


Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a orange solid (136 mg, 0.39 mmol, 74%).

MP 169-171 °C, Lit.[198] 178 °C

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 11.03 (s, 1H, N*H*), 8.42-8.38 (m, 2H, Ar*H*), 8.04-8.01 (m, 2H, Ar*H*), 7.55 (d, 1H, *J* = 8.7 Hz, Ar*H*), 7.30 (d, 1H, *J* = 2.5 Hz, Ar*H*), 7.11 (dd, 1H, *J* = 2.5, 8.7 Hz, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 149.99 (s), 144.05 (s), 137.05 (s), 131.52 (s), 131.34 (d), 128.18 (d), 126.70 (s), 124.81 (d), 121.42 (d), 121.09 (d) |
| IR (thin film) | $\nu_{max}$ 3240, 1523, 1471, 1350, 1312, 1169 cm$^{-1}$ |
| LRMS (ES) | 345 ([M – H]$^-$, 100%), 347 (45%) |
| HRMS (ES) | calcd for $C_{12}H_7Cl_2N_2O_4S$ ([M – H]$^-$): 344.9498 found 344.9502 |

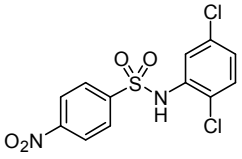
**_N_-(4-Cyanophenyl)4-nitrobenzenesulfonamide (116m)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give an orange solid (120 mg, 0.40 mmol, 75%).

| | |
|---|---|
| MP | 190-193 °C, Lit.[199] 193-196 (aq. Ethanol) |
| $^1$H NMR | (400 MHz, DMSO) δ 11.36 (s, 1H, N*H*), 8.42-8.38 (m, 2H, Ar*H*), 8.10-8.07 (m, 2H, Ar*H*), 7.76-7.73 (m, 2H, Ar*H*), 7.29-7.26 (m, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 150.05 (s), 144.22 (s), 141.42 (s), 133.78 (d), 128.22 (d), 124.86 (d), 119.02 (d), 118.47 (s), 106.09 (s) |
| IR (thin film) | $\nu_{max}$ 3215, 2225, 1606, 1532, 1348, 1167 cm$^{-1}$ |
| LRMS (CI) | 304 ([M+H]$^+$, 100%), 119 (30%) |
| HRMS (CI) | calcd for $C_{13}H_{10}N_3O_4S$ ([M+H]$^+$): 304.0392 found 304.0411 |

**_N_-(2,5-Dichlorophenyl)4-nitrobenzenesulfonamide (116n)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give an orange solid (162 mg, 0.47 mmol, 88%).

MP 168-170 °C

$^{1}$H NMR (400 MHz, DMSO) δ 10.75 (br. s, 1H, N*H*), 8.42-8.38 (m, 2H, Ar*H*), 7.99-7.95 (m, 2H, Ar*H*), 7.49-7.47 (m, 1H, Ar*H*), 7.38-7.35 (m, 2H, Ar*H*)

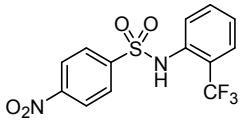
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 150.55 (s), 144.18 (s), 134.04 (s), 133.30 (s), 130.40 (d), 128.57 (d), 127.13 (d), 124.49 (d), 123.89 (s), 123.27(d)

IR (thin film) $\nu_{max}$ 3055, 1537, 1479, 1350, 1175 cm$^{-1}$

LRMS (ES) 345 ([M – H]$^-$, 100%), 347 (40%)

HRMS (ES) calcd for $C_{12}H_7Cl_2N_2O_4S$ ([M – H]$^-$): 344.9498 found 344.9501

**4-Nitro-*N*-(2-trifluoromethylphenyl)benzenesulfonamide (116o)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (128 mg, 0.37 mmol, 70%).

MP 147-148 °C

$^{1}$H NMR (400 MHz, DMSO) δ 10.46 (s, 1H, N*H*), 8.47-8.44 (m, 2H, Ar*H*), 8.05-8.02 (m, 2H, Ar*H*), 7.75 (dd, 1H, *J* = 1.3, 7.8 Hz, Ar*H*), 7.62-7.58 (m, 1H, Ar*H*), 7.50 (app. t, 1H, *J* = 7.6 Hz, Ar*H*), 7.02 (d, 1H, *J* = 8.0 Hz, Ar*H*)

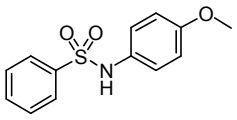
$^{13}$C NMR (101 MHz, DMSO) δ 149.67 (s), 146.46 (s), 133.44 (d), 133.25 (s), 129.06 (d), 128.14 (d), 127.94 (d), 127.14 (dq, $^{3}J_{CF}$ = 5.1 Hz), 126.52 (q, $^{2}J_{CF}$ = 29.6 Hz), 124.69 (d), 123.06 (q, $^{1}J_{CF}$ = 274 Hz)

IR (thin film) $\nu_{max}$ 3285, 3055, 1533, 1418, 1350, 1175, 1113 cm$^{-1}$

LRMS (ES) 345 ([M - H]$^-$, 100%)

HRMS (ES) calcd for $C_{13}H_8F_3N_2O_4S$ ([M - H]$^-$): 345.0151 found 345.0145

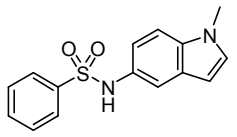
***N*-(4-Methoxyphenyl)benzenesulfonamide (117a)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (110 mg, 0.42 mmol, 79%).

| | |
|---|---|
| MP | 96-99 °C, Lit.[200] 95-96 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 7.74 -7.71 (m, 2H, Ar*H*), 7.53 (app. tt, 1H, *J* = 1.3, 7.4 Hz, Ar*H*), 7.44 -7.40 (m, 2H, Ar*H*), 7.00-6.96 (m, 2H, Ar*H*), 6.88 (br. s, 1H, N*H*), 6.77-6.73 (m, 2H, Ar*H*), 3.74 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 157.98 (s), 138.86 (s), 132.88 (d), 128.94 (d), 128.74 (s), 127.30 (d), 125.49 (d), 114.42 (d), 55.42 (q) |
| IR (thin film) | $\nu_{max}$ 3261, 3055, 1510, 1448, 1331, 1165cm$^{-1}$ |
| HRMS (CI) | 264 ([M + H]$^+$, 18%), 124 (100%) |
| HRMS (CI) | calcd for $C_{13}H_{14}NO_3S$ ([M + H]$^+$): 264.0689 found 264.0680 |

***N*-(1-methyl-1H-indol-5-yl)benzenesulfonamide (117b)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (129 mg, 0.45 mmol, 85%).

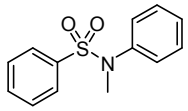
| | |
|---|---|
| MP | 139–141 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 9.85 (s, 1H, N*H*), 7.68-7.47 (m, 4H, Ar*H*), 7.28-7.26 (m, 2H, Ar*H*), 7.22 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.86 (dd, 1H, *J* = 2.0, 8.7 Hz, Ar*H*), 6.32 (dd, 1H, *J* = 0.7, 3.1 Hz, Ar*H*), 3.69 (s, 3H, C*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 140.05 (s), 134.61 (s), 132.94 (d), 130.96 (d), 129.48 (s), 129.44 (d), 128.39 (s), 127.15 (d), 117.52 (d), 114.56 (d), 110.37 (d), 100.67 (d), 32.97 (q) |

IR (thin film) $\nu_{max}$ 3255, 1530, 1347, 1310, 1166 $cm^{-1}$

LRMS (CI) 287 ($[M + H]^+$, 60%), 145 (100%)

HRMS (CI) calcd for $C_{15}H_{15}N_2O_2S$ ($[M + H]^+$): 287.0854 found 287.0842

**_N_-Methyl _N_-phenyl benzenesulfonamide (117c)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (104 mg, 0.42 mmol, 79%).

MP 79-81 °C, Lit.[201] 78-79 °C

$^1$H NMR (400 MHz, DMSO) δ 7.73-7.49 (m, 5H, Ar*H*), 7.37-7.26 (m, 3H, Ar*H*), 7.10-7.08 (m, 2H, Ar*H*), 3.14 (s, 3H, C*H*$_3$)

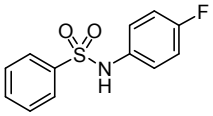
$^{13}$C NMR (101 MHz, DMSO) δ 140.98 (s), 135.84 (s), 133.19 (d), 129.11 (d), 128.80 (d), 127.28 (d), 127.14 (d), 126.05 (d), 37.80 (q)

IR (thin film) $\nu_{max}$ 3055, 2985, 1597, 1495, 1447, 1352, 1265, 1180, 1067 $cm^{-1}$

LRMS (CI) 248 ($[M + H]^+$, 95%), 106 (100%)

HRMS (CI) calcd for $C_{13}H_{14}NO_2S$ ($[M + H]^+$): 248.0745 found 248.0736

**_N_-(4-Fluorophenyl)benzenesulfonamide (117d)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (106 mg, 0.42 mmol, 80%).

MP 106-109 °C

$^1$H NMR (400 MHz, DMSO) δ 10.24 (br s, 1H, N*H*), 7.72-7.50 (m, 2H, Ar*H*), 7.64-7.52 (m, 3H, Ar*H*), 7.08 (d, 4H, *J* = 6.7 Hz, Ar*H*)

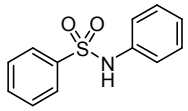
$^{13}$C NMR (100 MHz, DMSO) δ 158.86 (d, $^1J_{CF}$ = 241.0 Hz), 139.05 (s), 133.72 (d, $^4J_{CF}$ = 2.7 Hz), 132.85 (d), 129.16 (d), 126.54 (d), 122.74 (dd, $^3J_{CF}$ = 7.3 Hz), 115.79 (dd, $^2J_{CF}$ = 22.9 Hz)

IR (thin film) $\nu_{max}$ 3055, 2987, 1506, 1448, 1387, 1265, 1167, 1092 $cm^{-1}$

LRMS (CI) 252 ($[M + H]^+$, 25%), 164 (100%), 112 (80%)

HRMS (CI) calcd for $C_{12}H_{11}FNO_2S$ ($[M + H]^+$): 252.0489 found 252.0479

**_N_-Phenylbenzenesulfonamide (117e)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (118 mg, 0.51 mmol, 96%).

MP 112-114 °C, Lit.[202] 112-113 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H, Ar*H*), 7.54-7.40 (m, 3H, Ar*H*), 7.31 (br. s, 1H, N*H*), 7.25-7.07 (m, 5H, Ar*H*)

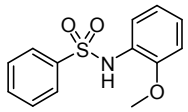
$^{13}$C NMR $\delta_C$ (100 MHz, $CDCl_3$) 138.90 (s), 136.41 (s), 133.04 (d), 129.32 (d), 129.05 (d), 127.23 (d), 125.39 (d), 121.61 (d)

IR (thin film) $\nu_{max}$ 3204, 1596, 1474, 1413, 1329, 1303, 1152 $cm^{-1}$

LRMS (CI) 234 ($[M + H]^+$, 35%), 94 (100%)

HRMS (CI) calcd for $C_{12}H_{12}NO_2S$ ($[M + H]^+$): 234.0583 found 234.0593

**_N_-(2-Methoxyphenyl)benzenesulfonamide (117f)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (125 mg, 0.47 mmol, 89%). Data in agreement with literature. [203]

MP 91-94 °C, Lit.[203] 88-89 °C

$^1$H NMR (400 MHz, DMSO) δ 9.48 (s, 1H, N*H*), 7.71-7.49 (m, 5H, Ar*H*), 7.20 (dd, 1H, *J* = 1.7, 7.8 Hz, Ar*H*), 7.11 (ddd, 1H, *J* = 1.7, 7.5, 8.2 Hz, Ar*H*), 6.90–6.84 (m, 2H, Ar*H*), 3.46 (s, 3H, OC*H*$_3$)

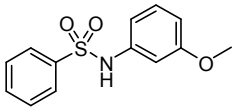
$^{13}$C NMR (101 MHz, DMSO) δ 152.24 (s), 140.43 (s), 132.38 (d), 128.67 (d), 126.59 (d), 126.51 (d), 125.17 (d), 125.09 (s), 120.27 (d), 111.66 (d), 55.26 (q)

IR (thin film) $\nu_{max}$ 3055, 1501, 1448, 1344, 1167, 1113 $cm^{-1}$

LRMS (CI) 263 ($[M + H]^+$, 35%), 123 (100%), 94 (30%)

HRMS (CI) calcd for $C_{13}H_{14}NO_3S$ ($[M + H]^+$): 264.0694 found 264.0679

**_N_-(3-Methoxyphenyl)benzenesulfonamide (117g)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (112 mg, 0.43 mmol, 80 %).

MP 82-84 °C, Lit.[204] 82.5-83.5 °C (aq. Ethanol)

$^1$H NMR (400 MHz, DMSO) δ 10.31 (s, 1H, N*H*), 7.78-7.76 (m, 2H, Ar*H*), 7.63-7.53 (m, 3H, Ar*H*), 7.14-7.10 (m, 1H, Ar*H*), 6.68-6.57 (m, 3H, Ar*H*), 3.65 (s, 3H, OC$H_3$)

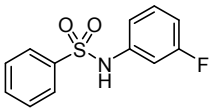
$^{13}$C NMR (101 MHz, DMSO) δ 159.55 (s), 139.34 (s), 138.78 (s), 132.83 (d), 129.91 (d), 129.17 (d), 126.56 (d), 111.78 (d), 108.93 (d), 105.57 (d), 54.88 (q)

IR (thin film) $\nu_{max}$ 3250, 1611, 1494, 1448, 1411, 1329, 1284, 1145 $cm^{-1}$

LRMS (CI) 264 ($[M + H]^+$, 75%), 124 (100%)

HRMS (CI) calcd for $C_{13}H_{14}NO_3S$ ($[M + H]^+$): 264.0689 found 264.0690

**_N_-(3-Fluorophenyl)benzenesulfonamide (117i)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (130 mg, 0.52 mmol, 98%).

MP 101-103 °C, Lit.[205] 97-98 °C

$^1$H NMR (400 MHz, DMSO) δ 10.61 (s, 1H, N*H*), 7.80-7.78 (m, 2H, Ar*H*), 7.66-7.55 (m, 3H, Ar*H*), 7.29-7.24 (m, 1H, Ar*H*), 6.93-6.82 (m, 3H, Ar*H*)

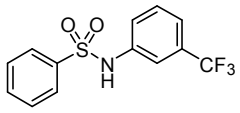
$^{13}$C NMR (101 MHz, DMSO) δ 162.10 (d, $^{1}J_{CF}$ = 242.5 Hz), 139.46 (d, $^{3}J_{CF}$ = 10.5 Hz), 139.03 (s), 133.08 (d), 130.89 (dd, $^{3}J_{CF}$ = 9.5 Hz), 129.31 (d), 126.55 (d), 115.24 (dd, $^{4}J_{CF}$ = 2.8 Hz), 110.42 (dd, $^{2}J_{CF}$ = 20.1 Hz), 106.42 (dd, $^{2}J_{CF}$ = 25.4 Hz)

IR (thin film) $\nu_{max}$ 3251, 1614, 1606, 1494, 1409, 1328, 1140, 1090 cm$^{-1}$

LRMS (CI) 252 ([M + H]$^{+}$, 65%), 143 (50%), 112 (100%)

HRMS (CI) calcd for $C_{12}H_{11}FNO_2S$ ([M + H]$^{+}$): 252.0489 found 252.0496

**_N_-(3-trifluoromethylphenyl)benzenesulfonamide (117j)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (140 mg, 0.46 mmol, 88%).

MP 77-79 °C

$^{1}$H NMR (400 MHz, DMSO) δ 10.75 (s, 1H, N*H*), 7.80-7.78 (m, 2H, Ar*H*), 7.66-7.56 (m, 3H, Ar*H*), 7.51-7.49 (m, 1H, Ar*H*), 7.39-7.37 (m, 3H, Ar*H*)

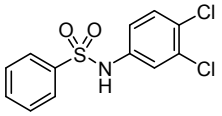
$^{13}$C NMR (101 MHz, DMSO) δ 138.86 (s), 138.51 (s), 133.21 (d), 130.33 (d), 129.74 (q, $^{2}J_{CF}$ = 32.9 Hz), 129.37 (d), 126.55 (d), 123.64 (q, $^{1}J_{CF}$ = 278.8 Hz), 123.18 (d), 120.35 (dq, $^{3}J_{CF}$ = 3.9 Hz), 115.51 (dq, $^{3}J_{CF}$ = 4.0 Hz)

IR (thin film) $\nu_{max}$ 3252, 1409, 1327, 1159, 1091 cm$^{-1}$

LRMS (CI) ([M + H]$^{+}$, 90%), 162 (88%), 142 (100%)

HRMS (CI) calcd for $C_{13}H_{11}F_3NO_2S$ ([M + H]$^{+}$): 302.0463 found 302.0459

**_N_-(3,4-Dichlorophenyl)benzenesulfonamide (117k)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (142 mg, 0.47 mmol, 89%).

MP 128-130 °C, Lit.[206] 130-130.5 °C

$^1$H NMR (400 MHz, DMSO) δ 10.72 (s, 1H, N*H*), 7.80-7.77 (m, 2H, Ar*H*), 7.68-7.63 (m, 1H, Ar*H*), 7.61-7.57 (m, 2H, Ar*H*), 7.51 (d, 1H, *J* = 8.8 Hz, Ar*H*), 7.28 (d, 1H, *J* = 2.6 Hz, Ar*H*), 7.10 (dd, 1H, *J* = 2.6, 8.8 Hz, Ar*H*)

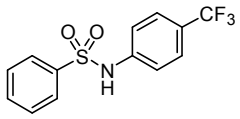
$^{13}$C NMR (101 MHz, DMSO) δ 138.74 (s), 137.82 (s), 133.28 (d), 131.32 (s), 131.16 (d), 129.43 (d), 126.54 (d), 125.91 (s), 120.74 (d), 119.53 (d)

IR (thin film) $\nu_{max}$ 3055, 1593, 1475, 1377, 1329, 1267, 1167 cm$^{-1}$

LRMS (CI) 304 (70%), 302 ([M + H]$^+$, 100%), 163 (32%), 161 (45%)

HRMS (CI) calcd for $C_{12}H_{10}Cl_2NO_2S$ ([M + H]$^+$): 301.9809 found 301.9812

***N*-(4-Trifluoromethylphenyl)benzenesulfonamide (117l)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (66 mg, 0.22 mmol, 41%).

MP 103-105 °C

$^1$H NMR (300 MHz, DMSO) δ 10.89 (s, 1H, N*H*), 7.83-7.80 (m, 2H, Ar*H*), 7.65-7.54 (m, 5H, Ar*H*), 7.27 (d, 2H, *J* = 8.7 Hz, Ar*H*)

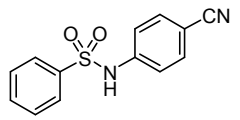
$^{13}$C NMR (151 MHz, DMSO) δ 139.65 (s), 138.72 (s), 133.53 (d), 129.33 (d), 127.17 (d), 126.98 (q, $^2J_{CF}$ = 32.8 Hz), 126.71 (dq, $^3J_{CF}$ = 3.4 Hz), 123.84 (q, $^1J_{CF}$ = 271.5 Hz), 120.01 (d)

IR (thin film) $\nu_{max}$ 3055, 1618, 1448, 1327, 1265, 1167, 1124, 1070, 916 cm$^{-1}$

LRMS (CI) 302 ([M + H]$^+$, 80%), 282 (64%), 171 (75%), 142 (100%)

HRMS (CI) calcd for $C_{13}H_{11}F_3NO_2S$ ([M + H]$^+$): 302.0463 found 302.0471

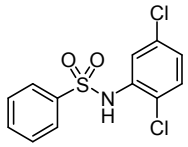
***N*-(4-Cyanophenyl)benzenesulfonamide (117m)**




Synthesised using general procedure E. The crude product was purified by column qchromatography (petroleum ether/ethyl acetate) to give a pale brown solid (116 mg, 0.45 mmol, 85%).

| | |
|---|---|
| MP | 172-175 °C, Lit.[207] 175-176 °C (ethanol) |
| $^1$H NMR | (400 MHz, DMSO) δ 11.07 (s, 1H, N*H*), 7.85-7.83 (m, 2H, Ar*H*), 7.72-7.57 (m, 5H, Ar*H*), 7.27-7.23 (m, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 142.08 (s), 138.92 (s), 133.61 (d), 133.37 (d), 129.48 (d), 126.56 (d), 118.58 (s), 118.41 (d), 105.35 (s) |
| IR (thin film) | $\nu_{max}$ 3247, 2222, 1606, 1507, 1464, 1329, 1155, 1089 cm$^{-1}$ |
| LRMS (CI) | 259 ([M + H]$^+$, 100%), 141 (60%), 119 (35%) |
| HRMS (CI) | calcd for $C_{13}H_{11}N_2O_2S$ ([M + H]$^+$): 259.0536 found 259.0539 |

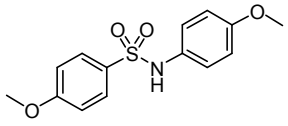
**_N_-(2,5-Dichlorophenyl)benzenesulfonamide (117n)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a pale brown solid (139 mg, 0.46 mmol, 87%).

| | |
|---|---|
| MP | 131-134 °C |
| $^1$H NMR | (300 MHz, DMSO) δ 10.29 (s, 1H, N*H*), 7.73-7.54 (m, 5H, Ar*H*), 7.43 (d, 1H, *J* = 8.1 Hz, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*) |
| $^{13}$C NMR | (75 MHz, DMSO) δ 139.8 (s), 134.8 (s), 133.1 (d), 131.6 (s), 131.2 (d), 129.3 (d), 127.5 (s), 127.3 (d), 126.6 (d), 126.5 (d) |
| IR (thin film) | $\nu_{max}$ 3055, 2986, 1585, 1481, 1391, 1342, 1265, 1169 cm$^{-1}$ |
| LRMS (CI) | 304 (34%), 302 ([M + H]$^+$, 45%), 279 (75%), 141 (100%), 84 (45%) |
| HRMS (CI) | calcd for $C_{12}H_{10}C1_2NO_2S$ ([M + H]$^+$): 301.9809 found 301.9815 |

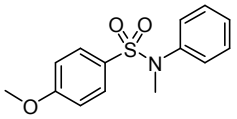
**_N_-(4-Methoxyphenyl)4-methoxybenzenesulfonamide (118a)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown glass (95 mg, 0.32 mmol, 61%). Data in agreement with literature.[208]

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 9.76 (s, 1H, N*H*), 7.62-7.58 (m, 2H, Ar*H*), 7.05-7.02 (m, 2H, Ar*H*), 6.97-6.94 (m, 2H, Ar*H*), 6.81-6.77 (m, 2H, Ar*H*), 3.79 (s, 3H, OC$H_3$), 3.66 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.14 (s), 156.28 (s), 131.00 (s), 130.26 (s), 128.75 (d), 123.15 (d), 114.13 (d), 55.49 (q), 55.02 (q) missing 1x d |
| LRMS (CI) | 294 ([M + H]$^+$, 100%), 123 (95%) |
| HRMS (CI) | calcd for $C_{14}H_{16}NO_4S$ ([M + H]$^+$) : 294.0800 found 294.0798 |

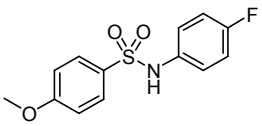
**4-Methoxy *N*-methyl *N*-phenyl benzenesulfonamide (118c)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (132 mg, 0.48 mmol, 90%).

| | |
|---|---|
| MP | 102-107 °C, Lit.[209] 109-110.3 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 7.44-7.40 (m, 2H, Ar*H*), 7.36-7.26 (m, 3H, Ar*H*), 7.11-7.07 (m, 4H, Ar*H*), 3.83 (s, 3H, OC$H_3$), 3.10 (s, 3H, NC$H_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.63 (s), 141.21 (s), 129.53 (d), 128.74 (d), 127.40 (s), 126.99 (d), 126.03 (d), 114.22 (d), 55.60 (q), 37.64 (q), |
| IR (thin film) | $\nu_{max}$ 3055, 2987, 1597, 1497, 1348, 1265, 1169, 1151 cm$^{-1}$ |
| LRMS (CI) | 278 ([M + H]$^+$, 45%), 107 (100%) |
| HRMS (CI) | calcd for $C_{14}H_{16}NO_3S$ ([M + H]$^+$): 278.0845 found 2.0849 |

***N*-(4-Fluorophenyl) 4-methoxybenzenesulfonamide (118d)**

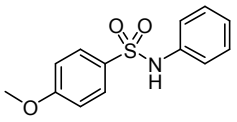


Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (132 mg, 0.47 mmol, 89%).

| | |
|---|---|
| MP | 114-116 °C |

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 10.09 (s, 1H, N*H*), 7.66-7.62 (m, 2H, Ar*H*), 7.08-7.03 (m, 6H, Ar*H*), 3.79 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.39 (s), 158.94 (d, $^1J_{CF}$ = 240.9 Hz), 134.08 (d, $^4J_{CF}$ = 2.6 Hz), 130.77 (s), 128.84 (d), 122.60 (dd, $^3J_{CF}$ = 8.2 Hz), 115.82 (dd, $^2J_{CF}$ = 22.7 Hz), 114.34 (d), 55.60 (q) |
| IR (thin film) | $\nu_{max}$ 3258, 3055, 1597, 1508, 1387, 1331, 1265, 1159, 1094 cm$^{-1}$ |
| LRMS (CI) | 282 ([M + H]$^+$, 35%), 171 (60%), 111 (65%), 97 (95%), 85 (90%), 71 (100%) |
| HRMS (CI) | calcd for $C_{13}H_{13}FNO_3S$ ([M + H]$^+$): 282.0600 found 282.0589 |

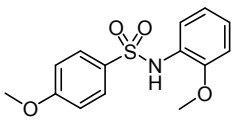
**4-Methoxy-*N*-phenylbenzenesulfonamide (118e)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (120 mg, 0.46 mmol, 86%).

| | |
|---|---|
| MP | 104-106 °C, Lit.[208] 105-106 °C |
| $^1$H NMR | (300 MHz, DMSO) δ 10.14 (s, 1H, N*H*), 7.68 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.23-7.17 (m, 2H, Ar*H*), 7.08-6.96 (m, 5H, Ar*H*), 3.77 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (75 MHz, DMSO) δ 162.3 (s), 137.9 (s), 131.1 (s), 129.1 (d), 128.8 (d), 123.8 (d), 119.8 (d), 114.3 (d), 55.5 (q) |
| IR (thin film) | $\nu_{max}$ 3055, 1597, 1497, 1421, 1265, 1159, 1095, 1028 cm$^{-1}$ |
| LRMS (CI) | 264 ([M + H]$^+$, 55%), 171 (100%) |
| HRMS (CI) | calcd for $C_{13}H_{14}NO_3S$ ([M + H]$^+$): 264.0694 found 264.0684 |

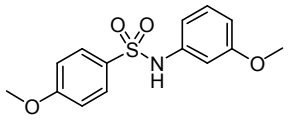
***N*-(2-Methoxyphenyl) 4-methoxybenzenesulfonamide (118f)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (111 mg, 0.38 mmol, 72%).

| | |
|---|---|
| MP | 103-105 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 9.28 (s, 1H, N*H*), 7.63-7.61 (m, 2H, Ar*H*), 7.20 (dd, 1H, *J* = 1.6, 7.9 Hz, Ar*H*), 7.10 (ddd, 1H, *J* = 1.7, 7.5, 8.2 Hz, Ar*H*), 7.05-7.01 (m, 2H, Ar*H*), 6.91-5.83 (m, 2H, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.52 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.10 (s), 151.90 (s), 132.03 (s), 128.76 (d), 126.20 (d), 125.50 (s), 124.34 (d), 120.26 (d), 113.82 (d), 111.63 (d), 55.51 (q), 55.37 (q) |
| IR (thin film) | $\nu_{max}$ 3055, 2972, 1597, 1499, 1464, 1342, 1265, 1159, 1113 cm$^{-1}$ |
| LRMS (CI) | 293 ([M + H]$^+$, 20%), 122 (100%), 94 (48%) |
| HRMS (CI) | calcd for $C_{14}H_{16}NO_4S$ ([M + H]$^+$): 293.0716 found 293.0719 |

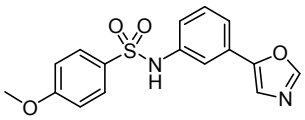
**_N_-(3-Methoxyphenyl)4-methoxybenzenesulfonamide (118g)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown oil (140 mg, 0.48 mmol, 90%).

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 10.16 (s, 1H, N*H*), 7.72-7.68 (m, 2H, Ar*H*), 7.13-7.04 (m, 3H, Ar*H*), 6.67-6.64 (m, 2H, Ar*H*), 6.58 (ddd, 1H, *J* = 0.9, 2.4, 8.3 Hz, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.66 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.32 (s), 159.55 (s), 139.05 (s), 130.99 (s), 129.87 (d), 128.79 (d), 114.29 (d), 111.58 (d), 108.69 (d), 105.34 (d), 55.52 (q), 54.88 (q) |
| IR (thin film) | $\nu_{max}$ 3055, 1597, 1498, 1394, 1331, 1261, 1151, 1093 cm$^{-1}$ |
| LRMS (CI) | 294 ([M + H]$^+$, 100%), 123 (95%) |
| HRMS (CI) | calcd for $C_{14}H_{16}NO_4S$ ([M + H]$^+$): 294.0800 found 294.0798 |

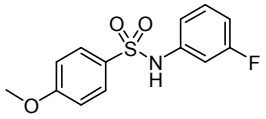
***N*-[3-(2-Amino-1-hydroxyvinyl)-phenyl] 4-methoxybenzenesulfonamide (118h)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a yellow solid (116 mg, 0.35 mmol, 66%).

| | |
|---|---|
| MP | 154-157 °C |
| $^{1}$H NMR | (400 MHz, DMSO) δ 10.37 (s, 1H, N*H*), 8.45 (s, 1H, Ar*H*), 7.74-7.71 (m, 2H, Ar*H*) 7.63 (s, 1H, Ar*H*), 7.45-7.38 (m, 2H, Ar*H*), 7.33 (app. t, 1H, *J* = 7.9 Hz, Ar*H*), 7.09-7.05 (m, 3H, Ar*H*), 3.78 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.41 (s), 151.91 (d), 149.80 (s), 138.67 (s), 130.78 (s), 129.96 (d), 128.81 (d), 128.09 (s), 122.28 (d), 119.61 (d), 119.47 (d), 114.37 (d), 114.62 (d), 55.53 (q) |
| IR (nujol) | $\nu_{max}$ 2850, 1593, 1464, 1377, 1339, 1258, 1161, 1089 cm$^{-1}$ |
| LRMS (CI) | 331 ([M + H]$^{+}$, 100%), 266 (50%), 171 (50%) |
| HRMS (CI) | calcd for $C_{16}H_{15}N_2O_4S$ ([M + H]$^{+}$): 331.0753 found 331.0733 |

***N*-(3-Fluorophenyl) 4-methoxybenzenesulfonamide (118i)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown oil (117 mg, 0.42 mmol, 78%).

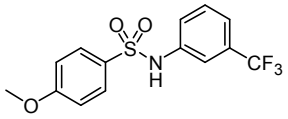
| | |
|---|---|
| $^{1}$H NMR | (400 MHz, DMSO) δ 10.46 (s, 1H, N*H*), 7.74-7.70 (m, 2H, Ar*H*), 7.29-7.23 (m, 1H, Ar*H*), 7.10-7.06 (m, 2H, Ar*H*), 6.92-6.81 (m, 3H, Ar*H*), 3.80 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.57 (s), 162.20 (d, $^{1}J_{CF}$ = 243.6 Hz), 139.81 (d, $^{3}J_{CF}$ = 10.6 Hz), 130.92 (dd, $^{3}J_{CF}$ = 9.5 Hz), 130.70 (s), 128.89 (d), 115.10 (dd, $^{4}J_{CF}$ = 2.7 Hz), 114.5 (d), 110.2 (dd, $^{2}J_{CF}$ = 21.0 Hz), 105.97 (dd, $^{2}J_{CF}$ = 25.4 Hz), 55.63 (q) |

IR (thin film) $\nu_{max}$ 3258, 1597, 1499, 1331, 1265, 1161, 1094 $cm^{-1}$

LRMS (CI) 282 ($[M + H]^+$, 52%), 171 (100%), 112 (50%)

HRMS (CI) calcd for $C_{13}H_{13}FO_3S$ ($[M + H]^+$): 282.3060 found 282.0589

**4-Methoxy *N*-(3-trifluoromethylphenyl)benzenesulfonamide (118j)**



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown oil (121 mg, 0.37 mmol, 69%).

$^1H$ NMR (400 MHz, DMSO) δ 10.61 (s, 1H, N*H*), 7.73-7.70 (m, 2H, Ar*H*), 7.50-7.46 (m, 1H, Ar*H*), 7.38-7.36 (m, 3H, Ar*H*), 7.10-7.06 (m, 2H, Ar*H*), 3.79 (s, 3H, OC$H_3$)

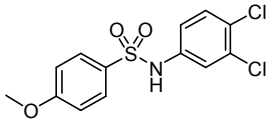
$^{13}C$ NMR (101 MHz, DMSO) δ 162.58 (s), 138.77 (s), 130.47 (d), 130.43 (s), 129.71 (q, $^2J_{CF}$ = 31.5 Hz), 128.82 (d), 123.67 (q, $^1J_{CF}$ = 271.6 Hz), 122.86 (d), 120.06 (dq, $^3J_{CF}$ = 3.8 Hz), 115.23 (dq, $^3J_{CF}$ = 3.9 Hz), 114.47 (d), 55.59 (q)

IR (thin film) $\nu_{max}$ 3055, 1597, 1499, 1418, 1331, 1265, 1157, 1130, 1094 $cm^{-1}$

LRMS (CI) 332 ($[M + H]^+$, 100%), 171 (80%), 162 (25%)

HRMS (CI) calcd for $C_{14}H_{13}F_3NO_3S$ ($[M + H]^+$): 332.0568 found 332.0580

***N*-(3,4-Dichlorophenyl) 4-methoxybenzenesulfonamide (118k)**



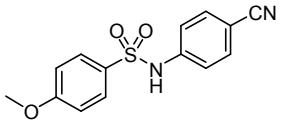
Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (149 mg, 0.45 mmol, 85%).

MP 98-100 °C

$^1H$ NMR (400 MHz, DMSO) δ 10.58 (s, 1H, N*H*), 7.73-7.70 (m, 2H, Ar*H*), 7.51 (d, 1H, *J* = 8.8 Hz, Ar*H*), 7.27 (d, 1H, *J* = 2.5 Hz, Ar*H*), 7.11-7.07 (m, 3H, Ar*H*), 3.81 (s, 3H, OC$H_3$)

| | |
|---|---|
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.63 (s), 138.10 (s), 131.28 (s), 131.12 (d), 130.30 (s), 128.82 (d), 125.63 (s), 120.49 (d), 119.30 (d), 114.54 (d), 56.59 (q) |
| IR (thin film) | $\nu_{max}$ 3252, 3055, 1597, 1475, 1323, 1265, 1159, 1094 cm$^{-1}$ |
| LRMS (CI) | 333 (55%), 331([M + H]$^+$, 25%), 123 (70%), 107 (100%) |
| HRMS (CI) | calcd for $C_{13}H_{12}Cl_2NO_3S$ ([M + H]$^+$): 331.9915 found 331.9914 |

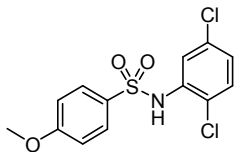
**_N_-(4-Cyanophenyl)-4-methoxybenzenesulfonamide (118m)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a brown solid (129 mg, 0.45 mmol, 84%).

| | |
|---|---|
| MP | 191-193 °C |
| $^1$H NMR | (400 MHz, DMSO) δ 10.92 (s, 1H, N*H*), 7.79-7.75 (m, 2H, Ar*H*), 7.72-7.68 (m, 2H, Ar*H*), 7.25-7.21 (m, 2H, Ar*H*), 7.11-7.08 (m, 2H, Ar*H*), 3.80 (s, 3H, OC*H*$_3$) |
| $^{13}$C NMR | (101 MHz, DMSO) δ 162.70 (s), 142.32 (s), 133.57 (d), 130.44 (s), 128.88 (d), 118.65 (s), 118.22 (d), 114.58 (d), 105.07 (s), 55.61 (q) |
| IR (thin film) | $\nu_{max}$ 3274, 2226, 1607, 1593, 1508, 1495, 1332, 1266, 1144 cm$^{-1}$ |
| LRMS (CI) | 289 ([M + H]$^+$, 100%), 171 (65%), 119 (55%) |
| HRMS (CI) | calcd for $C_{14}H_{13}N_2O_3S$ ([M + H]$^+$): 289.0647 found 289.0655 |

**_N_-(2,5-Dichlorophenyl)-4-methoxybenzenesulfonamide (118n)**

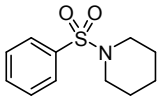



Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a pale brown solid (153 mg, 0.46 mmol, 97%).

| | |
|---|---|
| MP | 115-117 °C |

| | |
|---|---|
| $^1$H NMR | (400 MHz, DMSO) δ 10.11 (s, 1H, N*H*), 7.68-7.65 (m, 2H, Ar*H*), 7.46-7.43 (m, 1H, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*), 7.11-7.07 (m, 2H, Ar*H*), 3.82 (s, 3H, OC$H_3$) |
| $^{13}$C NMR | (100 MHz, DMSO) δ 162.59 (s), 135.02 (s), 131.50 (s), 131.35 (s), 131.17 (d), 128.82 (d), 127.03 (s), 126.94 (d), 125.99 (d), 114.35 (d), 55.61 (q) |
| IR (thin film) | $\nu_{max}$ 3055, 1597, 1481, 1391, 1339, 1265, 1163, 1096 cm$^{-1}$ |
| LRMS (EI) | 331 ($M^+$, 25%), 171 (100%), 107 (45%) |
| HRMS (EI) | calcd for $C_{13}H_{11}Cl_2NO_3S$ ($M^+$): 330.9831 found 330.9835 |

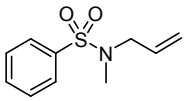
**1-Benzenesulfonylpiperidine (124)**



Synthesised using general procedure F. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give a pale yellow solid (51 mg, 0.23 mmol, 73%).

| | |
|---|---|
| MP | 89-92 °C, Lit.[210] 86-87 °C |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.77-7.75 (m, 2H, Ar*H*), 7.61-7.57 (m, 1H, Ar*H*), 7.54-7.51 (m, 2H, Ar*H*), 2.99 (t, 4H, *J* = 5.5 Hz, C$H_2$), 1.66-1.60 (m, 4H, C$H_2$), 1.44-1.39 (m, 2H, C$H_2$) |
| $^{13}$C NMR | (126 MHz, $CDCl_3$) δ 136.43 (s), 132.61 (d), 128.99 (d), 127.73 (d), 47.01 (t), 25.243 (t), 23.58 (t) |
| IR (thin film) | $\nu_{max}$ 2928, 2840, 1445, 1335, 1164, 1093 cm$^{-1}$ |
| LRMS (ES) | 226 ($[M + H]^+$, 100%), 473 (15%) |
| HRMS (ES) | calcd for $C_{11}H_{16}NO_2S$ ($[M + H]^+$): 226.0896 found 226.0901 |

***N*-Allyl-*N*-methyl-benzenesulfonamide (125)**



Synthesised using general procedure F. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give colourless oil (35 mg, 0.17 mmol, 53%). Data in agreement with literature.[211]

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.81-7.79 (m, 2H, Ar*H*), 7.61-7.58 (m, 1H, Ar*H*), 7.55-7.52 (m, 2H, Ar*H*), 5.75-5.67 (m, 1H, $CH_2HC{=}CH_2$), 5.21 (app dq, 1H, *J*=5.0, 1.3 Hz, CH=C*H*H), 5.18-5.20 (m, 1H, CH=C*H*H), 3.65 (d, 2H, *J* = 6.6 Hz, $CH_2$-CH=$CH_2$), 2.67 (s, 3H, $CH_3$)

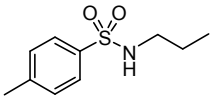
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.62 (s), 132.68 (d), 132.56 (d), 129.15 (d), 127.50 (d), 119.27 (t), 53.11 (t), 34.27 (q)

IR (thin film) $\nu_{max}$ 2920, 1447, 1336, 1165 cm$^{-1}$

LRMS (ES) 212 ([M + H]$^+$, 100%)

HRMS (ES) calcd for $C_{10}H_{14}NO_2S$ ([M + H]$^+$): 212.0740 found 212.0744

**4-Methyl *N*-propylbenzenesulfonamide (126)**



Synthesised using general procedure C. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give a colourless oil (45 mg, 0.21 mmol, 75%). Data in agreement with literature.[212]

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.76-7.74 (m, 2H, Ar*H*), 7.30-7.29 (m, 2H, Ar*H*), 4.74 (1H, t, *J* = 6.0 Hz, N*H*), 2.90-2.86 (m, 2H, $CH_2CH_2CH_3$), 2.42 (s, 3H, Ar$CH_3$), 1.50-1.42 (m, 2H, $CH_2CH_2CH_3$), 0.87 (t, 3H, *J* = 7.4 Hz, $CH_3$)

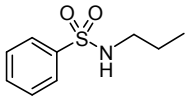
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.37 (s), 137.10 (s), 129.75 (d), 127.17 (d), 45.02 (t), 22.97 (t), 21.58 (q), 11.18 (q)

IR (thin film) $\nu_{max}$ 3281, 2966, 1599, 1425, 1320, 1155, 1091 cm$^{-1}$

LRMS (ES) 214 ([M + H]$^+$, 100%), 231 (55%)

HRMS (ES) calcd for $C_{10}H_{16}NO_2S$ ([M + H]$^+$): 214.0896 found 214.0898

***N*-Propylbenzenesulfonamide (127)**

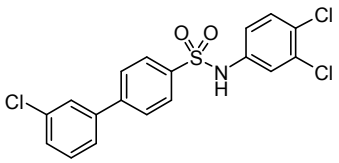


Synthesised using general procedure F. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give a colourless oil (28 mg, 0.14 mmol, 45%).

| | |
|---|---|
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H, Ar*H*), 7.60-7.56 (m, 1H, Ar*H*), 7.54-7.50 (m, 2H, Ar*H*), 4.49 (1H, br. s, N*H*), 2.93 (app. q, 2H, *J* = 6.6 Hz, C*H*$_2$CH$_2$CH$_3$), 1.52-1.45 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.87 (t, 3H, *J* = 7.3 Hz, C*H*$_3$) |
| $^{13}$C NMR | (151 MHz, $CDCl_3$) δ 140.11 (s), 132.65 (d), 129.16 (d), 127.10 (d), 45.06 (t), 23.04 (t), 11.15 (q) |
| IR (thin film) | $\nu_{max}$ 3283, 2966, 1447, 1424, 1320, 1155, 1092 cm$^{-1}$ |
| LRMS (CI) | 200 ([M + H]$^+$, 100%), 421 (30%) |
| HRMS (CI) | calcd for $C_9H_{14}NO_2S$ ([M + H]$^+$): 200.0740 found 200.0743 |

# Experimental for Chapter 3

**Biphenyl 4-sulfonic acid (3,4-dichlorophenyl)amide (144)**




Synthesised using general procedure E. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a pale brown solid (139 mg, 0.34 mmol, 89%).

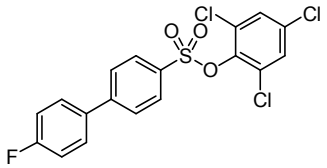
| | |
|---|---|
| MP | 139-141 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 10.81 (br. s, 1H, N*H*), 7.95-7.93 (m, 2H, Ar*H*), 7.88-7.85 (m, 2H, Ar*H*), 7.81-7.80 (m, 1H, Ar*H*), 7.71-7.68 (m, 1H, Ar*H*), 7.55-7.48 (m, 3H, Ar*H*), 7.33 (d, 1H, *J* = 2.5 Hz, Ar*H*), 7.14 (dd, 1H, *J* = 2.5, 8.8 Hz, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 143.06 (s), 140.24 (s), 138.26 (s), 137.88 (s), 133.90 (s), 131.48 (s), 131.32 (d), 130.92 (d), 128.48 (d), 127.93 (d), 127.30 (d), 126.89 (d), 126.03 (s), 125.84 (d), 120.76 (d), 119.53 (d) |
| IR (thin film) | $\nu_{max}$ 3243, 1592, 1561, 1470, 1383, 1326, 1158, 1095 cm$^{-1}$ |
| LRMS (CI) | 416 (22%), 414 (55%), 412 ([M + H]$^+$, 55%), 164 (65%), 162 (100%) |
| HRMS (CI) | calcd for $C_{18}H_{13}Cl_3NO_2S$ ([M + H]$^+$): 411.9727 found 411.9716 |

## Suzuki Reactions

### General Procedure G

To a solution of the 2,4,6 trichlorophenyl ester (2.4 mmol) in anhydrous dioxane (20 mL) was added bis(triphenylphosphine)palladiumdichloride (3 mol%), sodium tetraborate (7.2 mmol) and a solution of the boronic acid (2.9 mmol) in ethanol (4 mL). The reaction mixture was heated to reflux for 14h and then cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated *in vacuo* to yield the crude product.

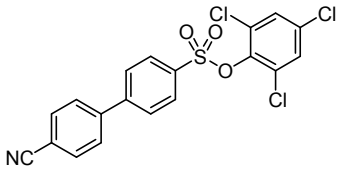
### 4'-Fluorobiphenyl 4-sulfonic acid 2,4,6-trichlorophenyl ester (132)




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (770 mg, 1.8 mmol, 74%).

| | |
|---|---|
| MP | 156-157 °C |
| $^{1}$H NMR | (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H, Ar*H*), 7.76-7.73 (m, 2H, Ar*H*), 7.65-7.60 (m, 2H, Ar*H*), 7.37 (s, 2H, Ar*H*), 7.23-7.17 (m, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 163.39 (d, $^{1}J_{CF}$ = 248.9 Hz), 146.53 (s), 142.33 (s), 135.45 (s), 134.96 (d, $^{4}J_{CF}$ = 3.3 Hz), 132.97 (s), 130.93 (s), 129.22 (d), 129.21 (dd, $^{3}J_{CF}$ = 8.2 Hz), 129.19 (d), 127.59 (d), 116.23 (dd, $^{2}J_{CF}$ = 21.8 Hz) |
| IR (thin film) | $\nu_{max}$ 3069, 1594, 1560, 1435, 1378, 1228, 1180 cm$^{-1}$ |
| LRMS (CI) | 435 (10%), 433 (30%), 431 ($[M + H]^+$, 29%), 235 (100%), 199 (12%), 197 (15%) |
| HRMS (CI) | calcd for $C_{18}H_{11}Cl_3FO_3S$ ($[M + H]^+$): 430.9479 found 430.9479 |

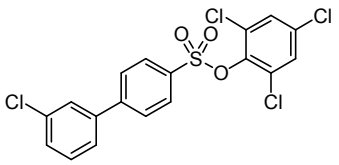
**4'-Cyanobiphenyl 4-sulfonic acid 2,4,6-trichlorophenyl ester (133)**



Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (800 mg, 1.8 mmol, 76%).

| | |
|---|---|
| MP | 161-164 °C |
| $^1$H NMR | (300 MHz, $CDCl_3$) δ 8.13 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.82-7.70 (m, 6H, Ar*H*), 7.37 (s, 2H, Ar*H*) |
| $^{13}$C NMR | (75 MHz, $CDCl_3$) δ 145.4 (s), 143.2 (s), 142.3 (s), 136.9 (s), 133.1 (s), 132.9 (d), 130.9 (s), 129.4 (d), 129.3 (d), 128.2 (d), 128.0 (d), 118.4 (s), 112.7 (s) |
| IR (thin film) | $\nu_{max}$ 3071, 2225, 1560, 1437, 1379, 1230, 1186, 1137, 1094 cm$^{-1}$ |
| LRMS (CI) | 440 (67%), 438 ($[M + H]^+$, 68%), 242 (100%), 199 (35%), 197 (40%), 180 (46%) |
| HRMS (CI) | calcd for $C_{19}H_{11}Cl_3NO3S$ ($[M + H]^+$): 437.9525 found 437.9543 |

**3'-Chlorobiphenyl 4-sulfonic acid 2,4,6-trichlorophenyl ester (134)**



Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (1.02 g, 2.3 mmol, 94%).

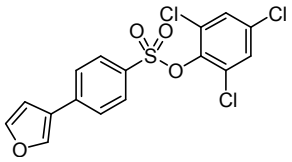
| | |
|---|---|
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2H, Ar*H*), 7.79-7.75 (m, 2H, Ar*H*), 7.64-7.62 (m, 1H, Ar*H*), 7.54-7.50 (m, 1H, Ar*H*), 7.45-7.42 (m, 2H, Ar*H*), 7.37 (s, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 146.1 (s), 140.6 (s), 136.1 (s), 135.2 (s), 133.0 (s), 130.9 (s), 130.4 (d), 129.2 (d), 129.2 (d), 129.0 (d), 127.8 (d), 127.6 (d), 125.6 (d) |

IR (thin film) $\nu_{max}$ 1607, 1562, 1441, 1379, 1231, 1173, 1136 $cm^{-1}$

LRMS (CI) 448 (10%), 446 ($[M + H]^+$, 8%), 253 (86%), 251 (35%), 187 (43%), 152 (100%)

HRMS (CI) calcd for $C_{18}H_{12}Cl_3NO_2S$ ($[M + H]^+$): 446.9183 found 411.9195

**4-Furan-3-yl benzenesulfonic acid 2,4,6-trichlorophenyl ester (135)**




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (917 mg, 2.3 mmol, 95%).

MP 132-134 °C

$^1H$ NMR (400 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H, Ar*H*), 7.89 (dd, 1H, *J* = 1.0, 1.4 Hz, Ar*H*), 7.69-7.66 (m, 2H, Ar*H*), 7.55 (app. t, 1H, *J* = 1.8 Hz, Ar*H*), 7.36 (s, 2H, Ar*H*), 6.77 (dd, 1H, *J* = 0.9, 1.9 Hz, Ar*H*)

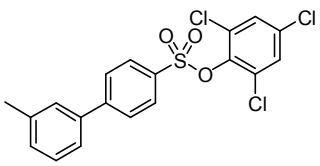
$^{13}C$ NMR (101 MHz, $CDCl_3$) δ 144.54 (d), 142.36 (s), 140.32 (d), 139.05 (s), 134.77 (s), 132.91 (s), 130.94 (s), 129.27 (d), 129.20 (d), 126.14 (d), 124.88 (s), 108.52 (d)

IR (thin film) $\nu_{max}$ 1601, 1559, 1420, 1379, 1170 $cm^{-1}$

LRMS (CI) 407 (10%), 405 (24%), 403 ($[M + H]^+$, 25%), 207 (100%)

HRMS (CI) calcd for $C_{16}H_{10}Cl_3O_4S$ ($[M + H]^+$): 402.9365 found 402.9357

**3'-Methylbiphenyl-4-sulfonic acid 2,4,6-trichlorophenyl ester (136)**

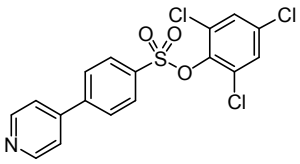



Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (570 mg, 1.3 mmol, 55%).

MP 137-138 °C

| | |
|---|---|
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H, Ar*H*), 7.80-7.77 (m, 2H, Ar*H*), 7.46-7.39 (m, 3H, Ar*H*), 7.37 (s, 2H, Ar*H*), 7.28 (br. s, 1H, Ar*H*), 2.45 (s, 3H, C*H*$_3$) |
| $^{13}$C NMR | (151 MHz, $CDCl_3$) δ 147.77 (s), 142.35 (s), 138.91 (s), 138.79 (s), 135.19 (s), 132.91 (s), 130.94 (s), 129.70 (d), 129.20 (d), 129.08 (d), 129.05 (d), 128.17 (d), 127.75 (d), 124.55 (d), 21.54 (q) |
| IR (thin film) | $\nu_{max}$ 1561, 1443, 1376, 1182, 1137, 1096 cm$^{-1}$ |
| LRMS (CI) | 430 (12%), 428 (30%), 426 ($M^+$, 28%), 231 (100%), 167 (62%) |
| HRMS (CI) | calcd for $C_{19}H_{13}Cl_3O_3S$ ($M^+$): 425.9651 found 425.9658 |

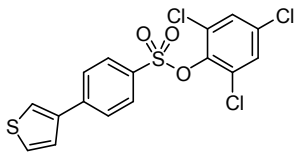
**4-Pyridin-4-yl benzenesulfonic acid 2,4,6-trichlorophenyl ester (137)**




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a pink solid (843 mg, 2.0 mmol, 85%).

| | |
|---|---|
| MP | 173-175 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.77-8.76 (m, 2H, Ar*H*), 8.17-8.13 (m, 2H, Ar*H*), 7.86-7.83 (m, 2H, Ar*H*), 7.56-7.55 (m, 2H, Ar*H*), 7.38 (s, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 150.73 (d), 146.02 (s), 144.50 (s), 142.25 (s), 137.28 (s), 133.12 (s), 130.87 (s), 129.37 (d), 129.26 (d), 127.85 (d), 121.78 (d) |
| IR (thin film) | $\nu_{max}$ 3040, 1590, 1445, 1384, 1181 cm$^{-1}$ |
| LRMS (CI) | 416 (20%), 414 ($[M + H]^+$, 18%), 391 (20%), 149 (100%) |
| HRMS (CI) | calcd for $C_{17}H_{11}Cl_3NO_3S$ ($[M + H]^+$): 413.9525 found 413.9517 |

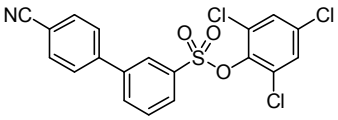
**4-Thionphen-3-yl benzenesulfonic acid 2,4,6-trichlorophenyl ester (138)**



Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (899 mg, 2.1 mmol, 89%).

| | |
|---|---|
| MP | 134-136 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H, Ar*H*), 7.81-7.78 (m, 2H, Ar*H*), 7.51 (dd, 1H, *J* = 1.1, 3.7 Hz, Ar*H*), 7.45 (dd, 1H, *J* = 1.1, 5.1 Hz, Ar*H*), 7.36 (s, 2H, Ar*H*), 7.16 (dd, 1H, *J* = 3.7, 5.1 Hz, Ar*H*) |
| $^{13}$C NMR | (100 MHz, $CDCl_3$) δ 142.34 (s), 141.67 (s), 140.51 (s), 134.93 (s), 132.93 (s), 130.93 (s), 129.35 (d), 129.21 (d), 128.65 (d), 127.55 (d), 125.97 (d), 125.67 (d) |
| IR (thin film) | $\nu_{max}$ 3077, 1591, 1561, 1438, 1368, 1176 cm$^{-1}$ |
| LRMS (CI) | 421 (62%), 419 ([M+H]$^+$, 60%), 225 (100%), 199 (50%), 197 (52%) |
| HRMS (CI) | calcd for $C_{16}H_{10}Cl_3O_3S$ ([M + H])$^+$: 418.9137 found 418.9125 |

**4'-Cyano-biphenyl 3-sulfonic acid 2,4,6-trichlorophenyl ester (139)**

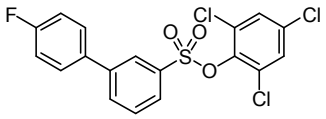


Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (782 mg, 1.8 mmol, 74%).

| | |
|---|---|
| MP | 154-155 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.23 (app. t, 1H, *J* = 1.8 Hz, Ar*H*), 8.09 (ddd, 1H, *J* = 1.1, 1.8, 7.9 Hz, Ar*H*), 7.94 (ddd, 1H, *J* = 1.1, 1.7, 7.8 Hz, Ar*H*), 7.82-7.79 (m, 2H, Ar*H*), 7.75-7.71 (m, 3H, Ar*H*), 7.38 (s, 2H, Ar*H*) |

| | |
|---|---|
| $^{13}$C NMR | (100 MHz, $CDCl_3$) δ 143.07 (s), 142.25 (s), 140.58 (s), 138.12 (s), 133.18 (d), 132.99 (d), 130.82 (s), 130.15 (d), 129.29 (d), 128.35 (d), 127.92 (d), 127.09 (d), 118.43 (s), 112.41 (s) |
| IR (thin film) | $\nu_{max}$ 2228, 1561, 1444, 1380, 1229, 1181 cm$^{-1}$ |
| LRMS (CI) | 440 (100%), 438 ($[M + H]^+$, 40%), 226 (85%), 199 (98%) |
| HRMS (CI) | calcd for $C_{19}H_{11}Cl_3NO_3S$ ($[M + H]^+$): 437.9525 found 437.9514 |

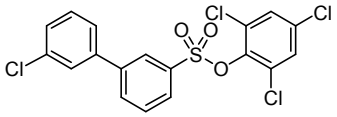
**4'-Fluorobiphenyl 3-sulfonic acid 2,4,6-trichlorophenyl ester (140)**




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (775 mg, 1.8 mmol, 75%).

| | |
|---|---|
| MP | 82-85 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.19 (app. t, 1H, *J* = 1.7 Hz, Ar*H*), 8.00 (ddd, 1H, *J* = 1.1, 1.8, 7.9 Hz, Ar*H*), 7.89 (ddd, 1H, *J* = 1.1, 1.8, 7.9 Hz, Ar*H*), 7.66 (app. t, 1H, *J* = 7.9 Hz, Ar*H*), 7.60-7.55 (m, 2H, Ar*H*), 7.37 (s, 2H, Ar*H*), 7.21-7.16 (m, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 163.14 (d, $^1J_{CF}$ = 248.4 Hz), 142.33 (s), 141.64 (s,), 134.89 (d, $^4J_{CF}$ = 3.3 Hz), 133.03 (s), 133.00 (d), 130.90 (s), 129.79 (d), 129.24 (d), 128.93 (d, $^2J_{CF}$ = 8.3 Hz), 127.06 (d), 126.81 (d), 116.20 (d, $^3J_{CF}$ = 21.6 Hz) |
| IR (thin film) | $\nu_{max}$ 1561, 1515, 1442, 1379, 1228, 1184 cm$^{-1}$ |
| LRMS (CI) | 434 (100%), 432 (75%), 197 (85%) |
| HRMS (CI) | calcd for $C_{18}H_{11}Cl_3FO_3S$ ($[M + H]^+$): 430.9479 found 430.9462 |

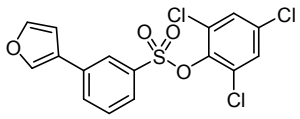
**3'-Chlorobiphenyl 3-sulfonic acid 2,4,6-trichlorophenyl ester (141)**




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (800 mg, 1.8 mmol, 74%).

| | |
|---|---|
| MP | 101-104 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.20 (app. t, 1H, *J* = 1.8 Hz, Ar*H*), 8.03 (ddd, 1H, *J* = 1.1, 1.8, 7.9 Hz, Ar*H*), 7.91 (ddd, 1H, *J* = 1.1, 1.7, 7.8 Hz, Ar*H*), 7.68, (app. t, 1H, *J* = 7.9 Hz, Ar*H*), 7.60-7.59 (m, 1H, Ar*H*), 7.50-7.39 (m, 3H, Ar*H*), 7.37 (s, 2H, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 142.31 (s), 141.23 (s), 140.51 (s), 137.80 (s), 135.16 (s), 133.11 (d), 133.07 (s), 130.88 (s), 130.45 (d), 129.89 (d), 129.26 (d), 128.60 (d), 127.63 (d), 127.36 (d), 126.97 (d), 125.38 (d) |
| IR (thin film) | $\nu_{max}$ 1563, 1441, 1377, 1231, 1188 cm$^{-1}$ |
| LRMS (EI) | 448 (25%), 446 ($M^+$, 25%), 251 (75%), 187 (100%), 152 (90%) |
| HRMS (EI) | calcd for $C_{18}H_{10}Cl_4O_3S$ ($M^+$): 445.9099 found 445.9104 |

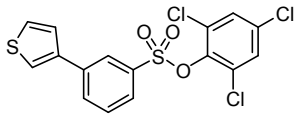
**3-Furan-3-yl benzenesulfonic acid 2,4,6-trichlorophenyl ester (142)**




Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (380 mg, 0.94 mmol, 39%).

| | |
|---|---|
| MP | 130-131 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.11 (app. t, 1H, *J* = 1.7 Hz, Ar*H*), 790 (ddd, 1H, *J* = 1.1, 1.8, 7.9 Hz, Ar*H*), 7.83-7.80 (m, 2H, Ar*H*), 7.59 (app. t, 1H, *J* = 7.9 Hz, Ar*H*), 7.54 (app. t, 1H, *J* = 1.7 Hz, Ar*H*), 7.37 (s, 2H, Ar*H*), 6.75 (dd, 1H, *J* = 0.9, 1.8 Hz, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 144.40 (d), 142.34 (s), 139.52 (d), 137.63 (s), 134.10 (s), 133.00 (s), 131.69 (d), 130.91 (s), 129.72 (d), 129.23 (d), 126.68 (d), 125.50 (d), 124.70 (s), 108.53 (d) |
| IR (thin film) | $\nu_{max}$ 1561, 1442, 1231, 1185, 1136 cm$^{-1}$ |
| LRMS (CI) | 405 (64%), 403 ($[M + H]^+$, 64%), 207 (100%) |
| HRMS (CI) | calcd for $C_{16}H_9Cl_3O_4S$ ($[M + H]^+$): 402.9365 found 402.9352 |

**3-Thionphen-3-yl benzenesulfonic acid 2,4,6-trichlorophenyl ester (143)**

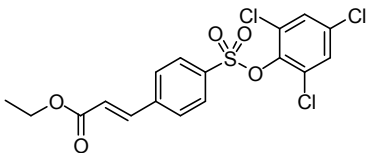


Synthesised using general procedure G. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a white solid (860 mg, 2.0 mmol, 85%).

| | |
|---|---|
| MP | 86-89 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.23 (app. t, 1H, *J* = 1.7 Hz, Ar*H*), 7.94-7.90 (m, 2H, Ar*H*), 7.60 (app. t, 1H, *J* = 7.9, Ar*H*), 7.43 (dd, 2H, *J* = 1.1, 3.7 Hz, Ar*H*), 7.39 (dd, 2H, *J* = 1.1, 5.1 Hz, Ar*H*), 7.37 (s, 2H, Ar*H*), 7.13 (dd, 1H, *J* = 3.7, 5.1 Hz, Ar*H*) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 142.32 (s), 141.56 (s), 137.74 (s), 135.89 (s), 133.03 (s), 131.66 (d), 130.91 (s), 129.83 (d), 129.24 (d), 128.48 (d), 126.90 (d), 126.58 (d), 125.40 (d), 124.81 (d) |
| IR (thin film) | $\nu_{max}$ 1565, 1444, 1381, 1231, 1184, 1136 cm$^{-1}$ |
| LRMS (CI) | 423 (35%), 421 (100%), 419 ([M + H]$^+$, 92%), 223 (95%) 159 (60%) |
| HRMS (CI) | calcd for $C_{16}H_{10}Cl_3O_3S_2$ ([M + H]$^+$): 418.9137 found 418.9120 |

## Heck Reactions

**3-[4-(2,4,6-Trichlorophenoxysulfonyl)phenyl]acrylic acid ethyl ester (146)**

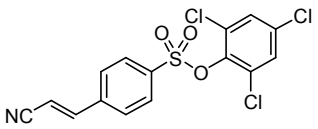


To a solution of 4-bromobenzene TCP sulfonate (**96**) (1.08 mmol) in DMF (4 mL) was added bis(triphenylphosphine)palladium dichloride (3 mol%), N-methyldicyclohexylamine (2.16 mmol) and ethyl acrylate (1.30 mmol). The resultant mixture was heated in the microwave for 20 minutes at 100 ºC. The reaction mixture was diluted with EtOAc (20 mL) and washed with 10% lithium chloride solution (3 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column

chromatography (petroleum ether/diethyl ether) to give a white solid (345 mg, 0.79 mmol, 73%).

| | |
|---|---|
| MP | 128-130 °C |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.11-7.99 (m, 2H, Ar*H*), 7.73 (d, *J* = 15.9 Hz, 1H, C*H*C*H*), 7.73-7.71 (m, 2H, Ar*H*), 7.38 (s, 2H, Ar*H*), 6.60 (d, *J* = 16.0 Hz, 1H, C*H*C*H*), 4.31 (q, *J* = 7.1 Hz, 2H, OC$H_2$CH$_3$), 1.37 (t, *J* = 7.1 Hz, 3H, C$H_3$) |
| $^{13}$C NMR | (151 MHz, $CDCl_3$) δ 166.06 (s), 142.21 (s), 141.79 (d), 140.53 (s), 137.67 (s), 133.08 (s), 130.83 (s), 129.23 (d), 129.12 (d), 128.45 (d), 122.64 (d), 61.04 (t), 14.29 (q) |
| IR (thin film) | $\nu_{max}$ 3076, 1714, 1641, 1560, 1440, 1388, 1314, 1195, 1177 cm$^{-1}$ |
| LRMS (EI) | 436 ([M+H]$^+$, 1%), 239 (50%), 102 (100%) |
| HRMS (EI) | calcd for $C_{17}H_{13}Cl_3O_5S$ ($M^+$): 433.9544 found 433.9545 |

**4-(2-Cyanovinyl)benzenesulfonic acid 2,4,6-trichlorophenyl ester (148)**




To a solution of 4-bromobenzene TCP sulfonate (**96**) (0.54 mmol) in DMF (2 mL) was added bistriphenylphosphinepalladium dichloride (3 mol%), N-methyldicyclohexylamine (1.08 mmol) and acrylonitrile (0.65 mmol). The resultant mixture was heated in the microwave for 30 minutes at 100 ºC. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% lithium chloride solution (3 x 5 mL) and water (5 mL). The organic portion was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give a pale yellow solid (77 mg, 0.20 mmol, 37%).

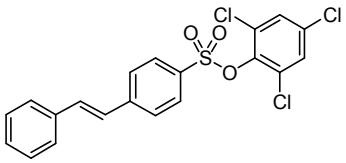
| | |
|---|---|
| $^1$H NMR | (400 MHz, CDCl3) δ 8.21-7.95 (m, 2H, Ar*H*), 7.79-7.59 (m, 2H, Ar*H*), 7.48 (d, *J* = 16.7, 1H, C*H*CH), 7.38 (s, 2H, Ar*H*), 6.09 (d, *J* = 16.7, 1H, CHC*H*) |
| $^{13}$C NMR | (126 MHz, CDCl3) δ 147.99 (d), 142.21 (s), 139.17 (s), 138.90 (s), 133.30 (s), 130.84 (s), 129.39 (d), 129.33 (d), 127.94 (d), 117.02 (s), 101.17 (d) |

IR (thin film) $\nu_{max}$ 3078, 2220, 1559 1442, 1386, 1193, 1178, 1135, 1090 $cm^{-1}$

LRMS (CES) 389 (50%), 386 ($[M-H]^-$, 50%), 208 (100%)

HRMS (ES) calcd for $C_{15}H_7Cl_3NO_3S$ ($[M-H]^-$): 385.9218 found 385.9222

**4-Styryl-benzenesulfonic acid 2,4,6-trichloro-phenyl ester (149)**




To a solution of 4-bromobenzene TCP sulfonate (**96**) (1.08 mmol) in DMF (4 mL) was added bis(triphenylphosphine)palladium dichloride (3 mol%), N-methyldicyclohexylamine (2.16 mmol) and styrene (1.30 mmol). The resultant mixture was heated in the microwave for 150 minutes at 100 ºC. The reaction mixture was diluted with $Et_2O$ (20 mL) and washed with 10% lithium chloride solution (3 x 10 mL) and water (10 mL). The organic portion was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (petroleum ether/diethyl ether) to give a white solid (243 mg, 0.55 mmol, 51%).

MP 129-132 °C

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.02-7.98 (m, 2H, Ar*H*), 7.72-7.68 (m, 2H, Ar*H*), 7.58-7.56 (m, 2H, Ar*H*), 7.44-7.33 (m, 3H, Ar*H*), 7.37 (s, 2H, Ar*H*), 7.31 (d, *J* = 16.4, 1H, C*H*CH), 7.16 (d, *J* = 16.4, 1H, CHC*H*)

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.76 (s), 142.35 (s), 136.15 (s), 134.91 (s), 133.26 (d), 132.88 (s), 130.94 (s), 129.19 (d), 129.07 (d), 128.92 (d), 128.85 (d), 127.03 (d), 126.86 (d), 126.37 (d)

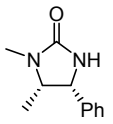
IR (thin film) $\nu_{max}$ 3081, 1591, 1560, 1439, 1383, 1177 $cm^{-1}$

LRMS (EI) 440 (5%), 438 (5%, $M^+$), 195 (52%), 178 (100%), 152 (48%)

HRMS (EI) calcd for $C_{20}H_{13}Cl_3O_3S$ ($M^+$): 437.9645 found 437.9642

## DKR

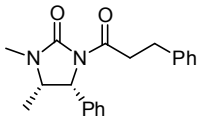
### (4*R*, 5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (173)




(1*R*, 2*S*)-(-)-Ephedrine hydrochloride (10.0 g, 49.6 mmol) and urea (8.9 g, 148.7 mmol) were heated under an atmosphere of argon at 190 ºC for 5h. The reaction mixture was cooled to room temperature and then the crude product was purified by column chromatography (petroleum ether/ethyl acetate). The desired product was obtained as a white solid (4.66 g, 24 mmol, 49%). Data in agreement with Jenkins.[145]

| | |
|---|---|
| MP | 171-173 ºC, Lit.[213] 175-177 ºC |
| $[\alpha]^{24}_D$ | -43.3 º (c = 1, MeOH), Lit.[213] $[\alpha]^{25}_D$ -44.5 (c = 0.90, MeOH) |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H, Ar*H*), 4.75 (d, *J* = 8.4 Hz, 1H, *CH*Ph), 4.67 (s, 1H, N*H*), 3.88 (dq, *J* = 6.6, 8.4 Hz, 1H, *CH*$CH_3$), 2.75 (s, 3H, *CH*$_3$N), 0.74 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH) |
| $^{13}$C NMR | (126 MHz, $CDCl_3$) δ 162.25 (s), 138.19 (s), 128.53 (d), 128.11 (d), 127.16 (d), 58.19 (d), 57.63 (d), 28.18 (q), 14.28 (q) |
| IR (thin film) | $\nu_{max}$ 3264, 1701, 1663, 1438, 1382, 762 cm$^{-1}$ |
| LRMS (ES) | 381 (35%), 191 (100%, $[M+H]^+$) |

### 1,5-Dimethyl 4-phenyl 3-(3-phenylpropionyl)imidazolidin-2-one (188)

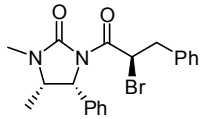



To a stirred solution of (4*R*, 5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (1.35 g, 7.1 mmol) in dichloromethane (40 mL) at 0 ºC under an argon atmosphere was added 2,6 lutidine (0.82 mL, 7.8 mmol) and 3-phenylpropionyl chloride (1.58 mL, 10.6 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 18 h. After cooling the reaction mixture to room temperature saturated aqueous ammonium chloride solution (20 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride solution (2 x 20 mL), saturated sodium bicarbonate solution (3 x 20 mL) and water (1 x 20 mL),

dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to yield a white solid (2.0 g, 6.2 mmol, 87%). Data in agreement with Treweeke.[147]

| | |
|---|---|
| MP | 120-122 ºC, Lit. [147] 118-120 ºC |
| $[\alpha]^{20}_D$ | -33.5º (c = 10.0, $CHCl_3$), Lit. [147] $[\alpha]^{25}_D$ = -40.5º (c = 1.0, $CHCl_3$) |
| 1H NMR | (500 MHz, $CDCl_3$) δ 7.44-6.84 (m, 10H, ArC*H*), 5.26 (d, J = 8.6 Hz, 1H, C*H*Ph), 3.85 (dq, J = 6.6, 8.5 Hz, 1H, C*H*$CH_3$), 3.38-3.22 (m, 2H, C$H_2$CO), 3.02-2.84 (m, 2H, C$H_2$Ph), 2.79 (s, 3H, C$H_3$N), 0.77 (d, J = 6.6 Hz, 3H, C$H_3$CH) |
| 13C NMR | (126 MHz, $CDCl_3$) δ 171.86 (s), 155.89 (s), 141.12 (s), 136.64 (s), 128.57 (d), 128.52 (d), 128.30 (d), 128.06 (d), 126.94 (d), 125.92 (d), 59.31 (d), 53.99 (d), 37.40 (t), 30.55 (t), 28.15 (q), 14.94 (q) |
| IR (thin film) | νmax 1717, 1678, 1382, 752, 699 $cm^{-1}$ |
| LRMS (ES) | 323 ($[M+H]^+$, 100%) |

**1-(2-Bromo-3-phenylprpionyl)3,4-dimethyl 5-phenylimidazolidin-2-one (2'*R*-189)**




To a solution of 1,5-dimethyl 4-phenyl 3-(3-phenylpropionyl)imidazolidin-2-one (2.0 g, 6.2 mmol) in THF (20 mL) at -78 ºC under argon was added LHMDS (1M solution in THF) (6.8 mL, 6.8 mmol) dropwise and then after 45 minutes bromine was added dropwise. After stirring for 1h at –78 ºC the reaction was quenched with saturated aqueous ammonium chloride solution (40 mL) and EtOAc (100 mL). The organic layer was washed with saturated aqueous ammonium chloride solution (2 x 40 mL) and the combined aqueous layers were extracted with EtOAc (20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate) to yield a white solid (1.57 g, 3.9 mmol, 63%). Data in agreement with Treweeke.[147]

| | |
|---|---|
| MP | 99-101 ºC, Lit. [147] 93-95 ºC |
| $[\alpha]^{20}_D$ | -125.8 (*c* = 1.0, MeOH), Lit. $[\alpha]^{30}_D$ -128.8 (*c* = 1.0, MeOH) |

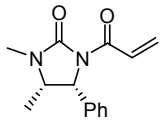
$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.10 (m, 10H, Ar*CH*), 6.16 (dd, *J* = 6.4, 9.1 Hz, 1H, *CH*Br), 5.21 (d, *J* = 8.8 Hz, 1H, *CH*Ph), 3.78 (dq, *J* = 6.6, 8.8 Hz, 1H, *CH*$CH_3$), 3.50 (dd, *J* = 9.1, 14.0 Hz, 1H, $CH_AH_B$Ph), 3.21 (dd, *J* = 6.4, 14.0 Hz, 1H, $CH_AH_B$Ph), 2.78 (s, 3H, $CH_3$N), 0.75 (d, *J* = 6.6 Hz, 3H, $CH_3$CH)

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.52 (s), 154.59 (s), 137.54 (s), 135.34 (s), 129.61 (d), 128.50 (d), 128.45 (d), 128.27 (d), 126.98 (d), 126.86 (d), 59.28 (d), 53.66 (d), 44.23 (d), 40.04 (t), 28.26 (q), 15.11 (q)

IR (thin film) $\nu_{max}$ 1713, 1679, 1377, 748 $cm^{-1}$

LRMS (ES) 418 (15), 403 (100%), 401 ($[M + H]^+$, 100%)

**1-Acryloyl 3,4-dimethyl 5-phenylimidazolidin-2-one (195)**




To a stirred solution of (4*R*, 5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (2.90 g, 15.2 mmol) in dichloromethane (100 mL) at 0 ºC under an argon atmosphere was added 2,6-lutidine (1.95 mL, 16.7 mmol) and then acryloyl chloride (1.85 mL, 22.9 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 24h. After cooling the reaction mixture to room temperature saturated aqueous ammonium chloride solution (40 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride solution (2 x 40 mL), sodium bicarbonate solution (3 x 40 mL) and water (1 x 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to yield a white solid (1.8 g, 7.4 mmol, 49%).

MP 145-148 ºC, Lit. [214] 135-140 ºC

$[\alpha]^{20}_D$ -103.1º (*c* = 10.0, $CHCl_3$), Lit. [214] $[\alpha]_D$ = -100.6º (*c* = 1.0, $CHCl_3$)

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 10.4, 17.1 Hz, 1H, CO*CH*$CH_2$), 7.44 – 7.09 (m, 5H, Ar*H*), 6.39 (dd, *J* = 2.0, 17.1 Hz, 1H, $CH_AH_BCH_2$), 5.76 (dd, *J* = 2.0, 10.4 Hz, 1H, $CH_AH_BCH_2$), 5.36 (d, *J* = 8.5 Hz, 1H, *CH*Ph), 3.93 (dq, *J* = 6.6, 8.5 Hz, 1H, Ph*CH*$CH_3$), 2.84 (s, 3H, $CH_3$N), 0.82 (d, *J* = 6.6 Hz, 3H, $CH_3$CH)

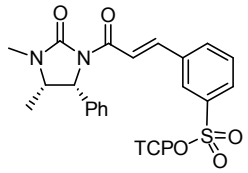
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.53 (s), 155.70 (s), 136.40 (s), 129.72 (t), 128.67 (d), 128.47 (d), 128.04 (d), 126.91 (d), 59.40 (d), 53.95 (d), 28.14 (q), 14.92 (q)

IR (thin film) $\nu_{max}$ 1708, 1668, 1395, 971, 750, 697 $cm^{-1}$

LRMS (EI) 244 ($M^+$, 25%), 189 (60%), 132 (100%)

HRMS (CI) calcd for $C_{14}H_{17}N_2O_2$ ($[M + H]^+$): 245.1285 found 245.1287

**3-[3-(3,4-Dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropenyl]benzene sulfonic acid 2,4,6-trichlorophenyl ester (196)**




A solution of 1-acryloyl 3,4-dimethyl 5-phenylimidazolidin-2-one (250 mg, 1.0mmo), 3-bromobenzene TCP sulfonate ester (355 mg, 0.85 mmol), bis(triphenylphosphine)palladiumdichloride (6 mg, 0.09 mmol) and P(*o*-tolyl)$_3$ (5 mg, 0.34 mmol) in toluene (4 mL) and triethylamine (2 mL) was heated in a microwave at 160 ºC for 30 min. This reaction was carried out six times and the resulting reaction mixtures were combined and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate) to give a white foam (2.31 g, 5.2 mmol, 65%).

$[\alpha]^{20}_D$ -21.0º (*c* = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 15.8 Hz, 1H, COCH*CH*Ar), 8.14 (t, *J* = 1.7 Hz, 1H, Ar*H*), 8.00 (ddd, *J* = 1.0, 1.7, 7.9 Hz, 1H, Ar*H*), 7.94 (app. d, *J* = 7.9 Hz, 1H, Ar*H*), 7.70 (d, *J* = 15.8 Hz, 1H, CO*CH*CHAr), 7.60 (app. t, *J* = 7.9 Hz, 1H, Ar*H*), 7.43-6.93 (m, 7H, Ar*H*), 5.44 (d, *J* = 8.5 Hz, 1H, *CH*Ph), 4.00 (dq, *J* = 6.6, 8.4 Hz, 1H, *CH*$CH_3$), 2.90 (s, 3H, *CH$_3$*N), 0.86 (d, *J* = 6.6, 3H, *CH$_3$*CH)

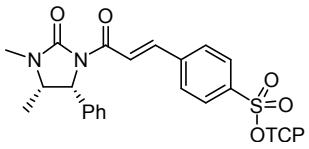
$^{13}$C NMR (101 MHz, CDCl3) δ 164.14 (s), 155.79 (s), 142.25 (s), 141.25 (d), 137.79 (s), 136.70 (s), 136.34 (s), 133.55 (d), 133.02 (s), 130.84 (s), 129.69 (d), 129.28 (d), 129.25 (d), 128.64 (d), 128.25 (d), 128.16 (d), 127.00 (d), 121.94 (d), 59.63 (d), 54.07 (d), 28.26 (q), 15.03 (q)

IR (thin film) $\nu_{max}$ 1722, 1668, 1622, 1562, 1355, 1181, 995 $cm^{-1}$

LRMS (ES) 581 ($[M+H]^+$, 100%)

HRMS (ES): calcd for $C_{26}H_{22}Cl_3N_2O_5S$ ($[M + H]^+$): 579.0310 found 579.0317

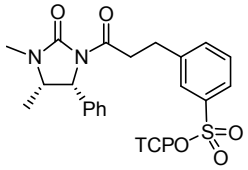
**4-[3-(3,4-Dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropenyl]benzene sulfonic acid 2,4,6-trichlorophenyl ester (197)**




Prepared as for **196** to give a white foam (2.18 g, 6.4 mmol, 61%)

| | |
|---|---|
| MP | 185-187 ºC |
| $[\alpha]^{20}_D$ | -1.1 (*c* = 10.0, $CHCl_3$) |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 15.8 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.73 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.67 (d, *J* = 15.8 Hz, 1H), 7.40 – 7.12 (m, 7H, Ar*H*), 5.41 (d, *J* = 8.5 Hz, 1H, *CH*Ph), 3.97 (dq, *J* = 6.6, 8.5 Hz, 1H, *CH*$CH_3$), 2.87 (s, 3H, *CH*$_3$N), 0.84 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH) |
| $^{13}$C NMR | (126 MHz, $CDCl_3$) δ 164.00 (s), 155.78 (s), 142.25 (s), 141.27 (s), 141.14 (d), 137.29 (s), 136.26 (s), 132.98 (s), 130.86 (s), 129.19 (d), 128.96 (d), 128.68 (d), 128.63 (d), 128.26 (d), 127.00 (d), 123.19 (d), 59.62 (d), 54.07 (d), 28.23 (q), 15.00 (q) |
| IR (thin film) | $\nu_{max}$ 1720, 1669, 1622, 1561, 1355, 1193 cm$^{-1}$ |
| LRMS (CI) | 583 (12%), 581 (20%), 579 ($M+H^+$, 15%), 355 (100%), 353 (70%) |
| HRMS (EI) | calcd for $C_{11}H_{14}N_2O$ ($M^+$): $C_{26}H_{21}Cl_3N_2O_5S$ 578.0231 found 578.0233 |

**3-[3-(3,4-Dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropyl]benzene sulfonic acid 2,4,6-trichlorophenyl ester (198)**

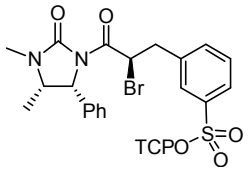



A suspension of 3-[3-(3,4-Dimethyl 2-oxo-5-phenylimidazolidin-1-yl) 3-oxopropenyl]benzenesulfonic acid 2,4,6-trichlorophenyl ester **5** (100 mg, 0.17 mmol) and dicolbalt octacarbonyl (59 mg, 0.17 mmol) in DME (255 µL) and $H_2O$ (100 µL) was heated to reflux for 3 h. The reaction mixture was cooled and concentrated *in*

*vacuo* and the crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give the product as a white foam (78 mg, 0.17 mmol, 78 %).

| | |
|---|---|
| $[\alpha]^{20}_{D}$ | -249.2 º (*c* = 1.0, $CHCl_3$) |
| $^1$H NMR | (600 MHz, CDCl3) δ 8.05–7.95 (m, 2H, Ar*H*), 7.73 (app. d, *J* = 8.0 Hz, 1H, Ar*H*), 7.61 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.54 – 7.40 (m, 5H, Ar*H*), 7.28 (d, *J* = 6.9 Hz, 2H, Ar*H*), 5.43 (d, *J* = 8.6 Hz, 1H, *CH*Ph), 4.06 (dq, *J* = 6.6, 8.5 Hz, 1H, *CH*$CH_3$), 3.51 (t, *J* = 7.6 Hz, 2H, *$CH_2$*$CH_2$), 3.19 (t, *J* = 7.6 Hz, 2H, *$CH_2$*$CH_2$), 2.99 (s, 3H, *$CH_3$*N), 0.96 (d, *J* = 6.6 Hz, 3H, *$CH_3$*CH) |
| $^{13}$C NMR | (151 MHz, CDCl3) δ 170.99 (s), 155.80 (s), 143.03 (s), 142.31 (s), 136.71 (s), 136.47 (s), 135.23 (d), 132.80 (s), 130.95 (s), 129.22 (d), 129.19 (d), 128.61 (d), 128.40 (d), 128.19 (d), 126.90 (d), 126.25 (d), 59.32 (d), 54.04 (d), 36.95 (t), 30.09 (t), 28.17 (q), 14.93 (q) |
| IR (thin film) | $\nu_{max}$ 1724, 1682, 1380, 1179 $cm^{-1}$ |
| LRMS (EI) | 584 (15%), 582($[M+H]^+$, 30%) , 580 (30%), 385 (100%) |
| HRMS (ES) | calcd for $C_{26}H_{23}Cl_3N_2O_5S$ ($M^+$): 581.0466 found 581.0469 |

**3-[2-Bromo-3-(3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropyl]-benzenesulfonic acid 2,4,6-trichlorophenyl ester (200)**

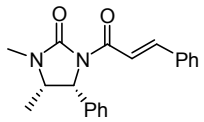



To a solution of 3-[3-(3,4-dimethyl 2-oxo 5-phenylimidazolidin-1-yl) 3-oxopropyl]benzene sulfonic acid 2,4,6-trichlorophenyl ester (200 mg, 0.34 mmol) in THF (1 mL) at -78 ºC under argon was added LHMDS (1M solution in THF) (380 µL, 0.38 mmol) dropwise.The mixture was stirred for 1 h and then bromine (21 µL, 0.41 mmol) was added dropwise. After stirring for 1 h at -78 ºC the reaction was quenched with sat. $NH_4Cl$ (aq) (10 mL) and EtOAc (20 mL). The organic layer was washed with sat. $NH_4Cl$ (aq) (2 x 10 mL) and the combined aqueous layers were back extracted with EtOAc (20 mL). The organic layers were combined, dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate) to yield a white foam (146 mg, 0.28 mmol, 64%).

| | |
|---|---|
| $[\alpha]^{20}_D$ | -0.54 º (*c* = 1.0, $CHCl_3$) |
| $^1$H NMR | (600 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H, Ar*H*), 7.64 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.54 (app. t, 1H, *J* = 7.8 Hz, Ar*H*), 7.39 (s, 2H, Ar*H*), 7.39-7.32 (m, 3H, Ar*H*), 7.23-7.22 (m, 2H, Ar*H*), 6.14 (app. t, 1H, *J* = 7.6 Hz, C*H*Br), 5.29 (d, 1H, *J* = 8.7 Hz, C*H*Ph), 3.90 (dq, 1H, *J* = 6.6, 8.7 Hz, C*H*$CH_3$), 3.60 (dd, 1H, *J* = 8.0, 14.3 Hz, PhCH*H*CHBr), 3.33 (dd, 1H, *J* = 8.0, 14.3 Hz, PhCH*H*CHBr), 2.05 (s, 3H, C*H*$_3$N), 0.82 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CHCHPh) |
| $^{13}$C NMR | (151 MHz, CDCl3) δ 167.09 (s), 154.45 (s), 142.26 (s), 139.36 (s), 137.07 (s), 136.22 (d), 135.19 (s), 132.92 (s), 130.89 (s), 129.46 (d), 129.32 (d), 129.24 (d), 128.61 (d), 128.42 (d), 127.17 (d), 127.00 (d), 59.28 (d), 53.77 (d), 43.81 (d), 39.42 (t), 28.34 (q), 15.17 (q) |
| IR (thin film) | $\nu_{max}$ 1729, 1686, 1441, 1387, 1181 $cm^{-1}$ |
| LRMS (ES) | 663 (70%), 661 (100%), 659 (50%, $M^+$) |
| HRMS (ES) | calcd for $C_{26}H_{23}Cl_3N_2O_5S$ ($M^+$): 658.9577 found 658.9606 |

# Experimental for Chapter 4

### 1,5-Dimethyl 4-phenyl 3-(3-phenylacryloyl)imidazolidin-2-one (191)

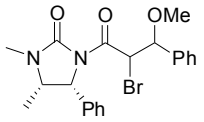



To a stirred solution of **173** (2.00 g, 10.1 mmol) in dichloromethane (100 mL) at 0 ºC under an argon atmosphere was added 2,6-lutidine (1.34 mL, 11.6 mmol) and then acryloyl chloride (2.63 g, 15.8 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 24h. After cooling the reaction mixture to room temperature saturated aqueous ammonium chloride solution (40 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride solution (2 x 40 mL), saturated sodium bicarbonate solution (3 x 40 mL) and water (1 x 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to yield a white solid (2.3 g, 7.1 mmol, 67 %). Data in agreement with Treweeke.[147]

| | |
|---|---|
| MP | 165-167 ºC, Lit.[215] 160 ºC |

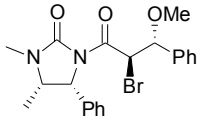
| | |
|---|---|
| $[\alpha]^{20}_D$ | -23.9° (*c* = 1.0, $CHCl_3$), Lit.[215] $[\alpha]_D$ -23.9° (*c* = 1.1, $CHCl_3$) |
| $^1$H NMR | (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 15.8 Hz, 1H, COCH*CH*Ph), 7.72 (d, *J* = 15.8 Hz, 1H, CO*CH*CHPh), 7.62-7.58 (m, 2H, Ar*H*), 7.43 – 7.09 (m, 8H, Ar*H*), 5.44 (d, *J* = 8.5 Hz, 1H, *CH*Ph), 3.97 (dq, *J* = 6.6, 8.4 Hz, 1H, *CH*$CH_3$), 2.89 (s, 3H, *CH*$_3$N), 0.85 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH) |
| $^{13}$C NMR | (101 MHz, $CDCl_3$) δ 164.96 (s), 156.02 (s), 144.40 (d), 136.63 (s), 135.13 (s), 130.05 (d), 128.74 (d), 128.56 (d), 128.42 (d), 128.10 (d), 127.01 (d), 118.81 (d), 59.61 (d), 54.02 (d), 28.25 (q), 15.05 (q) |
| IR (thin film) | $\nu_{max}$ 1716, 1665, 1615, 1360, 998, 755 $cm^{-1}$ |
| LRMS (EI) | 320 ($M^+$, 100%), 292 (70%) |
| HRMS (ES) | calcd for $C_{20}H_{20}N_2O_2$ ($[M + H]^+$): 321.1598 found 321.1600 |

**1-(2-Bromo-3-methoxy-3-phenyl-propionyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (241)**




To a mixture of 1,5-Dimethyl-4-phenyl-3-(3-phenyl-acryloyl)-imidazolidin-2-one (160 mg, 0.5 mmol) and silver triflate (154 mg, 0.6 mmol) was added chloroform (5 mL) and methanol (5 mL). The resultant solution was cooled to -78 ºC, bromine (31 µL, 0.6 mmol) was added and the mixture was stirred for 2 h. $H_2O$ (10 mL) was added and the organic solvents were removed *in vacuo*. $Et_2O$ (10 mL) was added and the aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude mixture was purified by column chromatography (diethyl ether/petroleum ether).

**241-**major




Tentative assignment

White foam (167 mg, 0.39 mmol, 77 %)

$[\alpha]^{20}_D$ -0.28 º (*c* = 1.0, $CHCl_3$)

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.79 – 7.10 (m, 10H, Ar*H*), 6.36 (d, *J* = 10.0 Hz, 1H, *CH*Br), 5.42 (d, *J* = 8.7 Hz, 1H, *CH*Ph), 4.50 (d, *J* = 10.0 Hz, 1H, *CH*OMe), 3.99 (dq, *J* = 6.6, 8.7 Hz, 1H, *CH*$CH_3$), 2.97 (s, 3H, O*CH*$_3$), 2.90 (s, 3H, *CH*$_3$N), 0.86 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH)

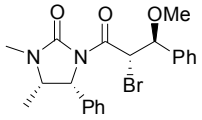
$^{13}$C NMR (151 MHz, CDCl3) δ 168.36 (s), 155.08 (s), 137.61 (s), 135.80 (s), 128.71 (d), 128.44 (d), 128.30 (d), 128.26 (d), 128.04 (d), 127.22 (d), 85.15 (d), 59.92 (d), 57.40 (d), 53.69 (d), 45.16 (q), 28.32 (q), 15.13 (q)

IR (thin film) $\nu_{max}$ 1726, 1688, 1380, 1087 $cm^{-1}$

LRMS (CI) 433 (5%), 431($[M + H]^+$, 5%), 191 (100%)

HRMS (ES) calcd for $C_{21}H_{24}BrN_2O_3$ ($[M + H]^+$): 431.0965 found 431.0968

**241**-minor




Tentative assignment

White foam (22 mg, 0.051 mmol, 10 %)

$[\alpha]^{20}_D$ 0.93 º (*c* = 1.0, $CHCl_3$)

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.73-7.00 (m, 10H, Ar*H*), 6.12 (d, *J* = 10.2 Hz, 1H, *CH*Br), 5.43 (d, *J* = 8.7 Hz, 1H, *CH*Ph), 4.67 (d, *J* = 10.2 Hz, 1H, *CH*OMe), 4.00 (dq, *J* = 6.6, 8.7 Hz, 1H, *CH*$CH_3$), 3.20 (s, 3H, O*CH*$_3$), 2.88 (s, 3H, *CH*$_3$N), 0.84 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH)

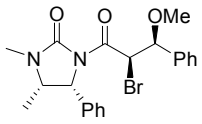
$^{13}$C NMR (151 MHz, $CDCl_3$) δ 167.31 (s), 154.77 (s), 137.50 (s), 135.51 (s), 128.70 (d), 128.56 (d), 128.49 (d), 128.26 (d), 126.92 (d), 83.31 (d), 59.49 (d), 57.64 (d), 53.69 (d), 45.13 (q), 28.30 (q), 15.17 (q)

IR (thin film) $\nu_{max}$ 1731, 1685, 1375, 1090 $cm^{-1}$

LRMS (CI) 433 (5%), 431($[M + H]^+$, 5%), 191 (100%)

HRMS (ES): calcd for $C_{21}H_{24}BrN_2O_3$ ($[M + H]^+$): 431.0965 found 431.0962

**1-(2-Bromo-3-methoxy-3-phenyl-propionyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (2*R*,3*S*-241)**

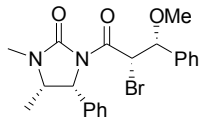



Epimer of **241**-major – tentative assignment

**241**-major (1.04 mmol) and tetra butyl ammonium bromide (5.22 mmol) in NMP (5 mL) were heated in the microwave for 60 min at 120 °C. The reaction mixture was portioned between $Et_2O$ (20 mL) and 10% lithium chloride solution (10 mL). The aqueous layer was extracted with with $Et_2O$ (2 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The product was isolated by column chromatography (petroleum ether/diethyl ether) as a white foam (54 mg, 0.13 mmol, 25%).

| | |
|---|---|
| $[\alpha]^{20}_D$ | -1.04 º (*c* = 1.0, $CHCl_3$) |
| $^1$H NMR | (500 MHz, $CDCl_3$) δ 7.40-7.26 (m, 8H, Ar*H*), 7.14-7.12 (m, 2H, Ar*H*), 6.36 (d, *J* = 9.8 Hz, 1H, *CH*Br), 4.97 (d, *J* = 8.7 Hz, 1H, *CH*Ph), 4.57 (d, *J* = 9.8 Hz, 1H, *CH*OMe), 3.55 (dq, *J* = 6.6, 8.5 Hz, 1H, *CH*$CH_3$), 3.23 (s, 3H, O*CH*$_3$), 2.72 (s, 3H, *CH*$_3$N), 0.70 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CH) |
| $^{13}$C NMR | (126 MHz, CDCl3) δ 166.17 (s), 154.34 (s), 137.59 (s), 135.26 (s), 128.63 (d), 128.56 (d), 128.48 (d), 128.32 (d), 127.01 (d), 83.53 (d), 59.26 (d), 57.14 (d), 53.48 (d), 45.27 (q), 28.23 (q), 15.01 (q) missing 1 x d |
| IR (thin film) | $\nu_{max}$ 3031, 1725, 1683, 1380, 1194, 1107 $cm^{-1}$ |
| LRMS | 433 (100%), 431 (100%, $[M+H]^+$), 401 (40%), 399 (40%) |
| HRMS (ES): | calcd for $C_{21}H_{24}BrN_2O_3$ ($[M+H]^+$): 431.0965 found 431.0957 |

**1-(2-Bromo-3-methoxy-3-phenyl-propionyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (2*S*,3*R*-241)**




Epimer of **241**-minor – tentative assignment

**241**-minor (0.5 mmol) and tetra butyl ammonium bromide (2.5 mmol) in NMP (5 mL) were heated in the microwave for 90 min at 120 °C. The reaction mixture was portioned between $Et_2O$ (20 mL) and 10% lithium chloride solution (10 mL). The aqueous layer was extracted with with $Et_2O$ (2 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The product was isolated by column chromatography (petroleum ether/diethyl ether) as a white foam (12 mg, 0.028 mmol, 22%).

| | |
|---|---|
| $[\alpha]^{20}_D$ | -15.98 º (*c* = 0.1, $CHCl_3$) |
| $^1$H NMR | (600 MHz, $CDCl_3$) δ 7.32-7.10 (m, 6H, Ar*H*), 7.08-7.05 (m, 2H, Ar*H*), 6.52 (d, *J* = 9.48Hz, 1H, *CH*Br), 6.49 (br.s, 2H, Ar*H*), 5.20 (d, *J* = 8.64 Hz, 1H, *CH*Ph), 4.58 (d, *J* = 9.46 Hz, 1H, O*CH*$_3$), 3.86 (dq, *J* = 6.58, 8.56 Hz, 1H, *CH*$CH_3$), 3.22 (s, 3H, *CH*$_3$N), 2.79 (s, 3H), 0.68 (d, *J* = 6.65 Hz, 3H, *CH*$_3$CH) |
| $^{13}$C NMR | (151 MHz, $CDCl_3$) δ 166.49 (s), 154.41 (s), 136.80 (s), 135.35 (s), 128.58 (d), 128.51 (d), 128.45 (d), 128.28 (s), 127.47 (d), 126.24 (d), 83.34 (d), 59.33 (d), 56.92 (d), 53.48 (d), 45.49 (q), 28.29 (q), 14.89 (q) |
| IR (thin film) | $\nu_{max}$ 2933, 1726, 1684, 1378, 1195, 1109 cm$^{-1}$ |
| LRMS | 433 (100%), 431 (100%, $[M+H]^+$), 401 (40%), 399 (40%) |
| HRMS (ES): | calcd for $C_{21}H_{24}BrN_2O_3$ ($[M+H]^+$): 431.0965 found 431.0961 |

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