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CATALYTIC FUNCTIONALISATION OF SP$^3$ BONDS

Scarlett Maria Walton

A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Huddersfield

September 2017

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In Loving Memory of my Dear Uncle Peter

‘There Is A Light That Never Goes Out’
List of Publications:

This following publication(s) is/are based on work presented in this thesis:

i: Catalytic sp$^3$-sp$^3$ Functionalisation of Sulfonamides: Late-Stage Functionalisation of Drug-Like Molecules


ii: Simple $\alpha$-functionalisation of sulfonamides


*Manuscript in press.*

iii: Electrospray source-induced rearrangement of $\alpha$-aryl tertiary sulfonamides via sulfur dioxide extrusion


*Manuscript in press.*
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ABSTRACT

Reported herein is an investigation into palladium-catalysed \( \alpha \)-allylation employing sulfonamide nucleophiles. Anions of benzylsulfonamides have been shown to react with a series of allyl acetates in the presence of Pd\(^0\) catalysts, phosphine ligands and base at room temperature, enabling the synthesis of sp\(^3\)-functionalised sulfonamides. The developed methodology has allowed access to a library of novel allylated sulfonamides, varying both amine substituent and allylic functionality. In addition, we have applied our methodology to a series of known sulfonamide drug targets, to demonstrate our reaction as a useful late-stage functionalisation tool, whilst populating chemical space.

The performed mechanistic study using a stereospecific electrophile confirms benzylsulfonamides behave as soft carbon nucleophiles in the Tsuji-Trost reaction, as a ‘net retention’ of stereochemistry is observed (confirmed by X-ray crystallography).

Moreover, the asymmetric synthesis of allylated sulfonamides is probed, although obtaining enantioselectivity \( \alpha \)-to SO bonds is naturally difficult, due to the conformational preferences of sulfonamide carbanions.

Traditional methods for direct \( \alpha \)-alkylation of sulfonamides require strong bases, reactive electrophiles, low temperatures and use of stoichiometric amounts of additives. Therefore, in addition to a catalytic method, we report an alternative method reacting benzylsulfonamides with allyl bromide electrophiles via a nucleophilic substitution reaction, using mild conditions (LDA, THF at \(-20^\circ\)C).
Table of Contents

Acknowledgements .................................................................................................................. 5
Abstract .................................................................................................................................. 6
Abbreviations .......................................................................................................................... 9
Chapter 1 Introduction ............................................................................................................ 11
1.1 Palladium-Catalysed Cross-Coupling Overview ............................................................... 11
1.2 Asymmetric Allylic Alkylation .......................................................................................... 16
   1.2.1 Overview .................................................................................................................. 16
   1.2.2 The Tsuji-Trost Reaction ...................................................................................... 16
   1.2.3 Electrophiles .......................................................................................................... 17
   1.2.4 Mechanism ............................................................................................................. 18
   1.2.5 Mechanistic Study .................................................................................................. 19
1.3 Soft Nucleophiles ............................................................................................................ 21
   1.3.1 Carbon Nucleophiles ........................................................................................... 21
   1.3.2 Nitrogen Nucleophiles ......................................................................................... 24
   1.3.3 Oxygen and Sulfur Nucleophiles ........................................................................ 25
1.4 Hard Nucleophiles .......................................................................................................... 26
   1.4.1 Reactions with Hard Nucleophiles ....................................................................... 26
   1.4.2 Softening Hard Nucleophiles ................................................................................ 28
   1.4.3 Lowering the pKa barrier ..................................................................................... 30
1.6 Enantioselectivity ............................................................................................................. 31
   1.6.1 Mechanism for Enantiodiscrimination ................................................................ 31
   1.6.2 Chiral Ligands ........................................................................................................ 32
1.7 Sulfonamides ................................................................................................................... 36
   1.7.1 Sulfonamides in Medicinal Chemistry ................................................................. 36
   1.7.2 Functionalisation of Sulfonamides ......................................................................... 37
   1.7.3 Traditional Alkylation of Sulfonamides ................................................................. 38
   1.7.4 Catalytic sp²-sp³ Coupling of Sulfonamides .......................................................... 39
   1.7.5 Catalytic Sp²-Sp³ Coupling of Sulfonamides .......................................................... 41
1.8 Project Goals .................................................................................................................... 45
Chapter 2 Results and Discussion ......................................................................................... 46
2.1 Palladium-Catalysed Allylation of Sulfonamides .............................................................. 46
   2.1.1 Investigation ........................................................................................................... 46
   2.1.2 Substrate Scope ..................................................................................................... 52
   2.1.3 Diallylation ............................................................................................................ 55
   2.1.4 Amine Substituent .................................................................................................. 56
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.5 Medicinal Chemistry Targets</td>
<td>62</td>
</tr>
<tr>
<td>2.1.6 Conclusion</td>
<td>65</td>
</tr>
<tr>
<td>2.2 Mechanistic Study</td>
<td>65</td>
</tr>
<tr>
<td>2.2.1 Investigation</td>
<td>65</td>
</tr>
<tr>
<td>2.2.2 Conclusion</td>
<td>76</td>
</tr>
<tr>
<td>2.3 Attempts at Enantioselective Synthesis</td>
<td>76</td>
</tr>
<tr>
<td>2.3.1 Investigation of Chiral Ligands</td>
<td>76</td>
</tr>
<tr>
<td>2.3.2 Conclusion</td>
<td>85</td>
</tr>
<tr>
<td>2.4 Alternative Methods for (\alpha)-alkylation of Sulfonamides</td>
<td>85</td>
</tr>
<tr>
<td>2.4.1 Investigation</td>
<td>85</td>
</tr>
<tr>
<td>2.4.2 Enantioselective Synthesis</td>
<td>91</td>
</tr>
<tr>
<td>2.4.3 Conclusion</td>
<td>91</td>
</tr>
<tr>
<td>2.5 Future Work</td>
<td>92</td>
</tr>
<tr>
<td>Chapter 3 Experimental</td>
<td>93</td>
</tr>
<tr>
<td>3.1 Palladium-Catalysed Allylation</td>
<td>94</td>
</tr>
<tr>
<td>3.1.1 General Procedures</td>
<td>94</td>
</tr>
<tr>
<td>3.1.2 Experimental Data</td>
<td>96</td>
</tr>
<tr>
<td>3.2 Alternative Methods for (\alpha)-Alkylation</td>
<td>123</td>
</tr>
<tr>
<td>3.2.1 General Procedures</td>
<td>123</td>
</tr>
<tr>
<td>3.2.2 Experimental Data</td>
<td>124</td>
</tr>
<tr>
<td>Chapter 4 References</td>
<td>137</td>
</tr>
<tr>
<td>Chapter 5 Appendix</td>
<td>141</td>
</tr>
<tr>
<td>5.1 NMR Data</td>
<td>141</td>
</tr>
<tr>
<td>5.2 Crystal Data</td>
<td>196</td>
</tr>
<tr>
<td>5.3 HPLC Data</td>
<td>197</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
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<td>AAA</td>
<td>asymmetric allylic alkylation</td>
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<tr>
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</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>APTS</td>
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</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
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<td>2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl</td>
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<td>dba</td>
<td>dibenzylideneacetone</td>
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<td>1,8-diazobicyclo[5.4.0]undec-7-ene</td>
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<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIOP</td>
<td>(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>d.r</td>
<td>diastereomeric ratio</td>
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<td>ESI</td>
<td>electrospray ionisation</td>
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<td>Et</td>
<td>ethyl</td>
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<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>IPA</td>
<td>isopropanol</td>
</tr>
<tr>
<td>KOtBu</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
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<td>methanol</td>
</tr>
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<td>mp</td>
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<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PMTDA</td>
<td>N,N,N',N'',N'''-pentamethyldiethylenetriamine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>R_F</td>
<td>retention factor</td>
</tr>
<tr>
<td>r.t</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N''-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Troc</td>
<td>trichloroethyloxycarbonyl</td>
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<tr>
<td>X-Phos</td>
<td>2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl</td>
</tr>
<tr>
<td>Xantphos</td>
<td>4,5-bis(diphenylphosphino)-9,9-dimethylxanthene</td>
</tr>
</tbody>
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CHAPTER 1 INTRODUCTION

1.1 Palladium-Catalysed Cross-Coupling Overview

The ability to form carbon-carbon bonds using sustainable methods has become a major focus of research and development, in particular for medicinal chemistry and the total synthesis of natural products.\textsuperscript{1,2} Since Kolbe demonstrated the first laboratory example of a C-C bond forming reaction (1845) in a synthesis of acetic acid, carbon-carbon bond forming reactions have been at the epicentre of the development of organic synthesis. There are a plethora of methods available that have become essential to the synthetic chemists’ toolbox, allowing the extension of complex carbon backbone structures and the synthesis of a myriad of organic compounds.\textsuperscript{3}

In the late 20\textsuperscript{th} century, a new approach to the formation of carbon-carbon bonds emerged. The introduction of transition-metal catalysis transformed the way synthetic chemists design syntheses, producing new opportunities in total synthesis, medicinal chemistry and process chemistry.\textsuperscript{4} The development of transition-metal catalysed reactions has played an important role in asymmetric synthesis and the production of enantioenriched material.\textsuperscript{5} The demand for enantiomerically pure bioactive compounds has driven the development of catalytic reactions, as more efficient and sustainable synthetic methods have been sought.

Among transition-metal catalysed processes, palladium-catalysed cross-coupling reactions have become an essential part of organic synthesis and the formation of carbon-carbon bonds. Cross-coupling reactions generally involve the combination of an organic electrophile with a nucleophilic coupling partner, reacting in the presence of sub-stoichiometric transition-metal catalyst.\textsuperscript{6}

The most commonly applied palladium-catalysed cross-couplings include: the Mizoroki-Heck, Stille, Suzuki-Miyaura, Sonogashira, Negishi and Tsuji-Trost reactions. These reactions can be grouped into three categories based on mechanism: migratory insertion (Heck), transmetalation (Suzuki, Stille, Sonagashira, and Negishi) and π-allyl (Tsuji-Trost). The impact of these methods was recognised in 2010 as Richard Heck, Ei-Ichi Negishi and Akira Suzuki were awarded the Nobel Prize in Chemistry\textsuperscript{7} for their contributions towards palladium catalysed reactions, highlighting the pivotal role they played in the development of modern chemistry.

The Mizoroki-Heck reaction reported first by Mizoroki (1971) and later improved by Heck (1972), generally couples sp\textsuperscript{2} aryl halides or triflates with olefins, resulting in a product formally arising from the substitution of a hydrogen in the alkene coupling partner (Scheme 1).\textsuperscript{8,9} Firstly, a palladium(II) catalyst is reduced to generate a Pd(0) species (step a), allowing for the oxidative addition of an aryl halide to the Pd(0) complex, to give a σ-aryl palladium(II) halide (step b). Co-ordination of the alkene to the palladium(II) complex (step c), followed by migratory insertion (step d) enables the formation of the new carbon-carbon bond. Syn β-hydride elimination (step e) allows the cross-coupled product to be released, leaving Pd-hydride complex to undergo reductive elimination with base to reform the active Pd(0) catalytic species (step f).\textsuperscript{10}
The Stille, Suzuki-Miyaura, Sonagashira, and Negishi reactions are similar to each other mechanistically as they all feature a transmetallation step, as shown in the catalytic cycle (Scheme 2). Again, oxidative addition (step b) of an aryl halide (or pseudohalide) to the Pd(0) complex generates a stable trans-σ-palladium(II) complex. Transmetalation of an organometallic species (depending on named reaction) forms a palladium(II) complex bearing both coupling partners (step c). Subsequent reductive elimination (step d) allows the cross coupled product to be released and the regeneration of Pd(0) into the catalytic cycle.\(^7\)

The Stille reaction, reported first in 1978, is recognised by the reaction of aryl halides with organostannane coupling partners (2, Scheme 2). Although organotin nucleophiles have proven toxic,\(^1^1\) the Stille reaction remains one of the most versatile palladium-catalysed cross-coupling reactions, owing to its wide application and sensitive functional group tolerance.\(^1^2\)

In 1979, Suzuki et al. reported a new palladium-catalysed carbon-carbon bond forming reaction using organoboron nucleophiles and organic (pseudo) halide electrophile in the presence of a base (3, Scheme 2).\(^1^3\) Since its discovery and development, the Suzuki-Miyaura reaction has become the most widely used cross-coupling reaction in medicinal chemistry, its popularity residing in the mild operating reaction conditions and broad functional group tolerance.\(^1^4\)
An alternative palladium-catalysed carbon-carbon bond formation protocol allows the coupling of terminal alkynes with aryl or vinyl halides, generally in the presence of a copper co-catalyst to accelerate the reaction. This transformation is known as the Sonogashira reaction and has proved an effective method in the synthesis of substituted alkynes (4, Scheme 2).\(^\text{15}\)

The Negishi reaction is a versatile palladium-catalysed cross coupling reaction employing organozinc reagents with aryl, alkyl, alkynyl or vinyl halides (5, Scheme 2). This reaction has been significantly developed due to the low toxicity of zinc reagents and their commercial availability.\(^\text{16}\)

---

### Scheme 2: Transmetallation reactions: Stille, Sonogashira, Suzuki-Miyaura and Negishi

2. Stille Reaction

\[
R^1\text{-SnR}^3 + R^2\text{-X} \xrightarrow{\text{cat. } [\text{Pd}^0\text{L}_n]} R^1\text{-}R^2
\]

- \(R_1 = \text{alkyl, alkynyl, aryl, vinyl}\)
- \(R_2 = \text{acyl, alkynyl, allyl, aryl, benzyl, vinyl}\)
- \(X = \text{Br, Cl, I, OAc, OTf}\)

3. Suzuki-Miyaura Reaction

\[
R^1\text{-B(OH)}_2 + R^2\text{-X} \xrightarrow{\text{cat. } [\text{Pd}^0\text{L}_n]} \text{base} R^1\text{-}R^2
\]

- \(R_1 = \text{alkyl, alkynyl, aryl, vinyl}\)
- \(R_2 = \text{acyl, alkynyl, aryl, benzyl, vinyl}\)
- \(X = \text{Br, Cl, I, OAc, OTs}\)

4. Sonogashira Reaction

\[
R^1\text{==H} + R^2\text{-X} \xrightarrow{\text{cat. } [\text{Pd}^0\text{L}_n]\text{ cat. CuX base}} R^1\text{-}R^2
\]

- \(R_1 = \text{alkyl, aryl, vinyl}\)
- \(R_2 = \text{aryl, benzyl, vinyl}\)
- \(X = \text{Br, Cl, I, OTf}\)

5. Negishi Reaction

\[
R^1\text{-ZnR}_2 + R^2\text{-X} \xrightarrow{\text{cat. } [\text{Pd}^0\text{L}_n]} R^1\text{-}R^1
\]

- \(R_1 = \text{alkyl, alkynyl, aryl, vinyl}\)
- \(R_2 = \text{acyl, aryl, benzyl, vinyl}\)
- \(X = \text{Br, I, OTf, OTs}\)

---
Unlike typical palladium-catalysed cross-couplings, the Tsuji-Trost reaction is mechanistically very different, proceeding occurs via a \( \pi \)-allyl palladium intermediate (6, Scheme 3).\(^4\)\(^7\) This palladium-catalysed cross-coupling reaction of allyl electrophiles (most commonly allyl acetates) with nucleophilic coupling partners (most commonly soft anions, generally formed from malonates or \( \beta \)-dicarbonyl compounds) is a synthetically useful strategy in the formation of carbon-carbon bonds.\(^5\)

The Tsuji-Trost allylic alkylation reaction constructs carbon-carbon bonds between sp\(^3\) hybridised carbons and can proceed via two mechanistic routes depending on the hardness (p\(K_a\)) of the pronucleophile. The catalytic species is generated by reduction of Pd(II) precatalyst to Pd(0) (a, Scheme 3), or alternatively the reaction can begin with a Pd(0) catalyst. The Pd(0) species can coordinate to the allylic substrate (b, Scheme 3), which in turn undergoes displacement of the leaving group (c, Scheme 3) to give a palladium \( \pi \)-allyl intermediate. Stabilised or ‘soft’ pronucleophiles (those which derive from conjugate acids with p\(K_a\)s \(\leq 25\)), such as malonate, proceed through direct attack of the nucleophile on the \( \pi \)-allylic termini, with no prior coordination to the Pd-complex (d, Scheme 3). Here, the product retains the stereochemistry of the carbon bonded to the leaving group (f, Scheme 3). Unstabilised or ‘hard’ pronucleophiles (those which derive from conjugate acids with p\(K_a\)s \(\geq 25\), for example Grignard reagents) coordinate to the Pd(II) species, forming intermediate (g, Scheme 3), after which reductive elimination takes place to form the allylated product (h, Scheme 3) with a net inversion of stereochemistry.\(^5\)
A plethora of palladium-catalysed cross couplings have emerged in the past half century, transforming the art of chemical synthesis. Palladium-catalysed cross-coupling reactions is an ever-expanding area of research both in academic and industrial research groups. This review will solely focus on the Tsuji-Trost reaction, specifically the extension of this methodology to encompass sulfonamide nucleophiles.
1.2 Asymmetric Allylic Alkylation

1.2.1 Overview

Asymmetric allylic alkylation (AAA) reactions use a transition metal catalyst to generate an asymmetric centre in the α-position of a racemic starting material (Scheme 4).\textsuperscript{17,18} AAA reactions have become a powerful method in constructing compounds with stereogenic centres, and have played an important role in the synthesis of biologically relevant compounds.\textsuperscript{5} Such transformations have been described with a large number of transition metal catalysts, including: gold,\textsuperscript{19} molybdenum,\textsuperscript{20} platinum,\textsuperscript{21} rhodium\textsuperscript{22} and more commonly palladium and iridium.\textsuperscript{23,24}

![Scheme 4: General reaction scheme for AAA](image)

This review will aim to focus on palladium-catalysed allylic alkylation reactions to give an insight into this ever-expanding area of chemistry. Both mechanistic discussion and application of the Tsuji-Trost reaction to various nucleophiles will be addressed.

1.2.2 The Tsuji-Trost Reaction

The first palladium mediated allylation was reported first by Tsuji in 1965, demonstrating that the anion of diethyl malonate (1) attacked stoichiometric allyl palladium(II) chloride dimer to yield both the mono and diallylated malonate 2a and 2b, respectively (Scheme 5).\textsuperscript{25}

![Scheme 5: First palladium-catalysed allylation reaction by Tsuji](image)
This new carbon-carbon bond-forming transformation was later developed by Trost in 1973 (Scheme 6).\textsuperscript{26} Formation of the $\pi$-allyl palladium complex with stoichiometric PdCl$_2$ and 1,1-dipropylethene (3) enables the reaction with the anion of diethylmalonate (1) in the presence of triphenylphosphine, accessing a mixture of three allylated compounds (4a, 4b and 4c).

\[
\begin{array}{c}
\text{3} + \text{PdCl}_2 \xrightarrow{\text{Na, THF/DMF}} \text{4a 54 \%} \quad \text{4b 11 \%} \quad \text{4c 12 \%}
\end{array}
\]

Scheme 6 Trost’s developed palladium-mediated reaction (1973)

Since these discoveries, significant progress has been made in this area, including the introduction of catalytic conditions,\textsuperscript{27,28} as well as the development of asymmetric alkylation.\textsuperscript{29} The Tsuji-Trost reaction has been the subject of many investigations in the past half century, from mechanistic discussion,\textsuperscript{26} its application in both medicinal chemistry and total synthesis,\textsuperscript{4} as well as presenting itself as a key player in asymmetric synthesis.\textsuperscript{18} This thesis will aim to discuss these factors in detail and highlight key reactions.

1.2.3 Electrophiles

An extensive range of unsaturated electrophiles, both cyclic and acyclic, can be employed in palladium-catalysed allylic alkylation reactions, making this a useful process for the formation of carbon-carbon bonds. Whilst the most commonly used substrates for this transformation are allylic acetates, a number of alternative leaving groups have also been exploited, including: alcohols,\textsuperscript{64, 30, 31} boronic esters,\textsuperscript{32} carbonates,\textsuperscript{89,90} epoxides\textsuperscript{33} and halides\textsuperscript{34} (Figure 1). The broad range of functional group compatibility has made the Tsuji-Trost reaction a versatile transformation.\textsuperscript{35}

\[
\begin{array}{cccc}
\text{OAc} & \text{OH} & \text{BPin} & \text{OCO}_2\text{R} \\
\text{O} & \text{X} & \text{X = Cl, Br, F} \\
\text{R = alkyl}
\end{array}
\]

Figure 1: Allylic electrophiles
1.2.4 Mechanism

The Tsuji-Trost reaction has been widely developed to utilise mild reaction conditions, synthesising allylic compounds via palladium-catalysed allylic alkylation of a nucleophile.\textsuperscript{5,17,18,23} As discussed in Section 1.1 the mechanism can proceed via two routes, since the mode of attack of nucleophiles on palladium \(\pi\)-allyl intermediates is related to the \(pK_a\) of the pronucleophile. Based on this well-known paradigm, nucleophiles can be divided into two classes: ‘soft’ or stabilised nucleophiles (from pronucleophiles with \(pK_a\)s < 25), and ‘hard’ or unstabilised nucleophiles (from pronucleophiles with \(pK_a\)s > 25).\textsuperscript{5,23} Since \(pK_a\) values are solvent and temperature dependent,\textsuperscript{36} the values discussed in this thesis correspond to DMSO organic solvent at 25 °C, unless otherwise stated.

‘Soft’ nucleophiles attack the \(\pi\)-allyl chain of the intermediate, giving rise to a product with a net retention of configuration. ‘Hard’ nucleophiles, on the other hand, co-ordinate firstly to the palladium of the \(\pi\)-allyl intermediate, and then transfer to the allylic carbon, thus forming a product with an overall net inversion of stereochemistry (Scheme 7).

As shown in Scheme 7, depending on the substitution of the allyl substrate, regioselectivity can be an issue in allylic alkylation. When the \(R_2\) group is not hydrogen the nucleophile can attack at either end of the allylic termini, thus potentially forming regioisomeric products. The regioselectivity of these reactions is influenced by several factors, including: the nature of \(R\) groups (steric and electronic effect), the ligands attached to the Pd complex, and the ability of the Pd intermediate to undergo \textit{syn:anti} isomerisation (Scheme 8).\textsuperscript{37}
19

Typically, palladium-catalysed allylation reactions using substituted \( \pi \)-allyl systems occur at the least substituted allylic terminus, thus leading to linear products, whereas other transition metal catalysed AAA reactions, for example iridium, preferentially form branched products.\(^{38}\)

### 1.2.5 Mechanistic Study

The division of nucleophiles into the two classes (hard or soft) was established by Trost in 1980.\(^{39}\) The initial mechanistic study utilised isomers of 3-acetoxy-5-carbomethoxy-1-cyclohexane (7a and 7b) to determine the stereochemical outcome of the cross-coupled product with a malonate nucleophile. \textit{Cis}-isomer 7a was prepared from methanolysis of racemic lactone 5 and subsequent acylation of alcohol 6a (1, Scheme 9).

\textit{Trans}-isomer 7b was prepared by a one-pot acid-catalysed isomerisation using perchloric acid and acylation with acetic anhydride of alcohol 6a gave the acylated compound as a mixture of isomers. Base-catalysed hydrolysis of the acetate gave alcohol 7ab, which could be selectively transformed to \textit{trans}-alcohol 6b and subsequently acylated to give \textit{trans}-isomer 7b (2, Scheme 9).\(^{39}\)

**Scheme 8: \textit{syn:anti} isomerisation**

1. **Synthesis 7a**

\[
\begin{align*}
\text{O} \\
\text{5} \\
\text{NaOMe, MeOH} \\
\text{r.t} 10 \text{ h} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{align*}
\]

2. **Synthesis 7b**

\[
\begin{align*}
\text{6a} \\
\text{1. Ac}_2\text{O, HClO}_4, \text{EtOAc, r.t} 2 \text{ h} \\
\text{2. NaOMe, MeOH} \\
\text{r.t} 7.5 \text{ h} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{NaOMe, C}_6\text{H}_6, \text{reflux, 3 h} \\
\text{quench 2M HCl} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Ac}_2\text{O, py} \\
r.t, 9 \text{ h} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{align*}
\]

**Scheme 9: Preparation of isomers of 3-acetoxy-5-carbomethoxy-1-cyclohexene 7a & 7b**
Cis-acetate 7a was subjected to palladium-catalysed allylation conditions with the sodium salt of dimethylmalonate 8 to obtain allylated compound 9a in a 92% yield as a 98:2 mixture of cis:trans isomers. Structure 9a was confirmed by $^1$H NMR, as the essential coupling ($J_{AD} = J_{BD} = J_{CD} = 12$ Hz) indicated that HA and HB are pseudoaxial (Scheme 10).

Similarly, dimethylmalonate nucleophile was successfully alkylated with trans-stereoprobe 7b, giving 9b in 80% yield. Structure 9b was also confirmed by $^1$H NMR, signals for Hc (δ 1.96, ddd J 13.5 Hz 9.5 Hz 5.5 Hz) and Hb (δ 1.80, dt J 13.5 Hz 4 Hz) were readily observed, thus suggesting that HA is pseudoequatorial and HB is pseudoaxial (Scheme 10).

In both cases the stereochemistry is retained, therefore this study demonstrates that dimethylmalonate 8 behaves as a soft nucleophile, as the nucleophile attacks the chain of the $\pi$-allyl palladium intermediate, juxtaposed with the co-ordination of the nucleophile to the palladium.

This study paved the way to a better understanding of allylic alkylation reactions and their mechanistic pathway. The Trost cis-stereoprobe 7a remains the most commonly used and is facile to synthesise in comparison to its trans-isomer 7b, however some mechanistic studies require access to a stereoprobe that cannot undergo competing deprotonation, for example when strong/excess base is used in the reaction. Therefore an alternative electrophile used is cis-5-phenyl-2-cyclohexen-1-yl acetate (13a) or its trans-isomer.
These stereoprobes can be synthesised from readily available phenylcyclohexane-1,3-dione (10) (Scheme 11). 40,41,42 Phenyldione 10 can be converted to enone 11 (step a, Scheme 11), which can undergo a Luche reduction to afford the racemic cis-alcohol 12 (step b, Scheme 11) in high diastereoselectivity (99%). Cis-alcohol 12 can be acylated using standard conditions to afford cis-acetate 13a (step c, Scheme 11). Access to the trans-acetate 13b can be achieved by reacting compound 12 under Mitsonobu conditions (step d).

\[ \text{Scheme 11: Synthesis of isomers of 5-phenyl-2-cyclohexen-1-yl acetate} \]

The development of the mechanistic study has been pivotal in understanding the behaviour of nucleophiles in the Tsuji-Trost reaction. Although the study has been modified throughout time with different stereodefined electrophiles, it is a widely accepted model to distinguish between hard or soft nucleophiles.

### 1.3 Soft Nucleophiles

#### 1.3.1 Carbon Nucleophiles

The ability to form carbon-carbon bonds by allylic alkylation reactions has become a major focus in organic synthesis, therefore it is no surprise that since the discovery of the Tsuji-Trost reaction, there are a myriad of examples in the literature with ‘soft’ carbon nucleophiles.

From the initial reaction by Tsuji in 1965 with diethylmalonate (1) (Scheme 5), other carbon nucleophiles have been reported to undergo palladium-catalysed allylic substitution reactions including: β-ketoesters, 43 ketone
enolates, aldehydes, amides, as well as stabilised carbanions of sulfones and thioamides to name but a few (Scheme 12).

The ability to create quaternary carbon centres in which the absolute stereochemistry can be controlled is of great importance in the synthesis of biologically active material. In 1988 Hayashi et al. demonstrated that β-ketoester 14 can undergo asymmetric allylic alkylation reactions with chiral ferrocene ligand L1, to yield alkylated product 15 (86 % ee) at –60 °C for 44 hours (1a, Scheme 12). Later in 1997, Trost developed this methodology (milder reaction conditions, 0 °C, and shorter reaction times, 3 hours) to obtain compound 15 in 86 % ee with the introduction of a new class of chiral phosphine ligand L2 (1b, Scheme 12).

Similarly, in 1999, Trost described the first asymmetric allylic alkylation of ketone enolates 16, also generating an all carbon chiral quaternary centre, with chiral ligand L2 (2, Scheme 12). These examples show the birth of a new class of chiral ligands that have since become extremely important in the design of ligands and the achievement of enantioselectivity in AAA reactions (further discussion in Section 1.6.2).

The 1990’s and early 2000 saw the expansion of this chemistry and its application to other soft carbon nucleophiles. In 2001, Tamaru et al. described the direct α-alkylation of aldehydes, both cyclic and acyclic to give 12 previously unreported compounds 19 (3, Scheme 12).

In 2008, the asymmetric α-allylation of amides was described by Hou et al. using chiral ferrocene ligand L1 to obtain compounds 21 with high enantioselectivities (4, Scheme 12). This reaction provides access to γ,δ-unsaturated amides, as well as demonstrating a useful tool to functionalise compounds that are valuable building blocks in organic synthesis.

In the same year, the α-C-H functionalisation of sulfones was also described via decarboxylative alkylation of sulfones derivatives 22, yielding compounds 23 in generally high yields (5, Scheme 12). In 2010, the same group were able to gain access into non-racemic compounds, although enantioselectivity was only achieved when using enantioenriched sulfone starting material. The difficulties of enantioselective functionalisation α-to sulfur will be discussed in detail later in Section 1.7.

The final example is the palladium-catalysed allylic alkylation of thioamide nucleophiles 24, which was reported firstly in 2013 by Zhao et al. and again in 2015 with the development of enantioselective synthesis (6, Scheme 12). Thioamides are synthetically useful and can easily be transformed into other functional groups such as amines, amides and acids.

The examples highlighted in Scheme 12 demonstrate the versatility of the palladium-catalysed allylic alkylation reactions and functional group tolerance. The examples presented show only a small number of the ever-growing library of soft carbon nucleophiles that can be applied to the Tsuji-Trost reaction.
1. **β-Ketoesters**  
   a) 1988
   
   \[
   \text{Scheme 12: Examples of soft carbon nucleophiles}
   \]
   
   14
   
   \[
   \text{[PdCl(C_3H_5)_2]_2} \rightarrow \text{CO}_2\text{Et}
   \]
   
   15
   
   100% conversion  
   81% ee
   
   L1
   
   NaH
   
   THF, -60 °C, 44 h
   
   14
   
   b) 1997
   
   \[
   \text{[PdCl(C_3H_5)_2]_2} \rightarrow \text{CO}_2\text{Et}
   \]
   
   15
   
   86% yield  
   86% ee
   
   L2
   
   Toluen, 0 °C, 3 h
   
   2. **Ketone Enolates** 1999
   
   16
   
   \[
   \text{[PdCl(C_3H_5)_2]_2 (2.5 mol %)} \rightarrow \text{LDA (3 eq)}
   \]
   
   17
   
   71% - 99% yield  
   80 - 88% ee
   
   L2 (5 mol %)
   
   THF, 0.5 h - 4 h
   
   R = Me, Et, CH2Ph
   
   3. **Aldehydes** 2001
   
   18
   
   \[
   \text{Pd(OAc)}_2 (10 mol %) \rightarrow \text{LHMDI (1 eq)}
   \]
   
   19
   
   12 examples  
   63 - 90% yield
   
   R = alkyl, phenyl
   
   4. **Amides** 2008
   
   20
   
   \[
   \text{[PdCl(C_3H_5)_2]_2 (1 mol %)} \rightarrow \text{LiCl (1 eq)}
   \]
   
   21
   
   12 examples  
   75 - 99% yield  
   82 - 91% ee
   
   L3
   
   THF, r.t.
   
   R1 = Me, Et, Pr, iPr, Ph, OTBS
   
   R2 = H, Me
   
   5. **Sulfones** 2008
   
   22
   
   \[
   \text{Pd_2dba_3 (5 mol %)} \rightarrow \text{rac-BINAP (10 mol %)}
   \]
   
   23
   
   13 examples  
   45 - 98%
   
   R1 = Me, Bn, Ph, allyl, F, Cl
   
   R2 = H, Me, Et, Ph, allyl
   
   6. **Thioamides** 2013
   
   24
   
   \[
   \text{[PdCl(C_3H_5)_2]_2 (5 mol %)} \rightarrow \text{dppb (11 mol %)}
   \]
   
   25
   
   15 examples  
   63 - 95%
   
   R = alkyl, aryl, heteroaryl
   
   Scheme 12: Examples of soft carbon nucleophiles

23
AAA using carbon nucleophiles have also been used in various total syntheses, including the synthesis of (−)-wine lactone (28) (Scheme 13). In 2000, Helmchen et al. used palladium-catalysed allylic substitution reaction of 8 and 2-cyclohexen-1-yl acetate (26) to provide compound 27 in high enantioselectivity, as a key first step in the total synthesis.

![Scheme 13: Palladium catalysed allylation in total synthesis of (−)-wine lactone](image)

1.3.2 Nitrogen Nucleophiles

Nitrogen nucleophiles are the second most commonly used nucleophiles in the Tsuji-Trost reaction. N-allylation has been reported for numerous nitrogen nucleophiles, including aliphatic and aromatic amines, amides, aziridines, and sulfonamides to name a few (Scheme 14).

In 1985 Inoue et al. reported a novel direct N-allylation of amides 29 with 2-allylisourea 30 under palladium-catalysed reaction conditions, obtaining a series of N-allylated amides in generally good yields (1, Scheme 14). In most cases a mixture of monoallylation 31a and diallylation 31b was observed, whereas in some cases only monoallylation was observed.

N-Allylation of primary amines has proven challenging due to potential over alkylation, whereas alkylation of secondary amines is more facile. In 1989, Hayashi et al. demonstrated an asymmetric allylic amination of both primary amines 32 and sulfonamide 35 with chiral ferrocene ligand L1 yielding compound 34 and 36 (2, Scheme 14). By using a bulkier electrophile 33 only monoallylation was observed.
Later in 2004, Yudin et al. reported the first example of allylic amination using unprotected aziridines 37 with allylic acetates to generate a library of compounds 38 (Scheme 14). In the cases where prenyl, geranyl and cinnamyl acetates were employed, branched isomers were formed exclusively over linear products.

1. Amides 1985

29
R¹ = Me, Ph, aryl, alkyl

30
R² = alkyl

Pd(dba)₂ (2 mol %)
dppe (2 mol %)
DMF 60 - 100 °C, 1 - 2 h

31 a
27 - 87 % yield

31 b

2. Amines and Sulfonamides 1989

32
Ph - NH₂

33
Ph - NH₂

CO₂Et

Pd₂dba₃·CHCl₃
L₁
THF, 40 °C, 3 - 108 h

34 84 % yield
97 % ee

35
OMe

36 67 % yield
88 % ee

3. Aziridines 2004

37
R¹ = Me, Cyclohexyl

38
R¹ = H, alkyl, Ph

[PtCl(C₃H₅)₂]₂ (1 mol %)
PPh₃ (4 mol %)
THF, r.t 30 min

12 examples
45 - 99 % yield

Scheme 14: Allylic alkylation with nitrogen nucleophiles

-N-allylation highlights the Tsuji-Trost reaction as a useful method in the formation of carbon-nitrogen bonds, with only a few of many examples presented in Scheme 14.⁶⁵ Although N-allylation is widely reported, controlling chemo-, regio-, and stereo-selectivities remains challenging, as well as over alkylation.⁶⁶

1.3.3 Oxygen and Sulfur Nucleophiles

The scope of palladium catalysed AAA reactions has also been demonstrated with oxygen and sulfur nucleophiles.⁶⁷,⁶⁸,⁶⁹ AAA reactions with oxygen nucleophiles include; alcohols,⁷⁰ carboxylates,⁷¹ carbonates⁷² and phenols.⁷³
Phenols represent a superior class of oxygen nucleophiles since stereogenic carbon atoms bearing an oxygen are present in many natural products. Palladium catalysed allylic substitution reactions of phenols have been applied in Trost's total synthesis of (−)-morphine, (−)-codeine and (−)-galanthamine. These syntheses all feature a palladium-catalysed allylic substitution reaction as a key step in installing chirality, accessing the highly functionalised phenolic compound 40 in high enantioselectivity (Scheme 15).

Furthermore, a variety of sulfur nucleophiles can be applied to palladium-catalysed allylic alkylation reactions, including sulfones and thiocarboxylates. The Tsuji-Trost reaction is a powerful tool in the formation of C-C, C-N, C-O and C-S bonds. Despite the high level of activity in this area, there are challenges that remain and nucleophiles that are yet to be studied.

1.4 Hard Nucleophiles

1.4.1 Reactions with Hard Nucleophiles

The Tsuji-Trost reaction has been intensely explored mechanistically, using a variety of nucleophiles. As discussed, the use of soft nucleophiles dominate the literature and reports of reactions with hard nucleophiles, those which are derived from conjugate acids whose pKa's are ≥ 25, are rare. This may be due to the difficulty of deprotonating a ‘hard’ position, which generally requires excess base, leading to the enantiomeric excess values being typically low for hard nucleophiles.

In 1990, Buono et al. reported the first example of a palladium-catalysed cross coupling of an unstabilised Grignard reagent 41 and allylic acetate 26 affording the cross coupled product 42 in an 85 % yield (Scheme 16). Although 42 was obtained in high yield, low ees were observed and high enantioselectivity could not be
obtained, despite screening an extensive array of chiral ligands. Proliphos (L6) was the most effective chiral ligand in the screening, giving compound 40 in 30 % ee.80

![Scheme 16: First palladium catalysed allylation with ‘hard’ nucleophile](image1)

One of the most successful application of non-stabilised nucleophiles involves hydride transfer with formic acid acting as the hydride donor. First reported by Yamamoto in 1991,81 Hayashi and co-workers later reported the first asymmetric example; chiral allylsilane 44 was obtained in high yield and high enantioselectivity from allyl carbonate 43 in the presence of chiral monodentate phosphine palladium catalyst L7 (Scheme 17).82

![Scheme 17: Asymmetric reaction with hydride transfer, Hayashi 1994](image2)

More recent advances of the Tsuji-Trost reaction with hard nucleophiles have been reported by Maulide and Morken (Scheme 18). In 2011, Morken et al. reported an asymmetric palladium-catalysed allylation reaction of allyl boronates to generate compounds 46 with an all carbon quaternary centre in high enantioselectivity.83 In 2013 Maulide et al. exploited this chemistry by employing allyl boronates as nucleophiles with lactones 47 to yield trans-cyclobutene carboxylic acid derivatives 48 in generally good yields and with moderate enantioselectivity.84

Additionally, in 2014, Maulide et al. demonstrated that dialkyl zinc reagents behave as hard nucleophiles in palladium-catalysed allylic substitution reactions with cyclic electrophiles 49 by developing the first asymmetric reaction of this kind, accessing compounds 50 with high enantioselectivity.85

27
Despite the recent success in obtaining high enantioselectivity in AAA using hard nucleophile, it is widely accepted that obtaining reactivity or enantioselectivity with hard pronucleophiles is difficult. Studies by Trost in 2008 showed how hard pronucleophiles could be 'softened' by use of activating agents that stabilise the resultant anionic charge. Trost showed that 2-methylpyridine derivatives 51 could be allylated using palladium-catalysed conditions with BF$_3$ complex as an activating agent, yielding compounds 52 in high enantioselectivity (1, Scheme 19). Prior to this work, when 2-methylpyridine (51a) anion was generated with n-BuLi and subjected to AAA reaction conditions, no conversion to the desired allylated product was observed. Trost confirmed that the anion of 2-methylpyridine (51a) behaved as a soft nucleophile as the reaction with trans-stereoprobe 53a proceeds with a net retention of configuration 54 (2, Scheme 19). Trost later applied this methodology to 2-substituted pyridine nucleophiles to expand the scope of softening hard nucleophiles.
Walsh focused on the softening of ‘harder’ pronucleophiles in an attempt to broaden the scope of nucleophiles that can be applied to the Tsuij-Trost reaction. In 2011, Walsh demonstrated that toluene pronucleophile derivatives (pK_a ~ 43) can undergo allylic alkylation by activation of the pronucleophiles with η^6-tricarbonyl chromium. More recently, in 2016, this chemistry was transferred to asymmetric allylic alkylation to access chiral compounds. High enantioselectivities of a library of toluene-based compounds were obtained using the Ph-Taniaphos chiral ligand L12 (1, Scheme 20).

A mechanistic study was performed using cis-stereoprobe 53b and chromium compound 55a, to yield cis-compound 57 in 63 % with 64 % ee, the net-retention of stereochemistry confirms the soft nature of the nucleophile (2, Scheme 20).

Scheme 19: Softening 2-methylpyridine nucleophiles
1.4.3 Lowering the pK\textsubscript{a} barrier

The route to establish whether a nucleophile follows the hard or soft catalytic pathway has been very well established, however some nucleophiles have been reported to not follow this trend.

In 2013 Walsh and co-workers reported that diarylmethane derivative (pK\textsubscript{a}'s of ~ 32)\textsuperscript{36} behave as ‘soft’ nucleophiles in palladium-catalysed allylic substitution reactions. A library of allylic functionalised diarylmethane compounds were described, as well as heterocyclic diarylmethanes. The mechanistic study for diphenylmethane (58) and di-(3-pyridyl)methane (60) was carried out using cis-stereoprobe 53b. In both cases a net retention of stereochemistry was observed, suggesting both diphenylmethane and di-(3-pyridyl)methane behave as soft nucleophiles in the Tsuji-Trost reaction (Scheme 21).\textsuperscript{90} These results raise a question as to whether the pK\textsubscript{a} limit for 'soft' nucleophiles should be raised from 25 to 32.
Scheme 21: Allylic substitution with retention of configuration

1.6 Enantioselectivity

1.6.1 Mechanism for Enantiodiscrimination

A significant advantage of transition-metal catalysed processes is the possibility of using chiral ligands to induce asymmetry. The general catalytic cycle of an AAA reaction offers at least five opportunities for enantiodiscrimination: enantiotopic complexation (A), ionisation (B), nucleophilic attack at the enantiotopic termini (C), enantioface discrimination of π-allyl complex (D), as well as enantiodiscrimination in the nucleophile (E) (Figure 2).

Enantiotopic complexation (mechanism A) shows how palladium can differentiate between the enantiotopic faces of the π-allyl system if the olefin is unsymmetrical. In meso substrates (mechanism B), palladium may insert into either end of the π-allyl system, therefore enantioselection occurs by desymmetrisation of the meso intermediate. If the π-allyl intermediate is not symmetrically 1,3-disubstituted (mechanism C), enantioselection will be dictated by the transition metal choosing a face of the allyl fragment to coordinate. Mechanism D is similar to that of mechanism A, whereby the π-allyl intermediates interconvert faster than they are attacked by a nucleophile, therefore enantioselectivity is derived from the differential rates of reaction. Enantioselectivity can also be obtained via enantiofacial discrimination by prochiral nucleophiles (mechanism E). In mechanism A and B, the metal induced ionisation of the leaving groups represents the enantiodiscrimination step; while in mechanisms C and D nucleophilic addition is the enantiodiscrimination step.
1.6.2 Chiral Ligands

1.6.2.1 \( C_2 \) Symmetric Ligands

The design and synthesis of chiral ligands has played an important role in the ability to achieve enantioselectivity in AAA reactions.\(^{23}\) The ability for a chiral catalyst to transfer asymmetry to a substrate generally relies on steric biasing and electronic effects. Many of the chiral ligands used in AAA reactions are bidentate and are either \( C_1 \) or \( C_2 \) symmetric.\(^{92}\)

\( C_2 \) symmetric ligands offer significant advantages in asymmetric reactions since the presence of a symmetry axis not only reduces the number of catalyst-substrate arrangements, but also reduces the number of competing reaction pathways.\(^{93}\) The first \( C_2 \) symmetric ligand developed for asymmetric catalysis was \((-\)\)DIOP \textbf{L13}, pioneered by Dang and Kagan in 1971 (Figure 3).\(^{94,95}\)
Trost and co-workers used (−)-DIOP in the first asymmetric allylic alkylation performed in 1977, reacting cis-3-acetoxy-5-carbomethoxycyclohexene (7a) with nucleophile 62 to obtain cis-functionalised product 63 in 77 \% yield and 46 \% ee (Scheme 22).\textsuperscript{29}

The design principles of DIOP have influenced the development of diphosphine ligands that have been synthesised in the past few decades.\textsuperscript{96} Of the vast library of chiral ligands synthesised so far, a small class of ligands, referred to as ‘privileged ligands’, have emerged due to of their broad applicability. These ligands have been widely used in AAA reactions, with ligands possessing C\textsubscript{2} symmetry dominating the literature.

The most popular of the ‘privileged ligands’ in AAA reactions are a class of C\textsubscript{2} symmetric diphosphine ligands, developed by Trost in the early 1990s.\textsuperscript{43,44} Trost developed a working model for the design of his chiral ligands, in which the chiral environment created around the allyl group is closely related to the P-Pd-P bite angle; increasing the bite angle moves the aryl groups away from the ligand backbone and further envelops the substrate (Figure 4).\textsuperscript{92,97} The P-Metal-P bite angle in transition metal complexes is generally measured by either crystal structures found in Cambridge Crystallographic Database, or by computer modelling.\textsuperscript{98} There are several factors known to affect the bite angle, including steric interactions of the ligand backbone, as well as electronic differentiation of coordinating atoms.\textsuperscript{99}
Based on the model in Figure 4, the Trost ligands were made so that the $N$-$C$-$C$-$N$ linkage maximises the dihedral angle, restricting the number of degrees of rotational freedom in the phosphine-metal complex (Figure 5).\textsuperscript{100} By limiting the specific degrees of freedom, the number of competing transition states is lowered, therefore there is greater probability of accessing high enantioselectivity.\textsuperscript{101} Ligands $L_2$, $L_{14}$ and $L_{15}$ are three of the more commonly used Trost ligands in AAA reactions and were designed to be stable in asymmetric catalysis and have the ability to form highly stereoselective systems.\textsuperscript{102}

In contrast to Trost's chiral diphosphine ligands, another class of privileged ligands used in AAA reactions are the $C_2$ symmetric oxazoline ligands.\textsuperscript{103} Chiral oxazoline based ligands, such as; bis(oxazoline) (Box) $L_{16}$, azabis(oxazoline) (azaBox) $L_{17}$ and pyridinebis(oxazoline) (pyBox) $L_{18}$, are a class of typical $N,N$-bidentate ligands, containing two oxazoline rings separated by a spacer (Figure 6). Since their synthetic development in 1990-1991,\textsuperscript{104,105} Box ligands and their derivatives have been successfully applied to AAA reactions, demonstrating high enantioselectivity.\textsuperscript{106}
Figure 6: Examples of chiral oxazoline ligands

Other key privileged ligands used in AAA reactions include BINAP L19, BINOL L20 and phosphoramidite L21 derivatives, all of which contain a binaphthyl core but vary in the co-ordination atom to the catalyst (Figure 7).\textsuperscript{107} These classes of ligands are stable to racemisation due to the high barrier of rotation about the central C-C bond, therefore are found in numerous applications in asymmetric reactions.\textsuperscript{108} Binaphthyl derived ligands are a large class of ligands that are extremely versatile as their structure allows for facile modification.\textsuperscript{109}

Figure 7: Binaphthyl core ligands

1.6.2.2 $C_1$ Symmetric Ligands

Although the use of $C_2$ symmetric ligands remains dominant in AAA reactions, $C_2$ symmetric ligands can struggle to distinguish between diastereotopic carbons of the allylic moiety.\textsuperscript{110} Therefore in the early 1990’s a new class of ligands were established, containing a mixture of P-N properties, as opposed to the more usual P-P and N-N in $C_2$ symmetric ligands.\textsuperscript{111,112,113} These $C_1$ symmetric ligands are more commonly known as the phosphinooxazolines (PHOX) L22 ligands, and were developed by Williams, Helmchen, Werner and Pfaltz (Figure 8).\textsuperscript{114}
These ligands were designed so that the contrasting (P-N) properties are able to constrain the reactivity of the metal centre to a single site of the ligand, giving rise to selective attack of the nucleophile at the allylic carbon.\textsuperscript{114} C\textsubscript{1} symmetric PHOX ligands have become extremely versatile ligands in allylic alkylation reactions, as numerous examples with differing backbone frameworks have demonstrated their ability to control enantioselectivity.\textsuperscript{115}

\subsection*{1.7 Sulfonamides}

\subsubsection*{1.7.1 Sulfonamides in Medicinal Chemistry}

The sulfonamide functional group is a frequently seen subunit in medicinal chemistry. Compounds bearing a sulfonamide functionality often exhibit anti-bacteria,\textsuperscript{116} anti-cancer,\textsuperscript{117} anti-inflammatory\textsuperscript{118} and anti-psychotic\textsuperscript{119} properties, demonstrating the widespread application of the sulfonamide moiety in drug-design. Sulfonamides are pharmacologically reliable motifs and appear in several drug substances, for example Sumatriptan, the first of the triptan class (Figure 9). Sumatriptan (Imitrex\textsuperscript{R}, GlaxoSmithKline) a licensed drug developed in 1991 is used in the treatment of migraines and cluster headaches.\textsuperscript{120}
More recently, the sulfonamide functional group has appeared in drug-like molecules (Figure 10). In 2013, a series of arylalkylsulfonyl piperazines 64 were shown to exhibit nanomolar binding affinities for sigma receptor ligands; varying the position of the phenyl substituent on piperazine ring proved to be the key to improvements.\(^\text{121}\)

In addition, sulfonamides have been screened in the development of anti-psychotic drugs. Cyclic sulfonamide 65 and varying derivatives have been screened as potential dopamine D\(_2\) and D\(_4\) selective receptor agonists, in the development of drugs to target and treat schizophrenia. Sultam 65 gave promising results in the study as it was a fully selective D\(_4\) compound.\(^\text{122}\)

Finally, in 2015 Torok et al. reported sulfonamide linker based inhibitors, for example compound 66, as a new class of potential drug candidates for the treatment of Alzheimer’s disease.\(^\text{123}\)

1.7.2 Functionalisation of Sulfonamides

The ability to form carbon-carbon or carbon-heteroatom bonds from a generally unreactive C-H bond has led to an array of C-H transformations reported in literature.\(^\text{124,125}\) C-H functionalisation techniques have become an important addition to the medicinal chemists’ toolbox, and as such, novel methods to functionalise at sp\(^2\) and sp\(^3\) centres has vastly expanded.\(^\text{126}\)

The literature is filled with a myriad of C-H functionalisation reactions, some of which include: arylation,\(^\text{127,128}\) alkylation,\(^\text{129}\) amination,\(^\text{130}\) oxidation,\(^\text{131}\) borylation\(^\text{132}\) and halogenation.\(^\text{133,134}\) Such C-H transformations have
paved the way in exploring chemical space and enabling access to diverse analogues of potential lead-like compounds.\textsuperscript{135,136} Therefore, C-H functionalisation has become a quintessential approach, rather than relying solely on conventional synthetic approaches.\textsuperscript{137,138}

Despite the wide pharmaceutical interest in sulfonamides, few methods to functionalise $\alpha$- to the sulfur have been reported. Bearing this in mind, along with the drive to develop practical late-stage functionalisation methods, there has been significant interest in the development of new methods to functionalise $\alpha$- to the sulfonyl moiety.

### 1.7.3 Traditional Alkylation of Sulfonamides

Traditional alkylation of sulfonamides often demands use of strong bases, reactive electrophiles, low temperatures and use of stoichiometric additives, such as tetramethylenediamine (TMEDA) and hexamethylphosphoramide (HMPA).\textsuperscript{139,140}

In 2002, Enders demonstrated that $\alpha$- functionalisation of sulfonamides was possible using chiral sulfonamide\textsuperscript{67}. Reacting \textsuperscript{67} with allyl bromide under relatively harsh reaction conditions ($n$-BuLi, HMPA, $-78$ °C for 24 hours) $\alpha$-allylated compound \textsuperscript{68} was obtained in 68 % yield and high diastereoselectivity (Scheme 23).\textsuperscript{140}

\begin{center}
\textbf{Scheme 23: $\alpha$-Alkylation of sulfonamides via nucleophilic substitution reaction}
\end{center}

![Scheme 23: $\alpha$-Alkylation of sulfonamides via nucleophilic substitution reaction](image)

Although there are reported alkylation methods to functionalise at the $\alpha$-carbon of sulfonamides,\textsuperscript{140,141} there is a lack of practical methods available, especially ones that do not use carcinogenic additives.
1.7.4 Catalytic sp²-sp³ Coupling of Sulfonamides

Several reports have described metal-catalysed sp²-sp³ coupling of sulfonamides, demonstrated first by Parkinson et al. in 2005 with the palladium-catalysed α-arylation of methylsulfonamide 69 with phenyl bromide, yielding compound 70 in 66 %. (Scheme 24). However, when varying substituents on the nitrogen subunit, as well as the on the aryl bromide, the yields of α-arylated product decreased (less than 30 %) due to both steric and electronic effects.

![Scheme 24: First palladium catalysed arylation of methanesulfonamides](image-url)

In 2007 Northrup, at Merck, developed Parkinson’s previous work by introducing an ester group to activate the α-CH position, which after functionalisation could be removed easily by decarboxylation. α-Arylation of 71 was achieved using palladium-catalysed reaction conditions with various aryl and pyridyl bromides to yield compounds 72 (Scheme 25). Nonetheless, lower yields were obtained for sterically bulkier aryl bromides, for example 2-bromo-m-xylene gave only 7 % yield of the desired arylated sulfonamide.

![Scheme 25: Northrup synthesis of benzylic sulfonamides](image-url)

After the C-H arylation reaction, Northrup described how the functionalised compound (72a Scheme 26) can undergo a one pot sulfonamide metathesis with dimethylamine and subsequent decarboxylation to afford the desired product 73 (Scheme 26). This example highlights a practical method in obtaining α-arylated sulfonamides, with the ability to replace the amine group after the functionalisation reaction.
In 2008, Zhou et al. reported a new strategy for providing a practical route to benzylic sulfonamides. Their method highlighted a Negishi cross-coupling of sulfonamide zinc reagents, prepared in situ, with varying aryl coupling partners (Scheme 27). This methodology allows \( \alpha \)-arylation of sulfonamide 74, without the need for an electron withdrawing group present, such as an ester in the previous Northrup’s example.

Similarly, Knauber and Tucker have explored the Negishi type \( \alpha \)-arylation of sulfonamides and sulfones, developing a method in which \( \text{TMP-ZnClLiCl} \) can be used dually as a base and source of zinc in the coupling reaction. Using microwave irradiation, which reduced reaction times to two hours (from 16 hours at 60 °C in a sealed vial), a broad reaction scope of aryl bromides (aromatic and heteroaromatic) and alkyl sulfonamides 76 (several different nitrogen substituents) were coupled in modest to good yields, demonstrating the significant scope of the reaction (Scheme 28).
1.7.5 Catalytic Sp$^3$-Sp$^3$ Coupling of Sulfonamides

To date, there have been few disclosures of methods to enable catalytic sp$^3$-sp$^3$ coupling of sulfonamides, functionalising at the carbon $\alpha$- to the sulfur moiety. In 2014, Fu et al. developed an enantioselective nickel-catalysed Negishi arylation and alkenylation of both sulfones and sulfonamides.\textsuperscript{146} Fu showed that racemic bromosulfonamides \textbf{78} could undergo Negishi alkenylation with alkenylzirconium reagents \textbf{79} with chiral bisoxazoline ligands. The desired cross-coupled products \textbf{80} were obtained in good yields and high enantioselectivity (Scheme 29). This work was the first method for catalytic asymmetric synthesis of sulfonamides, whereas asymmetric synthesis of sulfones had been previously reported.\textsuperscript{147,148}

Prior to the work of Fu et al, there had been no reported catalytic methods to obtain enantioenriched sulfonamides and few reports for sulfones,\textsuperscript{147} as controlling the stereochemistry at the carbon $\alpha$- to the sulfur is inherently difficult.

Investigations into the configurational stability of $\alpha$-sulfonyl carbanions were led by Gais \textit{et al.} in the late 1980s-early 1990s.\textsuperscript{149,150} The crystal structure presented in (Figure 11) shows that lhiiosulfone anions prefer a staggered confirmation, in which the filled p-orbital at $\text{C}_\alpha$ is gauche to both oxygens.\textsuperscript{151,152} The stabilisation of
the negative charge by inductive effects of the R₃ group dictates the conformational stability, which in turn controls the asymmetric outcome of potential reactions.¹⁴⁹

Figure 11: Conformation of lithiosulfone anion

In 1989, Gais et al. found that lithiotrifluoromethyl sulfones (lithiotriflones) are more configuratively stable than lithio(phenyl)sulfones i.e. the barrier of racemisation of lithiotriflones is larger than that of lithio(phenyl)sulfones.¹⁵³ Extensive studies have since shown that fluorine substitution has a significant effect on the energy of α-sulfonyl carbanions. Not only does fluorination strongly affect the acidity of sulfones, since trifluoromethylsulfones are approximately 10 pKₐ units more acidic than phenyl sulfones, it also affects the height of the C-α-S rotational barrier.¹⁵⁴ Studies in 1996 showed that when the R₃ substituent of the favoured staggered conformer (Figure 11) is electron withdrawing F or CF₃, the S-CF₃ and S-O bonds are lengthened, highlighting that the interaction between the anionic lone pair orbital and S-R₃ is more effective than the less stable eclipsed conformer.¹⁵⁴

These results gave evidence that negative hyperconjugation (nₓ – σ*ₓₛ) plays an important role in the configurational stability of α-sulfonyl carbanions.¹⁵⁴,¹⁵⁵,¹⁵⁶ When an electronegative atom (F or CF₃) is attached to the sulfur that is bound to the anionic carbon, the S-F/CF₃ bond becomes strongly polarised. This polarisation allows for strong overlap between the non-bonding electron pair of the anionic centre and the anti-bonding orbital of the S-X bond. Subsequently, this interaction leads to the stabilisation of the anion and partial double bond character between the C-S bond, raising the barrier to rotation and therefore racemisation.¹⁵³,¹⁵⁴ In contrast, when CF₃ is replaced with a more electropositive group, such as CH₃, the anion is less stable and is able to rotate more freely, therefore racemisation is more likely to occur.

In 2007, Nakamura described the first catalytic and enantioselective reaction with α-lithiated trifluoromethylsulfone (81) and various aromatic aldehydes to give syn products 82 in excellent diastereoselectivity and high enantioselectivity (Scheme 30). Attempts at asymmetric lithiation using benzyl sulfones that do not bear the CF₃ group α– to sulfur were unsuccessful and low ee values were obtained (4 % - 32 %), thus confirming previous reports that an electron withdrawing fluorine substituent is essential to generate a more configurationally stable anion.¹⁴⁷
The results of these studies highlight the difficulty in controlling the stereoselectivity of the $\alpha$-carbon of sulfonyl functional groups. Although success has been achieved with enantioselective $\alpha$-functionalisation of trifluoromethylsulphones, this remains a challenging research area, and little has been achieved with sulfones that do not bear a CF$_3$ group.

To date, asymmetric $\alpha$-CH functionalisation of sulfonamides has been achieved using chiral auxiliaries, for example Enders work in 2002, previously described in Scheme 23.$^{140}$ Scheme 31 shows how chiral sulfonamides 84 can be synthesised from readily available chiral amine auxiliaries 82. These sulfonamides 84 can then undergo alkylation via a nucleophilic substitution reaction with strong base, yielding compounds 85 in high diastereoselectivity. Finally, sulfonamides 85 can undergo racemisation-free cleavage of the auxiliary in acidic conditions, to give sulfonamides 86 in excellent enantioselectivity.
Based on previous structural investigations, Enders hypothesised that the lone pair of electrons would be orientated *gauche* to both sulfonyl oxygen atoms, with the sulfonamide group occupying the axial position on the dioxane core and the biphenyl group in the equatorial position (Figure 12). Therefore, asymmetric induction is achieved by the steric hindrance of the “biphenyl wall”, with the carbanionic centre being accessible from the less shielded face.
1.8 Project Goals

The main aim of this project was to develop a palladium-catalysed method to enable sp\(^3\)-sp\(^3\) coupling of sulfonamides, leading to the formation of novel compounds containing linear and cyclic allylic functionality α-to the sulfonyl moiety. This Tsuji-Trost type chemistry would intend to use mild reaction conditions that could be easily transferrable in drug synthesis. Therefore, a significant objective of the project was to apply the developed chemistry to reported drug-like molecules to demonstrate our method as a potentially useful late-stage functionalisation tool.

Performing a mechanistic study was essential to understand the behaviour of sulfonamide nucleophiles in the Tsuji-Trost reaction, learning whether they behave in a ‘hard’ or ‘soft’ manner.

Having successfully reached the targets set, further aims for this project would be to move into the asymmetric α-functionalisation of sulfonamides. Obtaining enantioselectivity α-to sulfur is known to be innately difficult, therefore to obtain any enantioselectivity would be a success in this area of chemistry. By screening a series of chiral ligands, we aimed to access enantioselective compounds with allylic functionality.

In addition, alongside the palladium-catalysed project, we sought to develop a simple and practical method for the α-alkylation of various benzylsulfonamides using lithiation conditions. The objective here was to synthesise similar novel compounds to those reported with catalytic conditions and present an alternative alkylation method, utilising mild reaction conditions. Ultimately, this project could also move into asymmetric synthesis by looking into the effect of chiral base (sparteine), as well as the use of chiral electrophiles.
CHAPTER 2 RESULTS AND DISCUSSION

2.1 Palladium-Catalysed Allylation of Sulfonamides

2.1.1 Investigation

Whilst palladium-catalysed α-arylation of alkyl sulfonamides has been widely reported,\textsuperscript{142,143,144,145} there have been few disclosures of sp\textsuperscript{3}-sp\textsuperscript{3} coupling involving sulfonamides.\textsuperscript{146} We report herein the first palladium-catalysed α-allylation of sulfonamides which can be applied to simple substrates, as well as medicinally relevant drug targets.

We hypothesised that anions from benzyl sulfonamides would be responsive to palladium-catalysed allylation, therefore began with the synthesis of \textit{N,N}-dimethyl-1-phenylmethanesulfonamide (89) from phenylmethanesulfonyl chloride (88) (Scheme 32).

![Scheme 32: Synthesis of \textit{N,N}-dimethyl-1-phenylmethanesulfonamide (89)](image)

We commenced our study with the reaction of \textit{N,N}-dimethyl-1-phenylmethanesulfonamide (89) and allyl acetate using palladium-catalysed allylation conditions, based on a report of the C-H allylation of thioamides.\textsuperscript{49} Firstly, [Pd(C\textsubscript{6}H\textsubscript{5})Cl]\textsubscript{2}, dppb ligand and NaO\textsubscript{t}-Bu were stirred at 25 °C in THF solvent for one hour, after which, the sulfonamide 89 and allyl acetate were added to the catalytic mixture and reacted at room temperature for 20 hours. Since this transformation had not previously been reported in literature, we were encouraged by the isolation of the desired sp\textsuperscript{3} functionalised product 90a, albeit in modest 54 % yield (Scheme 33).

![Scheme 33: First palladium-catalysed α-allylation of sulfonamide](image)
In an attempt to optimise the initial conditions, a series of screening reactions were carried out. Firstly, we performed a solvent screen, with solvents co-ordinating via nitrogen (MeCN), oxygen (THF, dioxane, EtOAc, DME, NMP, DMF) and non-coordinating solvents (CH₂Cl₂, benzene), with corresponding yields given in (Table 1).

![Reaction Scheme]

**Table 1: Solvent screen**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>NMP</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>C₆H₆</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>DME</td>
<td>79</td>
</tr>
</tbody>
</table>

The solvent proved to be extremely important in the reaction as it can play a role in the co-ordination to the palladium complex. It is evident that polar solvents (THF, dioxane, DMF, NMP and DME) work better in this reaction than non-polar solvents (C₆H₆ and CH₂Cl₂). Furthermore, DME (entry 9) was the leading solvent of those investigated and subsequently used in all future reactions.

To expand the scope of the reaction, several allylic electrophiles were submitted to the reaction conditions, varying the chain length (Table 2). It was clear that further investigation and screening reactions were necessary as the yields of the initial acetate screen proved extremely low, with neryl acetate (entry 6) providing no conversion to the desired allylated product.

![Reaction Scheme]

**Table 2: Initial acetate screen**

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47
In order to achieve higher yields in the acetate screen, various bases were trialled in the reaction. Since allyl acetate was already performing at optimal conditions (NaO\textsubscript{t}Bu, 1 eq), crotyl acetate was used as the electrophile of choice (Table 3). Lithium counterion bases (LiHMDS and n-BuLi, entries 5 and 7) do not give any conversion to 90b using both 1.2 equivalents and 3 equivalents of each base. Sodium counterion bases NaO\textsubscript{t}Bu (entry 1) and NaH (entry 9) were the only bases in the screen to give any conversion to allylated compound 90b using 1.2 equivalents of base, albeit the yields were very low, 5 % and 10 %, respectively. Upon increasing the amount of base in the reaction, the yields also increased, more so for sodium hydride, with 70 % being the highest yield obtained using six equivalents of sodium hydride (entry 9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>1.2 eq yield (%)</th>
<th>3.0 eq yield (%)</th>
<th>6.0 eq yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaO\textsubscript{t}Bu</td>
<td>5</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>NE\textsubscript{t}3</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>NaHMDS</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>KO\textsubscript{t}Bu</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>NaH</td>
<td>10</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>
The results of the base screen suggest the deprotonation of the C-H α sulfonamide is slow since conversion to allylated product is low even when an excess of NaH is used (3 equivalents). Deuteration experiments show that both protons are removed when using excess NaH (six equivalents) as both deuterons are incorporated in the 1H NMR (Figure 13).

![Diagram](image)

**Figure 13**: 1H NMR data for D2O quench

Although both deuterons are incorporated in the deuteration study, no diallylation of 89 was observed in the reaction using excess sodium hydride (6 eq), only unreacted starting material was left. In addition, NaH is not soluble in DME, therefore the reaction is heterogeneous. This may also be why more NaH is required for the reaction to proceed, as deprotonation is most likely slower. Moreover, the use of excess base could be an issue when attempting enantioselective allylation, however we did not see this as a problem in the development of a racemic method.

The yield of 90b was further increased from 70 % at 20 hours, to 86 % after 48 hours, therefore the reaction time was adjusted for all future reactions (Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time, h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 4: Time screen
Using the improved reaction conditions, we next turned our attention to the catalyst. Although we were already pleased with the performance of allyl palladium (II) chloride dimer catalyst ([PdCl(C₃H₅)]₂), it was important to screen for possible superior alternatives. The palladium catalyst screening was performed using N,N-dimethyl-1-phenylmethanesulfonamide (89) and more hindered electrophiles [(E)-2-hexenyl (entries 1-6), geranyl entries 9 & 10) and prenyl (entries 7 & 8) acetate] (Table 5).

Table 5: Palladium catalyst screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acetate</th>
<th>Pd catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-CH=CH-OAc</td>
<td>[PdCl(C₃H₅)]₂</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>R-CH=CH-OAc</td>
<td>PdCl₂(MeCN)₂</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>R-CH=CH-OAc</td>
<td>Pd(OAc)₂</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>R-CH=CH-OAc</td>
<td>Pd₂(dba)₃</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>R-CH=CH-OAc</td>
<td>Pd(PPh)₃</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>R-CH=CH-OAc</td>
<td>No catalyst</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>R-CH=CH-OAc</td>
<td>[PdCl(C₃H₅)]₂</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>R-CH=CH-OAc</td>
<td>PdCl₂(MeCN)₂</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>R-CH=CH-OAc</td>
<td>[PdCl(C₃H₅)]₂</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>R-CH=CH-OAc</td>
<td>PdCl₂(MeCN)₂</td>
<td>30</td>
</tr>
</tbody>
</table>

Both [PdCl(C₃H₅)]₂ and PdCl₂(MeCN)₂ performed well in the reaction with (E)-2-hexenyl acetate (entries 1 and 2). However [PdCl(C₃H₅)]₂ performed consistently better when comparing entries 1 and 2, 7 and 8, 9 and 10, and was therefore selected for all future reactions. Background experiments show that no reaction occurs in the absence of palladium (Table 5, entry 6) or phosphine ligand (Table 6, entry 1), suggesting there is no competing nucleophilic substitution reaction.

The final variable we screened was the phosphine ligand. Although dppb ligand had performed well in most of the previous screening reactions, it was important to screen alternatives to optimise the yields with bulkier
acetates (Table 6) since some examples (prenyl acetate, entry 7, Table 5 and neryl acetate, entry 9, Table 5) gave low conversion with dppb.

We chose to perform the phosphine ligand screen using allyl and prenyl acetate. The reaction without a ligand (entry 1) gave no conversion to product, thus the use of a phosphine ligand was necessary for the reaction to proceed. Reactions with allyl acetate (entry 1 and 2) performed better with dppb ligand yielding the allylated product in 79 % and 60 % respectively, whereas the reaction with prenyl acetate performed better with dppe ligand, yielding the prenylated product in 62 % (entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Phosphine Ligand (11 mol %)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>dppb</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>dppe</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>dppb</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>dppe</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>dppf</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Xantphos</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PPh₃</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(rac)-BINAP</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>DavePhos</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

It was clear that the relationship between the catalyst, ligand and electrophile was extremely important in relation to the conversion to α-functionalised product. We were pleased with the performance of dppb ligand
throughout the screening reactions, therefore we chose this as our regular ligand going forward. However, if low conversion did occur in the substrate scope, we knew we could potentially optimise the yield by varying the ligand.

After an extensive base, catalyst, solvent and ligand screen, we alighted to the use of \([\text{PdCl(C}_3\text{H}_5\text{)}_2]_2\), dppb, NaH in DME solvent at 25 °C as our standard set of reaction conditions.

The Tsuji-Trost reaction can be applied to a number of electrophiles including; acetates, alcohols, amines and carbamates. Therefore, we applied our chemistry to a series of allylic electrophiles (Table 7). The reaction with allyl alcohol and allyl amine were unsuccessful and no conversion to the desired allylated sulfonamide 90a was observed. Although allyl carbonate gave the allylated product in 54 % yield, allyl acetate gave a much higher yield (82 %), establishing the superiority of the acetate leaving group over carbonate, amine and alcohol.

### Table 7: Electrophile screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-\text{OAc})</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>(-\text{OH})</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(-\text{NH}_2)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>(-\text{OOC})</td>
<td>54</td>
</tr>
</tbody>
</table>

### 2.1.2 Substrate Scope

Having established a set of standard reaction conditions through a series of optimisation reactions, we first screened a range of allylic acetates with sulfonamide 89. Successful application of the optimised procedure led to the formation of 11 novel sulfonamides 90a-k in good to excellent yields (Table 8).
Table 8: Acetate screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acetate</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90a</td>
</tr>
<tr>
<td>2</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90b</td>
</tr>
<tr>
<td>3</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90c</td>
</tr>
<tr>
<td>4</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90d</td>
</tr>
<tr>
<td>5</td>
<td>( \text{PhOAc} )</td>
<td>( \text{Ph} )</td>
<td>90e</td>
</tr>
<tr>
<td>6</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90f</td>
</tr>
<tr>
<td>7</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90g</td>
</tr>
<tr>
<td>8</td>
<td>( \text{OAc} )</td>
<td>( \text{Ph} )</td>
<td>90h</td>
</tr>
</tbody>
</table>
The scope of the reaction demonstrates the use of simple allylic acetates, cyclic electrophiles, as well as bulky acetates with multiple alkene functionality. Experiments listed in entries 4, 6 and 10 (Table 8) were performed with dppe as the ligand and excess acetate (5 eq), whereas the experiments presented in entries 5 and 13 were performed using dppf as the ligand and excess acetate (5 eq), as higher yields were obtained than when using dppb.

Entries 12, 13 and 14 (Table 8) give interesting mechanistic insights into the reaction, especially about the π-allyl complex that is formed. In these examples, linear compounds 90b, 90e and 90d are formed preferentially to the branched compounds. This indicates the sulfonamide nucleophile attacks at the least sterically hindered position of the π-allyl intermediate (Figure 14).
2.1.3 Diallylation

All compounds described thus far are examples of monoallylated sulfonamides. However, the reaction conditions may be modified to obtain diallylation of 89 to yield compound 91 (Table 9). Increasing the amount of allyl acetate to two equivalents allowed isolation of diallyl compound 91 in moderate 36 % yield (entry 1). Further optimisation were achieved by increasing the amount of base (8 eq) and allyl acetate (5 eq) affording 91 in 96 % yield (entry 3).

Table 9: Diallylation of compound 64

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (eq)</th>
<th>Allyl acetate (eq)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>5</td>
<td>96</td>
</tr>
</tbody>
</table>

Ring closing metathesis can be performed using Grubbs 2nd generation catalyst to obtain the previously unreported cyclic sulfonamide 92 in a 93 % yield. This reaction is synthetically useful as a cyclic alkene is installed, which could be further functionalised to populate unexplored chemical space.
2.1.4 Amine Substituent

With a novel method in hand, we next looked to extend the scope of the reaction by varying the amine subunit. Sulfonamides 93-98 were synthesised from phenylmethanesulfonyl chloride (88) and their respective free amines in generally good yields (Table 10).

Table 10: Sulfonamide precursors

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc</td>
<td><img src="image1.png" alt="Image" /></td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td><img src="image2.png" alt="Image" /></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td><img src="image3.png" alt="Image" /></td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td><img src="image4.png" alt="Image" /></td>
<td>81</td>
</tr>
</tbody>
</table>
Subsequently, the reaction with these sulfonamides and various allylic acetates using the standard palladium-catalysed conditions, generated a range of novel allylated compounds (99a-l, Table 11) in moderate to excellent yields. Reactions of the piperazine, morpholine, piperidine, tetrahydropyridine and pyrrolidine sulfonamides with allyl acetate (entries 1, 6, 9, 10 & 11) all proceeded in generally good yields (52-82%). Reactions of Boc-piperazine sulfonamides with more hindered acetates [crotyl (entry 2), hexenyl (entry 3), neryl (entry 4), and prenyl (entry 5)] were poorer than the reaction with the less hindered allyl acetate (entry 1). Interestingly, methyl hydroxylamine sulfonamide 98 (entry 12) gave diallylated sulfonamide 99l exclusively using the standard reaction conditions.

Table 11: Sulfonamide amine screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>99a</td>
<td>71°</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>99b</td>
<td>59°</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
<td>99c</td>
<td>52°</td>
</tr>
</tbody>
</table>
In order to access the mono-allylated compound of N-methoxy sulfonamide 98, we investigated the amount of base that was necessary for this reaction to occur, since all other examples prior to this required six equivalents of sodium hydride (Table 12). We found that three equivalents of sodium hydride gave a mixture of di- and mono-allylated sulfonamide, whereas only one equivalent of sodium hydride (entry 3) gave monoallylated product 100a in a 76 % yield. Similarly, mono allylation occurred with milder base NaOtBu in 75 % yield (entry 4). This result interested us as we believed the methyl hydroxylamine group could potentially be acting as a directing group. Several possible explanations could support the fact that monoallylated sulfonamide 100a is more reactive; perhaps the alpha proton of monoallylated 100a is more labile (due to Na+ binding with OMe group) than the alpha proton of compounds 99a-k, therefore enabling disubstitution. Alternatively, binding of Na+ with OMe group may be less sterically hindered than Na+ bound to groups of sulfonamides 99a-k, which could favour disubstitution.

Since NaOtBu is a milder and easier to handle base, we decided to investigate this further to see if the reaction could proceed with alternative acetates (Table 13). With a new set of mild reaction conditions in hand, we were pleased to see that methyl hydroxylamine sulfonamide 98 could be functionalised with linear chained acetates (entries 1, 2, 3 and 6), bulky acetates (entry 4 and 6), as well as cyclic acetate (entry 5).

In contrast to previous reaction conditions, we changed the ligand to (rac)-BINAP, as allylated compounds were generally obtained in much higher yields than when dppb was used as the ligand, thus demonstrating the importance of the behaviour of ligand within the reaction.
Table 13: Acetate screen with revised milder conditions

\[
\begin{array}{c}
\text{Entry} & \text{Product} & \text{Yield with BINAP, \%} & \text{Yield with dppb, \%} \\
1 & \begin{array}{c}
\text{Ph} \\
98
\end{array} & 75 & 75 \\
2 & \begin{array}{c}
\text{Ph} \\
100b
\end{array} & 71 & 45 \quad (E:Z = 79:21) \\
3 & \begin{array}{c}
\text{Ph} \\
100c
\end{array} & 85 & 75 \quad (E:Z = 100:0) \\
4 & \begin{array}{c}
\text{Ph} \\
100d
\end{array} & 56 & 0 \\
5 & \begin{array}{c}
\text{Ph} \\
100e
\end{array} & 30 & 14 \quad (d.r = 64:36) \\
6 & \begin{array}{c}
\text{Ph} \\
100f
\end{array} & 67 & 30 \\
7 & \begin{array}{c}
\text{Ph} \\
100g
\end{array} & 60 & 0 \quad (E:Z = 100:0)
\end{array}
\]
We hoped these milder reaction conditions would prove useful when used for the enantioselective synthesis of allylsulfonamides (Section 2.3).

Following the screen of the amine substituent, we set out to use secondary sulfonamides, wondering if we could achieve allylation on both the N-H and at the Cα of the sulfonamide sequentially. N-allylation of sulfonamides has been previously reported, therefore using the developed palladium-catalysed reaction conditions, we would expect a free N-H to be allylated, as well as at the α-carbon.

N-Methyl-1-phenylmethanesulfonamide (101) was synthesised from phenylmethanesulfonyl chloride (88) and methylamine (Scheme 35).

\[
\text{SOCl}_2 \quad \text{H}_2\text{N} \xrightarrow{\text{NEt}_3, \text{CH}_2\text{Cl}_2} \quad \text{SO}\text{N} \quad \text{Ph} \\
\text{88} \quad \text{r.t. 16 h} \quad \text{50 % yield} \quad \text{101}
\]

**Scheme 35: Synthesis of N-Methyl-1-phenylmethanesulfonamide**

Under the standard palladium-catalysed conditions, and using two equivalents of allyl acetate, diallylation of 101 was successful, yielding the desired product 102 in 93 % yield (Scheme 36).

\[
\text{SO} \quad \text{H} \xrightarrow{[\text{PdCl(C}_3\text{H}_5)]_2 (2.5 \text{ mol %})} \quad \text{SO} \quad \text{Ph} \\
\text{101} \quad \text{2.0 eq} \quad \text{25 °C, 48 h} \quad \text{102} \quad 93 \%
\]

**Scheme 36: Diallylation of sulfonamides**

Ring closing metathesis of 102 using Grubbs 2nd generation catalyst leads to the formation of the previously unreported seven-membered sultam 103 in an unoptimised 55 % yield (Scheme 37). Sultam 103 is a potentially interesting compound which could allow for further derivatisation to access diverse analogues of seven-membered functionalised sulfonamides.
2.1.5 Medicinal Chemistry Targets

Late-stage functionalisation of drug molecules is extremely desirable for medicinal chemists to develop structural complexity by creating new analogues of lead-like compounds. We envisaged applying our developed methodology to specific drug-like molecules to demonstrate our reaction as a useful late-stage functionalisation tool.

Recent studies by Sadeghzadeh and co-workers\textsuperscript{121} have shown a series of arylalkylsulfonylpiperazine based derivatives as potential sigma receptor ligands, a sub-type of opioid receptor (Figure 15). Since one of the main aims of our work was to apply our reaction to known medicinal chemistry targets, it seemed reasonable to do so with these relatively easy to synthesis sulfonamides 64a-f.

$$\text{Sulfonamides 64a-f were prepared in good yields using literature methods, by reacting phenylmethanesulfonyl chloride (88) with various benzyl piperazines (Table 14).}$$
Table 14: Synthesis of drug-like molecules 64a-f

Using our standard palladium catalysed conditions, sulfonamides 64a-f were subjected to the allylation reaction using various allylic acetates affording novel compounds 104a-h (Table 15).
Table 15: Allylation reaction screen using drug-like molecules

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonamide</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64a</td>
<td>104a</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>64a</td>
<td>104b</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>64b</td>
<td>104c</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>64f</td>
<td>104d &amp; 104e</td>
<td>62* (60:40)</td>
</tr>
<tr>
<td>5</td>
<td>64e</td>
<td>104f</td>
<td>63*</td>
</tr>
<tr>
<td>6</td>
<td>64d</td>
<td>104g</td>
<td>53</td>
</tr>
</tbody>
</table>

R¹ = H, OMe, Br  
R² = F, Cl, Me
We were gratified to observe allylation of compounds 104a-h proceeded smoothly in generally good yields. A variety of allylic acetates; allyl (entry 1, 3, 6 & 7), cinnamyl (entry 4), crotyl (entry 5) and hexenyl (entry 2) acetate were reacted with benzylpiperazine sulfonamides 64a-f to demonstrate the scope of the reaction. Surprisingly, the substitution pattern on the phenyl ring of the benzyl moiety had quite a high impact on the reactions with yields ranging from 37 % (entry 7) with p-methoxybenzyl piperazinesulfonamide (64c), to 76 % (entry 1) with benzyl piperazinesulfonamide (64a) for which allyl acetate was used. Interestingly, when using cinnamyl acetate (entry 4), both branched and linear compounds 104d and 104e were isolated, the first example of branched functionality of our 35 examples. We were also pleased to observe no side reaction with bromo-substituted 104f as the bromobenzene moiety was left untouched, which provides interesting orthogonal reactivity and allows for possible further derivatisation.

2.1.6 Conclusion

We have demonstrated the first palladium-catalysed α-allylation of a series of benzyl sulfonamides, generating a library of novel compounds. After a series of optimisation reactions, we were able to access functionalised sulfonamides, by varying both allylic chain length and amine substituent on the sulfonamide. Generally, allylated compounds were obtained in high yields, however we have demonstrated that higher yields for more difficult substrates can be obtained by changing the ligand. Furthermore, we have applied our chemistry to a range of drug-like molecules, highlighting our method as a potentially useful late-stage functionalisation tool.

2.2 Mechanistic Study

2.2.1 Investigation

The mechanism of the Tsuji-Trost reaction has been studied in great detail, using a variety of approaches.90 As previously discussed, the Tsuji-Trost reaction can proceed via one of two mechanistic pathways depending on the hardness of the pronucleophile (Scheme 38). Once the leaving group is displaced and the palladium π-allyl intermediate is formed (step c), soft pronucleophiles can attack the chain of the π-allyl intermediate (step d) to form a product with a net retention of stereochemistry (step f). Whereas hard pronucleophiles can co-
ordinate to the palladium (step e) and via reductive elimination form a product with a net inversion of stereochemistry (step h).

Scheme 38: Catalytic cycle of Tsuji-Trost reaction

To establish the route of our mechanism, it was important to perform a study to confirm the hardness of benzylsulfonamide nucleophiles since the pKa of our nucleophile was not precisely known. Based on literature precedent of compound 105\textsuperscript{157} (Figure 28), we hypothesised that sulfonamide 89 has an estimated pKa of approximately 24/25; therefore, based on the hard/soft nucleophile theory, our dimethylsulfonamide 89 should be on the border of behaving as either a hard or soft nucleophile. To understand the mechanistic pathway, we sought to confirm the hardness of our dimethylsulfonamide 89 by performing a mechanistic study.
The first mechanistic study, pioneered by Trost in 1980, uses isomers of 3-acetoxy-5-carbomethoxy-1-cyclohexene (7a & 7b) as an electrophilic stereoprobe.\textsuperscript{158} This study confirmed malonates as soft nucleophiles since the reaction of cis-acetate 7a and malonate nucleophile 8, under palladium-catalysed allylation conditions, gives cis-compound 9a (with a retention of configuration) in 92 % yield. Similarly, the reaction with trans-acetate 7b and malonate nucleophile 8 gives the trans-product 9b (also with a net retention of configuration) in 90 % yield. \textsuperscript{(Scheme 39)}\textsuperscript{39}

\begin{align*}
\text{cis-acetate } 7a + \text{NaCH(CO}_2\text{CH}_3)_2 & \rightarrow \text{cis-compound } 9a \\
\text{trans-acetate } 7b + \text{NaCH(CO}_2\text{CH}_3)_2 & \rightarrow \text{trans-compound } 9b
\end{align*}

\textbf{Scheme 39: Mechanistic study using isomers of 3-acetoxy-5-carbomethoxy-1-cyclohexene}

Trost reported $^1$H NMR data for cis-compound 9a, highlighting the essential coupling constants of $J_{AD}$, $J_{BD}$, $J_{CD}$ = 12 Hz, indicating both $H_a$ and $H_b$ are pseudo-axial, therefore the reaction occurs with complete retention of configuration with regards to the carbon undergoing nucleophilic substitution. The important coupling constants

\begin{align*}
J_{H_a} & = 12 \text{ Hz (trans-diaxial)} \\
J_{H_b} & = 12 \text{ Hz (trans-diaxial)}
\end{align*}
for the trans-product 9b are also highlighted: $J_{ab} = 5.5$ Hz $J_{bc} = 13.5$ Hz $J_{cd} = 9.5$ Hz $J_{ad} = 4$ Hz $J_{bc} = 4$ Hz, indicating H₄ is pseudo-equatorial, whereas H₆ is pseudo-axial.

Since this discovery, cis-stereoprobe 7a has been the most common substrate used in mechanistic studies of allylation reactions. Following the synthesis reported in 1976, (Z)-3-acetoxy-5-carbomethoxy-1-cyclohexene (7a) was prepared in five steps from 3-cyclohexene-1-carboxylic acid (106) (Scheme 40). iodolactonisation of 111, followed by elimination of iodide 107 with DBU gave the unsaturated lactone 5 in 86 % yield over two steps. Methanalysis of 5 with sodium methoxide in methanol converted 100 % to 6 as the sole isomer. The crude alcohol 6 was used without further purification in the acylation step to afford 3-acetoxy-5-carbomethoxy-1-cyclohexene 7a:7b as an inseparable mixture of cis-7a:trans-7b (98:2) by ¹H NMR.

![Scheme 40: Preparation of cis-3-acetoxy-5-carbomethoxy-1-cyclohexene 7a](image)

With our stereoprobe 7a in hand, the palladium-catalysed $\alpha$-allylation of N,N-dimethy-1-phenylsulfonamide (89) was carried out using the standard conditions (Scheme 41). However, no conversion to the desired cross-coupled product 108 was observed, and all starting materials were recovered.

![Scheme 41: Mechanistic study using cis-3-acetoxy-5-carbomethoxy-1-cyclohexene](image)
We rationalised this by assuming that the use of excess base in the reaction was deprotonating \( \alpha \) to the methylester of stereoprobe 7a, preventing the reaction from proceeding. Although the Trost electrophile 7a is the most commonly applied to this type of study, other stereoprobes have been used, an example of which (compound 53b) is shown in Figure 17.

![Figure 17: Alternative stereoprobe used in mechanistic studies](image)

Therefore, to avoid competing deprotonation, we sought to synthesise an alternative stereoprobe. Starting from racemic cis-lactone 5, alcohol 109 was made following a known procedure.\(^{159}\) Subsequent acylation of 110 provided cis-5-([(tert-butyldimethylsilyl]oxy)methyl)cyclohex-2-en-1-yl acetate (111) as a new stereodefined acetate for our mechanistic study (Scheme 42).

![Scheme 42: Preparation of cis-5-([(tert-butyldimethylsilyl]oxy)methyl)cyclohex-2-en-1-yl acetate](image)

To our knowledge, acetate 111 had never been used in a mechanistic study of the Tsuji-Trost reaction, therefore to test its suitability as a stereoprobe we first sought to repeat Trost’s initial mechanistic study, substituting the methyl ester stereoprobe 7a for our cis-acetate 116. Gratifyingly, allylation of malonate 8 with 111 yielded cis-compound 112 as a single diastereomer in 56 % yield (Scheme 43). \(^1^H\) NMR data for compound 112 is similar to that of compound 9a, the essential coupling \( J_{AD} = 12 \) Hz \( J_{CD} = 12 \) Hz is present, indicating stereoprobe 111 behaves in the same way as 7a.
With our newly developed cis-acetate 111, we then proceeded with the mechanistic study, reacting with sulfonamide 89 under the standard allylation conditions. We were pleased to see the reaction proceeded smoothly, obtaining the desired product 113 in 85 % yield as a mixture of two diastereomers in a 75:25 ratio based on ¹H NMR spectroscopy (Scheme 44).

Sulfonamide 113 has three asymmetric centres, therefore there are eight possible stereochemical structural outcomes (4 diastereomers and their enantiomers) according to the ²ⁿ rule (Figure 18). Structures 113a and 113b present the stereochemical outcomes if the sulfonamide pronucleophile is soft, as the protons at C¹ and C⁵ are on the same face. Whereas, structures 113c and 113d represent if the sulfonamide pronucleophile as hard, since protons at C¹ and C⁵ are on the opposite face.
To understand the stereochemical outcome, a sample of crude sulfonamide 113 was analysed by chiral HPLC, indicating a presence of two diastereomers and their enantiomers (113a & 113b or 113c & 113d, Figure 19). We know from experiments (that will be discussed in Section 2.23) that the hydrogen at C1 is epimerised under the excess basic conditions. In addition, the stereochemistry at C5 is fixed from the cis-acetate starting material, therefore it is reasonable to assume the allylation reaction is diastereoselective at C1 position. This reasoning implies that the sulfonamide nucleophile attacks either at the carbon of the π-allyl intermediate or at palladium, and not a mixture of the two. Therefore, based on the HPLC data (Figure 19), the four possible isomers are either structures 113a-b or 113c-d of Figure 18.
The two diastereomers of 113 were separated via column chromatography and analysed by 1D and 2D NMR. Pseudo-chair structures shown in (Figure 20) highlight the essential protons by which the structure was elucidated. $^1$H NMR for major diastereomer of compound 113 showed a peak at 1.02 ppm, app dt, $J$ 11.6 Hz and 12.6 Hz, indicating a dihedral relationship between proton H$_6$axial and H$_1$axial, similar to the coupling of the Trost example shown in Scheme 39.

![Figure 20](image)

nOesy data shows a clear interaction between proton H$_1$ and H$_5$ (Figure 21), therefore at this stage we were confident that proton H$_1$ and H$_5$ are pseudo-axial.
Similarly, $^1$H NMR data for the minor diastereomer of 113 revealed a peak at 0.75 (app q, $J$ 12.1 Hz), also indicative of a 1,3-diaxial relationship between H$_1'$ and H$_6$.

Therefore, based on the evidence obtained by the NMR data, it was reasonable to assume the sulfonamide behaved as a soft pronucleophile (structures 113a & 113b) however we sought to confirm the structure of the major diastereomer by obtaining X-ray crystal data.

Both the isolated major and minor diastereomer of compound 113 (113a &113b) were oily and crystallisation attempts of both proved unsuccessful, therefore an alternative approach was investigated. Deprotection of TBDMS group of the major diastereomer of 113 with TBAF gave alcohol 114 as a crude mixture (Scheme 45).
Scheme 45: Deprotection of TBDMS group

Following this, crude alcohol 114 was coupled with bulky \textit{p}-bromobenzoyl chloride (115) to yield 116 (single diastereomer) as an orange crystalline solid (Scheme 46).

Scheme 46: Synthesis of compound 116

Crystallisation of 116 (single diastereomer) from ethanol allowed a crystal structure to be obtained by single crystal X-ray crystallography (Figure 22). Coupled with the evidence from NMR data, the crystal structure shows that the protons at C_{1'} and C_{5'} are on the same face of the molecule, therefore the stereochemistry is retained.
This retention of stereochemistry indicates benzylsulfonamides behave as soft carbon nucleophiles in the palladium-catalysed allylation reaction. Therefore, of the eight structures presented in Figure 18, 113a & 113b are the isomers indicative of a soft nucleophile. The major isomer isolated in the mechanistic study is 113a and its enantiomer. In addition, the minor isomer isolated (confirmed by NMR but not by crystal data) is structure 113b and its enantiomer (Figure 23).
## 2.2.2 Conclusion

This study has shown that the anion of \( N,N \)-dimethy-1-phenylsulfonamide (89) behaves as a soft nucleophile when subjected to palladium-catalysed allylation reaction conditions. Structural evidence shows a net retention of stereochemistry, confirmed by extensive data analysis (NMR, HPLC and X-Ray Crystallography), thus indicating the anion of 89 attacks \( \pi \)-allyl intermediate, with no co-ordination to the palladium.

Although initial attempts using the common stereoprobe \((cis)-3\text{-acetoxy-5-carbomethoxy-1-cyclohexene (7a)}\) failed, we were able to synthesise an alternative \( cis \)-stereoprobe, \((cis)-5\text{-[(tert-butyl(dimethyl)silyl)oxy]methyl}\text{cyclohex-2-en-1-yl acetate (111)}\), which proceeded smoothly as an electrophile in our reaction conditions. Prior to this, the novel stereoprobe 111 was subjected to Trost's initial mechanistic study reaction conditions using dimethylmalonate (8), to validate its suitability as a stereoprobe.

## 2.3 Attempts at Enantioselective Synthesis

### 2.3.1 Investigation of Chiral Ligands

The natural progression of the project would be to develop an asymmetric version of the previous method, since the work thus far has delivered only racemic compounds. Although we knew enantioselective \( sp^3 \text{-} sp^3 \) coupling of sulfonamides would prove challenging, due to the difficulties of asymmetric \( \alpha \)-functionalisation of \( \text{SO}_2 \) bonds, we sought to develop an asymmetric catalytic method for the \( \alpha \)-functionalisation of sulfonamides.

Initial attempts at asymmetric reactions using the standard reaction conditions failed to induce any enantiomeric excesses, therefore we looked at the use of excess sodium hydride. It was highly likely that the excess base could cause racemisation at the C1 position. Therefore to confirm this, the enantiomers of 90a were separated by analytical chiral HPLC, obtaining ~5 mg of each enantiomer (Figure 24). Although the absolute stereochemistry of the proton at C1 is yet to be determined, the stereochemistry has been shown for clarity.
Having separated the enantiomers of 90a, a single enantiomer of this compound (first peak) was resubmitted to the palladium-catalysed standard reaction conditions (Figure 25). The reaction mixture was analysed by chiral HPLC, where two peaks (indicative of a racemic mixture) were attained (Figure 25). This confirms that under the standard reaction conditions, the stereocentre at C1 is epimerised. Additionally, the single enantiomer was also stirred in DME solvent with six equivalents of NaH for one hour, in the absence of palladium and dppb ligand, to also give a racemic mixture.
It was clear that to prevent epimerisation at C₁, less base had to be used. Since sulfonamide 89 required excess base in all reaction cases previously discussed, we turned to the methyl hydroxylamine sulfonamide 98 that was shown to undergo allylation in 75 % yield using one equivalent of NaOEtBu (Scheme 47).

We began investigating an enantioselective reaction by first substituting dppb for a variety of chiral ligands. The most common chiral ligands used in AAA reactions are the C₂ symmetric Trost ligands, pioneered by Trost in the early 1990’s.⁴³,⁴⁴ Therefore, it seemed reasonable to begin the chiral ligand screening process using various Trost ligands (Table 16). Trost DACH-pyridyl ligand L15 (entry 1) gave compound 100a in 35 % yield, however the product was racemic. Whereas, ligands Trost DACH-naphthyl L14 (entry 2) and DACH-phenyl L2 (entry 3) gave no conversion to product and all the starting material was recovered.
Table 16: Chiral ligand screen with C₂ symmetric Trost ligands

We next turned our attention to the C₁ symmetric PHOX ligands, (entry 1 and 2, Table 17), as well as bisoxaline C₂ symmetric ligands (entries 3 and 4, Table 17). Only PHOX ligand L22a (entry 1) gave the desired allylated sulfonamide, in 65 % yield, however product 100a was racemic. Unfortunately, the reactions with PHOX ligand L24 (entry 2) and bisoxazolines L17a & L16a (entry 3 and 4) were unsuccessful and only starting materials were recovered.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Chiral Ligand</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="L22a" /></td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="L24" /></td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="L17a" /></td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="L16a" /></td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Since little success (in terms of conversion to product) had been obtained with the ligands screened thus far, we began looking closer into the properties of chiral ligands, in order to narrow down the examples that may provide conversion to product, potentially in non-racemic fashion.

The electronic and steric properties of phosphine ligands have been found to have an influence on the reactivity of organometallic complexes. The concept of cone angle is widely accepted as a systematic approach to determine steric and electronic ligand effects. However, more recently, the introduction of ‘bite angle’ (P-M-P angle) has been developed as a useful paradigm to predict chelation preferences of bidentate ligands. Bite angle can be defined as the preferred chelation angle determined by the ligand backbone (Figure 26).
Therefore, bearing the concept of bite angle in mind, we hypothesised that ligands with a similar bite angle to dppb, dppe and dppf would most likely lead to conversion to desired product, as these achiral ligands were successful in our previous allylation reactions. According to data from literature and the Cambridge Crystallographic Database, dppb and dppf have similar preferred bite angles, whereas dppe has a lower bite angle of 85° (Figure 27).

Chiral ligands BINAP L19, DIOP L13 and Josiphos L25 seemed the most appropriate ligands in terms of similarity of P-M-P angle and structure related to the three achiral ligands dppe, dppb and dppf. Therefore, we next carried out the palladium-catalysed allylation of methyl hydroxylamine sulfonamide 98 with allyl acetate and the chiral ligands chosen based on bite angles. We were gratified to see that in all cases, conversion of allylated sulfonamide was observed, in good yields with respect to (R)- and (S)-BINAP L19a & L19b (entry 1 and 2, Table 18), and Josiphos L25 (entry 3, Table 18), as well as a modest yield for the example with (–)-DIOP ligand L13 (entry 4, Table 18). We were also pleased to see that (R) and (S)-BINAP (L19a & L19b) not only gave high yielding product, but also provided some enantioselectivity, albeit very low values (4 % ee).
Next, we screened various BINAP type ligands in order to expand the ligand scope and attempt to improve the low ee’s (Table 19). Monophosphorous ligands \textbf{L21a-d} (entries 1-4) were not successful in the reaction, with no conversion to the desired product. Whereas, allylation with BINAP derivative ligands \textbf{L19c-h} (entries 5-10, Table 19) all gave conversion to the desired allylated product in varied yields (16 – 92 %). (\(R\))-Segphos \textbf{L19f} (entry 8, Table 19) gave low conversion to product, however gave the highest enantioselectivity so far obtained 8 % ee. This result was encouraging as no such asymmetric catalytic C-H functionalisation of a sulfonamide has ever been reported.
Table 19: BINAP and monophosphorous ligand screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chiral Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L21a</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L21b</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>L21c</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>L21d</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>L19c</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>
It is not unusual to encounter some difficulty when moving into asymmetric synthesis. As discussed earlier, Walsh et al. reported the enantioselective C-H allylation of toluene based nucleophiles (Scheme 20). This reaction required a screen of over 140 enantioenriched mono- and bidentate phosphine ligands, with only the Ph-Taniaphos L12 ligand giving substantial turnover and enantioselectivity, demonstrating the difficulties of enantioselective synthesis of challenging substrates.
2.3.2 Conclusion

Having screened 21 chiral ligands in various asymmetric synthesis attempts, few examples were successful in terms of yielding the desired allylated product, whilst even fewer were successful in obtaining any enantioselectivity. Our correlation between the bite angle and conversion to product was a successful strategy, as ligands with similar bite angles to dppb and dppf (bite angle of less than 100°) generally BINAP type ligands, provided allylsulfonamides in high yields. Despite obtaining allylsulfonamides in high yields with a series of chiral ligands, we struggled to obtain any enantioselectivity. \((R)-\text{Segphos L19f}\) (Table 19, entry 8) gave 8 % ee as the highest enantiomeric excess, which remains extremely low. However, we were very pleased with this initial result as this transformation has never been reported enantioselectively.

This part of the project requires further investigation as only a small number of chiral ligands have been screened thus far. Several experiments could be carried out to give more understanding of the reaction and formation of anion. It could be possible that NaOt-Bu also racemises the hydrogen at C1 of methyl hydroxylamine sulfonamide 100, as this would give evidence that the base may racemise the \(\alpha\)-protons at C1. Alternatively, investigation into the order of addition of reactants may be pivotal in obtaining enantioselective compounds. An experiment to pre-form the sulfonamide anion 100, and then react with the palladium, chiral ligand and acetate, could avoid the issue with racemisation when using base, as all the base should be consumed in forming the anion.

2.4 Alternative Methods for \(\alpha\)-alkylation of Sulfonamides

2.4.1 Investigation

Although our fundamental interest was to develop a catalytic method, we believed we could also provide an alternative method to obtain similar compounds of interest. Typically, methods for direct alkylation of sulfonamides require strong bases, reactive electrophiles, low temperatures and use of polar additives such as TMEDA, HMPA and phenanthroline.\(^{139,140}\) Therefore, the focus of the work shifted to the development of a mild, simple, yet robust method for the nucleophilic substitution of both allyl and alkyl electrophiles with benzyl sulfonamides.

We chose to carry out our initial study using \(N,N\text{-dimethyl-1-phenylmethanesulfonamide (89)}\) and crotyl bromide by varying reaction conditions, including: base, solvent and temperature (Table 20).
Table 20: Initial optimisation of nucleophilic substitution reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Base (eq)</th>
<th>Electrophile eq</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–20</td>
<td>THF</td>
<td>LDA (1.1)</td>
<td>2.1</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>THF</td>
<td>LDA (1.1)</td>
<td>2.1</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>–20</td>
<td>DME</td>
<td>LDA (1.1)</td>
<td>2.1</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>–20</td>
<td>THF</td>
<td>LDA (2.2)</td>
<td>2.1</td>
<td>57&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>–20</td>
<td>THF</td>
<td>LDA (2.2)</td>
<td>1.0</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>–20</td>
<td>THF</td>
<td>NaH (1.1)</td>
<td>1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> 14 % of diallylated product

One would predict that the anion of sulfonamide <sup>89</sup> is fully deprotonated when one equivalent of LDA (pK<sub>a</sub> ~ 35) is used, since the pK<sub>a</sub> of our sulfonamide anion is predicted to be around 25 based on literature values of a similar benzylsulfonamide compound <sup>105</sup> (Figure 28). However, the conversion to allylated product is low when only one equivalent of LDA is used (between 32 % and 51 % depending on solvent, entries 1 – 3, Table 20). The yield of product is much higher (86 %, entry 5) when 2.2 equivalents of LDA is used in THF at –20 °C. The requirement of excess base for this reaction could be related to the absence of additives in this reaction. Lithium bases are known to form aggregates, therefore additives are generally used to breakdown the unreacted aggregates.<sup>164,165</sup> Although we know that NaH deprotonates sulfonamide <sup>89</sup>, as shown in previous palladium-catalysed α-allylation reaction, the sodium counterion base (entry 6) did not give any conversion to allylated product and all starting material sulfonamide <sup>89</sup> was recovered.

![pK<sub>a</sub> of benzylsulfonamides 90](image)

**Figure 28: pK<sub>a</sub> of benzylsulfonamides 90**

Since we did not want to use any additives in this reaction, we chose to use the optimised conditions (entry 5, Table 20). The excess of base did not appear to cause issues with over alkylation, therefore we were happy
to proceed with a series of experiments using N,N-dimethyl-1-phenylmethanesulfonamide (89) with various allylic bromides to demonstrate the scope (Table 21).

Compounds 90a-h, 117, 118 and 119 were obtained in generally good yields, allowing to install linear (entries 1-5), branched (entry 6) or cyclic allyl groups (entry 7). When using dibromide electrophiles (entries 8 and 10), the reaction is selective to eliminating the primary allylic bromide.

Table 21: Screening of allyl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (1 eq)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>90b</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>(E:Z 85:15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>90a</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>90d</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>117</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>(E:Z 90:10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>90e</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>(E:Z 100:0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>90f</td>
<td>99</td>
</tr>
</tbody>
</table>
Interestingly, the ratio of diastereomers of compound 90g (71:29) were different to that of the ratio of 90g in the palladium-catalysed allylation reaction (59:41). The major diastereomer of the LDA reaction corresponds to the minor diastereomer in the palladium-mediated reaction and the minor diastereomer of the LDA reaction relates to the major diastereomer of the palladium-catalysed reaction.

We next sought to vary both the amine and aryl substituent, all of which were synthesised from various arylmethanesulfonyl chlorides and their respective amines. Sulfonamides 94-97, 64a and 120-123 were allylated under the standard reaction conditions to yield the desired products 124a-g, 99j and 104a in generally high yields (Table 22). The reaction proceeded smoothly with various allylic bromides and differing amine substituents; morpholine (entry 1), pyrrolidine (entry 2), piperidine (entry 3), piperazine (entry 4) and tetrahydropyridine (entry 5). In addition, the reaction worked when varying the substituents on the aryl ring (entries 6-9). Reactions with electron withdrawing groups CF₃ (entry 6), Br (entry 9) and Cl (entry 8) proceeded in good yields.

Table 22: Expanding the substrate scope

```
\[ \text{ArSO}_2\text{N}R + \text{LDA (2.2 eq)} \rightarrow \text{THF, -20 °C, 1 h} \rightarrow \text{R} = \text{SO}_2\text{N}R \text{Ar} \rightarrow 62 - 99 \% \text{ yield} \]
```
<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Sulfonamide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{PhCH}<em>{2}\text{CH}</em>{2}\text{Br})</td>
<td><img src="image1" alt="Sulfonamide 94" /></td>
<td><img src="image2" alt="Product 124a" /></td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>(\text{PhCH} = \text{CHBr})</td>
<td><img src="image3" alt="Sulfonamide 97" /></td>
<td><img src="image4" alt="Product 124b" /></td>
<td>57 ((E:Z = 100:0))</td>
</tr>
<tr>
<td>3</td>
<td>(\text{BrCH}<em>{2}\text{CH}</em>{2}\text{Br})</td>
<td><img src="image5" alt="Sulfonamide 95" /></td>
<td><img src="image6" alt="Product 124c" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CH} = \text{CHBr})</td>
<td><img src="image7" alt="Sulfonamide 64a" /></td>
<td><img src="image8" alt="Product 104a" /></td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CH} = \text{CHBr})</td>
<td><img src="image9" alt="Sulfonamide 96" /></td>
<td><img src="image10" alt="Product 99j" /></td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>(\text{PhCH} = \text{CHBr})</td>
<td><img src="image11" alt="Sulfonamide 120" /></td>
<td><img src="image12" alt="Product 124d" /></td>
<td>63 ((E:Z = 100:0))</td>
</tr>
<tr>
<td>7</td>
<td>(\text{CH} = \text{CHBr})</td>
<td><img src="image13" alt="Sulfonamide 121" /></td>
<td><img src="image14" alt="Product 124e" /></td>
<td>49</td>
</tr>
</tbody>
</table>
Furthermore, this method was shown to work well with several alkyl bromides yielding compounds 125a-e (Table 23). We were pleased to see that alkylated sulfonamides could be accessed using these reaction conditions. Also, for the synthesis of compounds 125c and 125e (entries 3 and 5), higher reaction temperatures (r.t instead of –20 °C) and longer reaction times (overnight) were required to obtain any conversion to the desired products.

Table 23: Alkylation of sulfonamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me−I</td>
<td>125a</td>
<td>86(^a)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>125b</td>
<td>40(^a)</td>
</tr>
</tbody>
</table>

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<td>125a</td>
<td>86(^a)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>125b</td>
<td>40(^a)</td>
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<tbody>
<tr>
<td>1</td>
<td>Me−I</td>
<td>125a</td>
<td>86(^a)</td>
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<tr>
<td>2</td>
<td></td>
<td>125b</td>
<td>40(^a)</td>
</tr>
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</table>

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2.4.2 Enantioselective Synthesis

Attempts at asymmetric synthesis, using a method extrapolated from the alkylation project discussed (Section 2.4.1), was attempted by a member of the Sweeney group. Use of chiral base (+)-sparteine provided conversion to allylated product 90a in 41% unoptimised yield, however the product was racemic (Scheme 48). Further optimisation and enantioselective synthesis using alternative chiral bases is currently under investigation in our laboratories.

Scheme 48: Allylation using (+)-sparteine

2.4.3 Conclusion

We have demonstrated that α-alkylation of sulfonamides, to access novel racemic compounds, can be achieved using mild conditions (LDA, −20 °C, 3 hours), without the requirement of polar additives and long reaction times. The developed method has been used to synthesise 25 benzylsulfonamides, 20 of which were previously unreported, in generally good yields. This area of research has allowed our group to investigate the
possibility of developing an asymmetric method using a chiral base to induce asymmetry, however little progress has been made thus far.

2.5 Future Work

We have described the first palladium-catalysed $\alpha$-allylation of benzylsulfonamides, leading to the formation of a library of novel functionalised sulfonamides.\textsuperscript{166} Although we have demonstrated a wide reaction scope by varying the allyl electrophile and sulfonamide amine moiety to gain access to over 40 novel compounds, research into catalytic sp\textsuperscript{3}-sp\textsuperscript{3} coupling of sulfonamides remains under investigated. The use of alternative sulfonamide pronucleophiles have not yet been explored, for example, allylation of alkylsulfonamides and heteroaryl sulfonamides could allow for expansion of this chemistry and a greater scope of the reaction.

Moreover, further investigation into enantioselective synthesis of sulfonamides remains a major challenge. Recent work within our group has begun focusing on $\alpha$-allylation of cyclic sulfonamides \textbf{126}. Using similar palladium-catalysed conditions, $\alpha$-functionalised sultams \textbf{127} can be accessed (Scheme 49). The proton on the C$_{\alpha}$ to the sulfonyl moiety is more labile and requires less base than the examples described in this thesis. Therefore, exploration into using sultams as ideal candidates for enantioselective synthesis is desirable.

![Scheme 49: $\alpha$-Allylation of cyclic sulfonamides](image)

Finally, research into using alternative, more cost-effect transition metal catalysts for the $\alpha$-allylation of sulfonamides has become a focus in our research group. The use of nickel catalysts as cheaper alternatives for palladium has become of interest in recent years due to its efficiency in coupling reactions.\textsuperscript{167} Therefore correlation of our palladium-catalysed reaction to nickel catalysis would be an interesting strategy to apply to the $\alpha$-functionalisation of sulfonamides.
CHAPTER 3 EXPERIMENTAL

Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, Fluorochem and Tokyo Chemical Industry UK, and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent in accordance with the procedures of Perrin and Armarego. Dimethoxyethane and THF were distilled from sodium benzophenone ketyl radical while DCM was distilled from calcium hydride. All experiments were performed in oven-dry glassware under a protective atmosphere of nitrogen (dried by passage through anhydrous phosphorus pentoxide) as required. All acetates were commercial available or synthesised from their respected alcohols or ketones.

Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, phosphomolybdic acid and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher unless otherwise stated.

All melting points (mp) were obtained using a Smart SMP10 melting point instrument and are uncorrected.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 MHz spectrometer (1H NMR at 400 MHz, 13C NMR at 100 MHz) with samples dissolved in the appropriate deuterated solvent. Chemical shifts in 1H NMR spectra are expressed as ppm downfield from TMS and in 13C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (J) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz.

All Fourier transform infrared (FTIR) data was acquired as thin films using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumber ($\nu_{\text{max}}$) being reported in cm$^{-1}$.

Mass spectrometry (MS) was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm$^{-1}$.

HPLC was performed using Agilent 1100 Series, G1311A Pump using a chiral OD-3 column. Samples were ran in Hexane:IPA (95:5), at 25 °C oven temperature with an injection volume of 5 µl and 1 mL/min flow rate.
3.1 Palladium-Catalysed Allylation

3.1.1 General Procedures

General Procedure A: Palladium-catalysed sulfonamide allylation

To an oven-dried 10 mL round-bottomed flask, flushed with nitrogen, was added sodium hydride 60 % in mineral oil (120 mg, 3.0 mmol, 6 eq) and was immediately washed with petroleum ether (1 mL) and the petrol removed via syringe. To this, allyl palladium (II) chloride dimer $[\text{PdCl}(\text{C}_3\text{H}_5)_2]$ (4.7 mg, 0.0125 mmol, 0.025 eq), 1,4-bis(diphenylphosphino)butane (dppb, 23 mg, 0.055 mmol, 0.11 eq) in anhydrous DME (1 mL) was added and stirred for one hour at 25 °C. To this mixture, benzyl sulfonamide 89 (0.50 mmol, 1 eq) and allylic acetate (0.55 mmol, 1.1 eq) in anhydrous DME (1 mL) was added and stirred for 48 hours at 25 °C. After this time, the reaction mixture was quenched with H$_2$O (0.5 mL) and passed through a silica plug, washing with CH$_2$Cl$_2$. The crude mixture was purified by flash column chromatography (toluene:EtOAc, 95:5) to yield the titled compound.

General Procedure B: Palladium-catalysed allylation using modified reaction conditions

To an oven-dried 10 mL round-bottomed flask, flushed with nitrogen, was added, sequentially NaOt-Bu (48 mg, 0.5 mmol, 1 eq), allyl palladium (II) chloride dimer $[\text{PdCl}(\text{C}_3\text{H}_5)_2]$ (4.7 mg, 0.0125 mmol, 0.025 eq), (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (rac-BINAP, 23 mg, 0.055 mmol, 0.11 eq) in anhydrous DME (1 mL) and stirred for one hour at 25 °C. To this mixture, sulfonamide 98 (0.50 mmol, 1 eq) and allylic acetate (0.55 mmol, 1.1 eq) in anhydrous DME (1 mL) was added and stirred for 48 hours at 25 °C. After this time, the reaction mixture was passed through a silica plug, washing with CH$_2$Cl$_2$. The crude mixture was purified by flash column chromatography (toluene:EtOAc, 95:5) to yield the titled compound.
General procedure C: Synthesis of arylpiperazines

C1: Benzyl halide (10 mmol, 1.5 eq) and K$_2$CO$_3$ (5.25 g, 38 mmol, 5.5 eq) were added to a stirring solution of N-Boc piperazine (1.23 g, 6.6 mmol, 1 eq) in CH$_2$Cl$_2$ (40 mL). The mixture was heated to reflux and stirred for 16 hours, after which the solution was cooled and diluted with EtOAc (100 mL) and H$_2$O (100 mL). The organic phase was washed with brine (100 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (5:1 Hexane:EtOAc) to yield the intermediate Boc-protected benzyl piperazine compound to be used in the next step. (Only $^1$H NMR was obtained for these intermediate compounds).

C2: Trifluoroacetic acid (13.2 mL, 172 mmol, 36 eq) was added to a solution of the Boc-protected benzyl piperazine compound (4.8 mmol, 1 eq) in toluene (15 mL). The reaction was allowed to stir at room temperature for two hours, prior to the addition of 1M NaOH (50 mL). The mixture was extracted with CH$_2$Cl$_2$ (2 x 50 mL), dried over MgSO$_4$, filtered and the filtrate concentrated in vacuo to yield the titled benzyl piperazine, which was used without further purification. (Only $^1$H NMR data was obtained for these starting materials).

General procedure D: Synthesis of benzylpiperazine sulfonamides

To an oven-dried 25 mL round bottom flask, was added phenylmethanesulfonyl chloride (3 mmol, 1 eq), benzyl piperazine (3 mmol, 1 eq) and triethylamine (3 mmol, 1 eq) in CH$_2$Cl$_2$ (15 mL). The reaction mixture was allowed to stir for two hours at room temperature, prior to the addition of CH$_2$Cl$_2$ (25 mL) and H$_2$O (25 mL). The organic phase was washed successively with H$_2$O (2 x 25 mL) and sat. NaHCO$_3$ solution (2 x 25 mL). The organic extracts were combined, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo to yield the titled compound.
3.1.2 Experimental Data

*N,N*-Dimethyl-1-phenylmethanesulfonamide (89)

\[
\text{Ph} \quad \text{S} \quad \text{N}
\]

Phenylmethanesulfonyl chloride (5.72 g, 30 mmol, 1 eq) was dissolved in CHCl\(_3\) (150 mL) and cooled to 0 °C. Dimethylamine (8 M aq solution, 37.5 mL, 300 mmol, 10 eq) was added and the reaction mixture was allowed to warm to room temperature and stir for overnight. The organic layer was subsequently extracted from the aqueous layer and the combined organic extracts were washed with water (2 x 50 mL). The organic layer was dried over MgSO\(_4\), filtered and concentrated in vacuo to yield *N,N*-dimethyl-1-phenylmethanesulfonamide as a colourless solid (5.73 g, 96 %); \(^1\)H NMR (CDCl\(_3\) 400 MHz) \(\delta\) 7.37-7.40 (5H, m, Ar-H); 4.24 (2H, s, CH\(_2\)); 2.73 (6H, s, N-\(\text{C}_2\text{H}_3\)); \(^13\)C NMR (100 MHz) \(\delta\) 130.6 (2 x Ar-\(\text{C}_\text{H}\)); 129.1 (1 x Ar-\(\text{O}\)); 128.8 (1 x Ar-\(\text{CH}\)); 128.7 (2 x Ar-\(\text{CH}\)); 56.1 (1-\(\text{CH}_2\)); 37.7 (N-\(\text{C}_3\text{H}_3\)); \(\nu\)\(_{\text{max}}\) (solid, \(\text{cm}^{-1}\)) 1150 & 1333 (S=O); \(m/z\) (ESI\(^+\)) calculated for C\(_9\)H\(_{13}\)NO\(_2\)S [M-SO\(_2\)+H]\(^+\); 135.1048, found 135.1047.

*N,N*-Dimethyl-1-phenylbut-3-en-1-sulfonamide (90a)

\[
\text{Ph} \quad \text{S} \quad \text{N}
\]

*N,N*-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.50 mmol, 1 eq) and allyl acetate (0.06 mL, 0.55 mmol, 1.1 eq) were reacted following the general procedure A to yield *N,N*-dimethyl-1-phenylbut-3-en-1-sulfonamide (98 mg, 82 %) as a colourless solid; \(R_f=0.5\) (95:5 toluene: EtOAc); mp: 91 - 92 °C; \(^1\)H NMR (CDCl\(_3\) 400 MHz) \(\delta\) 7.34-7.42 (5H, m, Ar-H); 5.57 (1H, ddt, J 7.0 Hz 10.1 Hz 17.1 Hz, 3-H); 5.06 (1H, dd, J 1.4 Hz 17.0 Hz, 4-H\(_b\)); 4.99 (1H, dd, J 0.8 Hz 10.1 Hz, 4-H\(_b\)); 4.15 (1H, dd, J 4.2 Hz 11.3 Hz 1-H); 3.00-3.10 (2H, m, 2-H\(_2\)); \(^13\)C NMR (100 MHz) \(\delta\) 133.3 (3-\(\text{C}_\text{H}\)); 129.6 (2 x Ar-\(\text{CH}\)); 128.9 (1 x Ar-\(\text{CH}\)); 128.7 (1 x Ar-\(\text{CH}\)); 118.2 (4-\(\text{C}_\text{H}\)); 37.6 (N-\(\text{C}_3\text{H}_3\)); 34.3 (2-\(\text{C}_\text{H}_2\)); \(\nu\)\(_{\text{max}}\) (solid, \(\text{cm}^{-1}\)) 1137 & 1310 (sulfonamide S=O); \(m/z\) (ESI\(^+\)) calculated for C\(_{12}\)H\(_{17}\)NO\(_2\)S [M+Na]\(^+\); 262.0872, found 262.0869.
(E)-N,N-Dimethyl-1-phenylpent-3-ene-1-sulfonamide (90b)

\[
\text{Ph} \quad \text{O} \quad \text{S} \quad \text{N} \\
\text{3} \quad \text{2} \quad \text{1} \quad \text{4} \quad \text{5} \quad \text{6} \quad \text{7}
\]

N,N-Dimethyl-1-phenylmethanesulfonamide (92 mg, 0.5 mmol, 1 eq) and E-2-butenyl acetate (95 % E) (0.07 ml, 0.55 mmol, 1.1 eq) was reacted following the general procedure A, to yield (E)-N,N-dimethyl-1-phenylpent-3-ene-1-sulfonamide (E:Z 67:33) (103 mg, 82%) as a colourless solid; Rf = 0.52 (95:5 toluene:EtOAc); mp: 92 - 94 °C; Data for trans isomer 1H NMR (CDCl₃ 400 MHz) δ: 7.34-7.42 (m, 5H, Ar-H); 5.44-5.54 (1H, m, 3-H); 5.11-5.19 (1H, m, 4-H); 4.11 (1H, dd, J= 4.1 Hz 11.2 Hz, 1-H); 2.8-3.0 (2H, m, 2-H₂); 2.50 (6H, s, N-(CH₃)₂); 1.5 (3H, dd, J= 0.8 Hz 6.5 Hz, 5-H³); 13C NMR (100 MHz) δ: 133.4 (1 x Ar-C); 129.7 (2 x Ar-C); 128.9 (1 x Ar-C); 128.6 (2 x Ar-C); 128.7 (3-C); 125.6 (4-C); 67.6 (1-C); 37.6 (N-(CH₃)₂); 33.2 (2-C₂H₄); 17.8 (5-C); V_max (solid, cm⁻¹) 1137 & 1319 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₃H₁₉NO₂S [M+Na]^⁺; 267.1029, found 276.1025.

(E)-N,N-Dimethyl-1-phenyleth-3-ene-1-sulfonamide (90c)

\[
\text{Ph} \quad \text{O} \quad \text{S} \quad \text{N} \\
\text{1} \quad \text{2} \quad \text{3} \quad \text{4} \quad \text{5} \quad \text{6} \quad \text{7}
\]

N,N-Dimethyl-1-phenylmethanesulfonamide (0.099 g, 0.5 mmol, 1 eq) and E-2-hexenyl acetate (0.09 mL, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield (E)-N,N-dimethyl-1-phenyleth-3-ene-1-sulfonamide (137 mg, 98%) as a colourless solid; Rf = 0.60 (95:5 toluene:EtOAc); mp: 65 - 67 °C; 1H NMR δ: 7.34-7.41 (5H, m, Ar-H); 5.38-5.47 (1H, m, 4-H); 5.08-5.17 (1H, m, 3-H); 4.10 (1H, dd, J= 4.2 Hz 11.1 Hz, 1-H); 2.81-3.04 (2H, m, 2-H₂); 2.54 (6H, s, N-(CH₃)₂); 1.76-1.88 (2H, m, 5-H₂); 1.19-1.26 (2H, m, 6-H₂); 0.72 (3H, t, J= 7.1 Hz, 7-H); 13C NMR (100 MHz) δ: 134.5 (4-C); 133.4 (1 x Ar-C); 129.7 (2 x Ar-C); 128.8 (1 x Ar-C); 128.6 (2 x Ar-C); 124.5 (3-C); 67.6 (1-C); 37.6 (N-(CH₃)₂); 34.4 (2-C₂H₄); 33.2 (5-C); 22.3 (6-C); 13.4 (7-C); V_max (solid, cm⁻¹) 1137 & 1320 (sulfonamide S=O); 964 (E-alkene); m/z (ESI⁺) calculated for C₁₅H₂₀NO₂S [M+K]^⁺; 320.1081, found 320.1083.
**N,N-Trimethyl-1-phenylpent-3-ene-1-sulfonamide (90d)**

[N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol, 1 eq) and prenyl acetate (0.075 mL, 0.55 mmol, 1.1 eq) was reacted following the general procedure A, replacing dppb with 1,2-bis(diphenylphosphino)ethane as the ligand (21 mg, 0.055 mmol, 0.11 eq) to yield N,N-4-trimethyl-1-phenylpent-3-ene-1-sulfonamide (99 mg, 74 %) as a colourless solid; R₉ = 0.58 (95:5 toluene:EtOAc); mp: 90 - 92°C; ¹H NMR δH 7.34-7.42 (5H, m, Ar-H); 4.87 (1H, ddt J 1.4 Hz 3.0 Hz 7.3 Hz, 3-H); 4.07 (1H, dd J 4.0 Hz 11.3 Hz, 1-H); 3.05-2.84 (2H, m, 2-H); 2.50 (6H, s, N-(CH₃)₂); 1.56 (6H, s, 5-C(CH₃)₂, 4'-C(CH₃)₂); ¹³C NMR (100 MHz) δC 134.9 (1 x Ar-C); 133.6 (4-C); 129.6 (2 x Ar-CH); 128.7 (1 x Ar-CH); 128.6 (2 x Ar-CH); 128.5 (2 x Ar-CH); 127.4 (1 x Ar-CH); 126.2 (2 x Ar-CH); 124.8 (3-C); 67.4 (1-C); 37.6 (N-(CH₃)₂); 33.7 (2-CH₂); 25.6, 17.9 (4'-CH₃, 5'-CH₃); νmax (solid, cm⁻¹) 1133 & 1304 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₄H₂₁NO₂S [M+H]⁺; 268.1366, found 268.1366.](image)

**((E))-N,N-Dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (90e)**

[N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol, 1 eq) and cinnamyl acetate (440 mg, 2.5 mmol, 5 eq) was reacted following the general procedure A, replacing dppb with 1,1'-bis(diphenylphosphino)ferrocene (31 mg, 0.055 mmol, 0.11 eq) as the ligand, to yield ((E))-N,N-dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (125 mg, 79 %) as a colourless solid; R₉ = 0.5 (95:5 toluene:EtOAc); mp: 88 - 90 °C; ¹H NMR δH 7.36-7.46 (5H, m, Ar-H); 7.17 (5H, m, Ar-H); 6.43 (1H, d, J 15.6, 4-H); 5.93 (1H, dt, J 7.2, 15.7, 3-H); 4.22 (1H, dd, J 4.2, 10.8, 1-H); 3.25 (1H, dddd, J 1.0 Hz 4.2 Hz 7.6 Hz 14.2 Hz, 2-H); 3.08 (1H, dddd, J 1.1 Hz 6.8 Hz 10.9 Hz 14.2 Hz, 2-H); 2.55 (6H, s, N-(CH₃)₂); ¹³C NMR (100 MHz) δC 136.9 (1 x Ar-C); 133.2 (1 x Ar-C); 133.1 (4-C); 129.6 (2 x Ar-CH); 129.0 (1 x Ar-CH); 128.8 (2 x Ar-CH); 128.5 (2 x Ar-CH); 127.4 (1 x Ar-CH); 126.2 (2 x Ar-CH); 124.8 (3-C); 67.3 (1-C); 37.6 (N-(CH₃)₂); 33.7 (2-CH₂); νmax (solid, cm⁻¹) 1135.6 & 1317 (sulfonamide S=O); 926 (E-alkene); m/z (ESI⁺) calculated for C₁₈H₂₁NO₂S [M+Na]⁺; 338.1185, found 338.1184.](image)
(Z)-N,N,4,8-Tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (90f)

N,N-Dimethyl-1-phenylmethanesulfonamide (108 mg, 0.5 mmol, 1 eq) and neryl acetate (490 mg, 2.5 mmol, 5 eq) was reacted following the general procedure A, replacing dpbb with dppe as the ligand (21 mg, 0.055 mmol, 0.11 eq) to yield (Z)-N,N,4,8-tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (114 mg, 68 %) as a yellow oil; Rf = 0.62 (95:5 toluene:EtOAc); ¹H NMR δ_H (CDCl₃) 7.35-7.42 (5H, m, Ar-H); 5.07-5.09 (1H, m, 3'-H); 4.83-4.87 (1H, d, J 7.2, 7-H'); 4.05 (1H, dd, J 3.9 Hz 11.2 Hz, 1-H); 3.02-3.09 (1H, m, 2-H); 2.79-2.88 (1H, m, 2-H'); 2.54 (6H, s, (CH₃)$_3$); 2.00-2.03 (2H, m, 5-CH$_2$); 1.70 (2H, bs, 6-CH$_2$); 1.60 (3H, s, 8-CH$_3$); 1.57 (3H, s, 8-CH$_3$); 1.53 (3H, s, 4-CH$_3$). ¹³C NMR (100 MHz) δ_C 136.8 (C-4); 133.6 (1 x Ar-C); 131.8 (8-C); 129.6 (2 x Ar-CH); 128.8 (1 x Ar-CH); 128.6 (2 x Ar-CH); 123.9 (7-C); 119.5 (3-C); 67.6 (1-C); 37.6 (N-(CH$_3$)$_3$); 32.0 (5-C); 28.4 (2-C); 26.3 (6-C); 25.8 (8-C); 23.8 (8-C); 17.6 (4-C); 16.2 (4-C); $v_{max}$ (solid, cm⁻¹) 1136 & 1329 (sulfonamide S=O); 700 (cis alkene); m/z (ESI⁺) calculated for C$_{19}$H$_{29}$NO$_2$S [M+Na]$^+$; 358.1811, found 358.1805.

1-(Cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (90g)

N,N-Dimethyl-1-phenylmethanesulfonamide (98 mg, 0.5 mmol, 1 eq) and cyclohex-2-en-1-yl acetate (77 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield 1-(cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (d.r 59:41 determined by ¹H NMR) (105 mg, 74 %) as a colourless solid; Rf = 0.42 (95:5 toluene:EtOAc); mp: 119 - 121 °C; data for major diastereomer: ¹H NMR δ_H (CDCl₃) 7.36-7.43 (5H, m, Ar-H); 5.69-5.72 (1H, m, 3'-H); 5.46 (1H, bd, J 10.2 Hz, 2'-H); 3.99 (1H, d J 8.5 Hz, 1-H); 3.19-3.22 (1H, m, 1'-H); 2.44 (6H, s, (N-(CH$_3$)$_3$)); 2.13 (1H, dt J 6.3 Hz 11.0 Hz, 6'-H); 1.88-1.97 (2H, m, 4'-H); 1.58-1.63 (2H, m, 1-H, 6'-H); ¹³C NMR (100 MHz) δ_C 133.4 (1 x Ar-C); 130.1 (2 x Ar-CH); 129.7 (3'-C); 128.8 (1 x Ar-CH); 128.6 (2 x Ar-CH); 127.0 (2'-C); 71.8 (1'-CH); 37.5 (N-(CH$_3$)$_3$); 37.4 (1'-CH); 28.0 (6'-CH); 24.9 (4'-CH); 21.2 (5'-CH). Data for minor diastereomer: ¹H NMR δ_H (CDCl₃) 7.36-7.43 (5H, m, Ar-H); 6.22 (1H, dd J 2.3 Hz 10.5 Hz, 2'-H); 5.78-5.83 (1H, m, 3'-H); 4.07 (1H, d J 9.9 Hz, 1-H); 3.12-3.17 (1H, m, 1'-H); 2.42 (6H, s, N-(CH$_3$)$_3$); 1.92-1.97 (2H, m, 4'-CH$_2$); 1.52-1.63 (3H, 5'-H$_2$); 1.09-1.16 (1H, m, 6'-H); ¹³C NMR (100 MHz) δ_C 133.6 (1 x Ar-C); 130.0 (1 x Ar-CH); 128.7 (3'-CH$_2$); 4 x Ar-CH); 128.6 (2'-CH); 72.6 (1'-CH); 36.5
(N-(CH$_3$)$_2$); 30.9 (1'-CH); 26.7 (6'-CH$_2$); 25.0 (4'-CH$_2$); 20.6 (5'-CH$_2$); $\nu_{\text{max}}$ (solid, cm$^{-1}$) 1319 & 1136 (sulfonamide S=O); m/z (ESI$^+$) calculated for C$_{15}$H$_{21}$NO$_3$S [M+Na]$^+$; 302.1185, found 302.1180.

1-(Cyclopent-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (90h)

N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol, 1 eq) and cyclopent-2-en-1-yl acetate (70 mg, 0.55 mmol, 1.1 eq) was reacted following the general method A to yield 1-(cyclopent-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (d.r 50:50 determined by $^1$H NMR) (114 mg, 79 %) as a colourless solid; $R_F$ = 0.45 (95:5 toluene:EtOAc); mp: 88 - 91 °C; data for diastereomer 1: $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.35-7.37 (5H, m, Ar-H); 5.77 (1H, dd J 2.3 Hz 5.6 Hz, 2'-H); 5.42 (1H, dd J 1.7 Hz 5.5 Hz, 3'-H); 3.98 (2H, d J 8.8 Hz, 1'-H); 3.72-3.79 (1H, m, 1'-H); 2.47 (6H, s, N-(CH$_3$)$_2$); 2.31-2.36 (1H, m, 5'-H); 2.27-2.29 (2H, m, 4'-H); 1.88-1.93 (1H, m, 5'-H); $^{13}$C NMR (100 MHz) $\delta_{C}$: 134.2 (1 x Ar-C); 133.3 (2'-CH); 131.1 (3'-CH); 128.7 (2 x Ar-CH); 128.6 (1 x Ar-CH); 128.5 (2 x Ar-CH); 71.6 (1'-CH); 46.7 (1'-CH); 37.5 (N-(CH$_3$)$_2$); 32.3 (5'-CH); 29.2 (4'-CH). Data for diastereomer 2: $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.38-7.43 (5H, m, Ar-H); 6.27 (1H, dd J 2.2 Hz 5.7 Hz, 2'-H); 5.86 (1H, dd J 2.4 Hz 5.6 Hz, 3'-H); 3.98 (1H, d J 10.4 Hz, 1'-H); 3.66-3.70 (1H, m, 1'-H); 2.45 (6H, s, N-(CH$_3$)$_2$); 2.19-2.26 (2H, 4'-H$_2$); 1.83-1.86 (1H, m, 5'-H); 1.22-1.32 (1H, m, 5'-H); $^{13}$C NMR (100 MHz) $\delta_{C}$: 133.7 (1 x Ar-C); 132.9 (2'-CH); 132.2 (3'-CH); 130.0 (2 x Ar-CH); 129.7 (1 x Ar-CH); 128.7 (2 x Ar-CH); 72.4 (1'-CH); 46.9 (1'-CH); 37.4 (N-(CH$_3$)$_2$); 30.9 (4'-CH$_2$); 29.0 (5'-CH); $\nu_{\text{max}}$ (solid, cm$^{-1}$) 1316 & 1131 (sulfonamide S=O); m/z (ESI$^+$) calculated for C$_{14}$H$_{19}$NO$_2$S [M+Na]$^+$; 288.1029, found 288.1028.

N,N-3-Trimethyl-1-phenylbut-3-ene-1-sulfonamide (90i)

N,N-Dimethyl-1-phenylmethanesulfonamide (97 mg, 0.49 mmol, 1 eq) and 2-methylallyl acetate (72 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield N,N-3-trimethyl-1-phenylbut-3-ene-1-sulfonamide (102 mg, 82 %) as a colourless solid; $R_F$ = 0.50 (95:5 toluene:EtOAc); mp: 127 - 128 °C; $^1$H NMR $\delta$H 7.35-7.42 (5H, m, Ar-H); 4.67 (1H, bs, 3'-H$'$); 4.61 (1H, bs, 3'-H$''$); 4.30 (1H, dd, J 3.7 Hz 11.6 Hz, 1'-H); 2.88-3.06 (2H, m, 2'-H); 2.54 (6H, s, N-(CH$_3$)$_2$); 1.61 (3H, 4'-H$_3$); $^{13}$C NMR (100 MHz) $\delta_{C}$: 140.3 (3'-C); 133.3 (1 x Ar-C); 129.6 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.6 (2 x Ar-CH); 114.1 (3'-CH$_2$); 66.0 (N-(CH$_3$)$_2$); 37.7 (N-(CH$_3$)$_2$); 28.1 (5'-CH$_2$).
(E)-N,N,4,8-Tetramethyl-1-phenylthio-3,7-diene-1-sulfonamide (90j)

\[
\begin{align*}
&\text{N,N-Dimethyl-1-phenylmethanesulfonamide (101 mg, 0.5 mmol, 1 eq) and geranyl acetate (490 mg, 2.5 mmol, 5 eq) was reacted following the general procedure A, replacing dppb with dppf ligand (30 mg, 0.055 mmol, 0.11 eq) to yield (E)-N,N,4,8-tetramethyl-1-phenylthio-3,7-diene-1-sulfonamide (140 mg, 84%) as a colourless solid; Rf = 0.6 (95:5 toluene:EtOAc); mp: 52 - 53 °C; }^1\text{H NMR (400 MHz) } \delta \text{H 7.34-7.42 (5H, m, Ar-CH); 4.87-4.9 (1H, m, 7-H); 4.83-4.85 (1H, m, 3-H); 4.07 (1H, dd J 3.8 Hz, 11.3 Hz, 1-H); 3.00-3.07 (1H, m, 2-H); 2.82-2.89 (1H, m, 2-H); 2.54 (6H, s, N-CH3); 1.90-1.94 (2H, m, 6-H2); 1.83-1.89 (2H, m, 5-H2); 1.61 (3H, s, 8-CH3); 1.56 (3H, s, 4-CH3); 1.51 (3H, s, 9-CH3); }^{13}\text{C NMR (100 MHz) } \delta \text{C 138.5 (4-C); 133.6 (1 x Ar-C); 131.4 (8-C); 129.6 (2 x Ar-CH); 128.7 (1 x Ar-CH); 128.5 (2 x Ar-CH); 123.9 (7-CH); 118.9 (3-CH); 67.4 (1-CH); 39.5 (5-CH2); 37.7 (N-CH3); 28.7 (2-CH2); 26.4 (6-CH2); 25.6 (8-CH3); 17.6 (9-CH3); 16.2 (4-CH3); } \nu \text{max (solid, cm}^{-1}) 1323 \text{ & 1135 (sulfonamide S=O); 926 (alkene); } m/z (ESI+) \text{ calculated for C}_{19}H_{29}NO_2S [M+Na]^+; 358.1811, \text{found 358.1815.}
\end{align*}
\]

(E)-N,N-Dimethyl-1,2,4-triphenylbut-3-ene-1-sulfonamide (90k)

\[
\begin{align*}
&\text{N,N-Dimethyl-1-phenylmethanesulfonamide (99 mg, 0.5 mmol, 1 eq) and (±)-trans-diphenylallyl acetate (138 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield (E)-N,N-dimethyl-1,2,4-triphenylbut-3-ene-1-sulfonamide (d.r 80:20 determined by }^1\text{H NMR (172 mg, 87%)} \text{ as a colourless solid; Rf = 0.6 (95:5 toluene:EtOAc); mp: 131 - 133 °C; data for major diastereomer: }^1\text{H NMR } \delta \text{H 7.17-7.47 (15H, m, Ar-CH); 6.32-6.39 (2H, m, 3-H, 4-H); 4.61 (1H, t J 7.1 Hz, 2-H); 4.51 (1H, d J 7.1 Hz, 1-H); 2.44 (6H, s, N-(CH3)); }^{13}\text{C NMR (100 MHz) } \delta \text{C 141.4 (Ar-C); 137.2 (Ar-CH); 132.6 (4-CH); 132.4 (Ar-CH); 130.7 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.8 (3-CH); 128.6 (2 x Ar-CH); 128.5 (2 x Ar-CH); 128.4 (2 x Ar-CH); 128.3 (2 x Ar-CH); 127.4 (1}
\end{align*}
\]
x Ar-CH); 127.1 (1 x Ar-CH); 126.3 (2 x Ar-CH); 71.8 (1-CH); 50.2 (2-CH); 37.4 (N-(CH₃)₂); νₘₙₙ (solid, cm⁻¹) 1133 & 1459 (sulfonamide S=O); m/z (ESI⁺) calculated for C₂ₓHₓ₂₅NO₂S [M+K⁺]: 430.1238, found 430.1234.

\[
N,N\text{-Dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (91)}
\]

To an oven dried 10 mL round-bottomed flask flushed with nitrogen, sodium hydride 60 % in mineral oil (160 mg, 4 mmol, 6 eq) was added and immediately washed with petrol. To this, [PdCl(C≡C₅H₅)]₂ (4.8 mg, 0.0125 mmol, 0.025 eq) and dppb (22 mg, 0.055 mmol, 0.11) was added in DME (1 mL), stirred for one hour at 25 °C. To this mixture, N,N-dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol, 1 eq) and allyl acetate (250 mg, 2.5 mmol, 5 eq) was added in DME (1 mL) stirring at 25 °C for 48 hours. The reaction was quenched with water (0.2 mL) and purified using column chromatography to yield N,N-dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (131 mg, 96 %) as a colourless solid; Rf = 0.52 (95:5 toluene:EtOAc); mp: 80 - 83 °C; ¹H NMR (400 MHz) δₙ 7.59-7.61 (2H, m, Ar-CH); 7.35-7.42 (3H, m, Ar-CH); 5.86 (2H, ddt J 7.0 Hz 10.2 Hz 14.0 Hz, 2-CH, 6-CH); 5.19 ( 2H, dd J 1.2 Hz 17.0 Hz, 1-CH₆, 7-CH₃); 5.12 (2H, d J 10.3 Hz, 1-CH₃, 7-CH₃); 3.27 (2H, dd J 6.7 Hz 15.1 Hz, 3-CH, 5-CH); 3.01 (2H, dd J 7.1 Hz 15.1 Hz, 3-CH, 5-CH); 2.46 (6H, s, N-(CH₃)₂); ¹³C NMR (100 MHz) δc 135.9 (1 x Ar-C); 132.4 (1-CH, 6-CH); 129.3 (2 x Ar-CH); 128.4 (1 x Ar-CH); 128.2 (2 x Ar-CH); 119.3 (1-CH₂, 7-CH₂); 71.7 (4-C); 38.7 (N-(CH₃)₂); 36.7 (2-CH₂, 7-CH₂); νₘₙₙ (solid, cm⁻¹) 1312 & 1131 (sulfonamide S=O); 919 (mono-substituted alkene); m/z (ESI⁺) calculated for C₁₅H₁₃NO₂S [M+Na⁺]: 302.1185, found 302.1190.

\[
N,N\text{-Dimethyl-1-phenylcyclopent-3-ene-1-sulfonamide (92)}
\]

To an oven-dried 10 mL round bottomed flask, N,N-dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (100 mg, 0.36 mmol, 1 eq) and Grubbs 2nd generation catalyst (15.2 mg, 0.018 mmol, 0.05 eq) was dissolved in CH₂Cl₂ (6 mL). The reaction mixture was allowed to stir at 25 °C for overnight. The reaction mixture was passed through a silica plug and the solvent evaporated to dryness to yield N,N-dimethyl-1-phenylcyclopent-3-ene-1-sulfonamide (84 mg, 93 %) as a grey solid; mp: 111 - 114 °C; ¹H NMR (400 MHz, CDCl₃) δₙ 7.50-7.52 (2H, m, Ar-CH); 7.31-7.39 (3H, m, Ar-CH); 5.83 (2H, s, 3-CH, 4-CH); 3.55 (2H, d J 15.7, 2/5-CH₂); 3.15 (2H, d J 16.6, 2/5-CH₂); 2.64 (6H, s, (N-(CH₃)₂); ¹³C NMR (100 MHz) δc 139.1 (1 x Ar-C); 129.6 (2 x Ar-CH); 128.3 (3-CH, 4-
CH); 128.2 (1 x Ar-CH); 128.1 (2 x Ar-CH); 41.9 (2-CH₃, 5-CH₂); 38.9 (N-(CH₃)₂), νmax (solid, cm⁻¹) 1312 & 1131 (sulfonamide S=O); 705 (cis-alkene); m/z (ESI⁺) calculated for C₁₅H₁₇NO₂S [M+Na]⁺; 274.0872, found 274.0873.

4-(Benzylsulfonyl)morpholine (94)

![Chemical Structure Image]

To an oven-dried 100 mL round bottomed flask, phenylmethanesulfonylchloride (4.8 g, 25 mmol, 1 eq) was dissolved in dry benzene (50 mL) with stirring. To this, morpholine (4.3 mL, 50 mmol, 2 eq) was slowly added and stirred at room temperature for overnight. The solvent was removed under pressure and the resultant oil was added to water (50 mL) and subsequently extracted with CH₂Cl₂ (3 x 25 mL). The organic layers were combined, dried over MgSO₄, filtered and the filtrate concentrated in vacuo to yield 4-(benzylsulfonyl)morpholine as a colourless solid (5.5 g, 91 %); mp: 173 - 175 °C; ¹H NMR (400 MHz, CDCl₃) δH 7.36 - 7.43 (5H, m, Ar-CH); 4.24 (2H, s, CH₂); 3.62 (4H, t J 4.7 Hz, O-C(H₂)₂); 3.10 (4H, t J 4.7 Hz, O-C(H₂)₂); m/z (ESI⁺) calculated for C₁₁H₁₅NO₃S [M-SO₂⁺H⁺]; 177.1154, found 177.1150.

4-[[1-Phenylbut-3-en-1-yl]sulfonyl]morpholine (99f)

![Chemical Structure Image]

4-(Benzylsulfonyl)morpholine (120 mg, 0.5 mmol, 1 eq) and allyl acetate (60 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield 4-[[1-phenylbut-3-en-1-yl]sulfonyl]morpholine (274 mg, 98 %) as a colourless solid; Rf = 0.25 (95:5 Toluene:EtOAc); mp: 84 - 87 °C; ¹H NMR (400 MHz) δH 7.36-7.40 (5H, m, Ar-CH); 5.52 (1H, ddt J 7.0 Hz 10.0 Hz 17.0 Hz, 3-H); 5.04 (1H, dd J 1.2 Hz 17.0 Hz, 4-H); 4.96 (1H, d J 10.1 Hz, 4-H); 4.09 (2H, dd J 4.1 Hz 11.2 Hz, 1-H); 3.53 (2H, ddd J 3.0 Hz 6.3 Hz 11.5 Hz, O-CH₃); 3.44 (2H, ddd J 3.0 Hz 6.2 Hz 11.2 Hz, O-CH₃); 3.08-3.13 (1H, m, 2-H); 2.89 (1H, ddd J 6.8 Hz 11.2 Hz 14.0 Hz, 2-H); 3.02-3.07 (2H, m, N-CH₂); 2.76 (2H, bs, N-CH₂); ¹³C NMR (100 MHz) δC 133.0 (3-CH); 132.8 (1 x Ar-C); 129.7 (2 x Ar-CH); 129.2 (1 x Ar-CH); 128.9 (2 x Ar-CH); 118.4 (4-CH₂); 67.9 (1-CH); 66.8 (N-(CH₃)₂); 46.1 (O-(CH₃)₂); 34.4 (2-CH₂); νmax (solid, cm⁻¹) 1335 & 1125 (sulfonamide S=O); 1110 (mono-substituted alkene); m/z (ESI⁺) calculated for C₁₄H₁₉NO₂S [M+Na⁺]; 304.0978, found 304.0978.
(E)- 4-([1-Phenyhept-3-en-1-yl]sulfonyl)morpholine (99g)

4-(Benzylsulfonyl)morpholine (124 mg, 0.5 mmol, 1 eq) and trans-2-hexenyl acetate (82 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield (E)- 4-([1-phenyhept-3-en-1-yl]sulfonyl)morpholine (102 mg, 79 %) as a colourless solid; $R_f = 0.25$ (95:5 Toluene:EtOAc); mp: 69 - 71 °C; $^1$H NMR (400 MHz) $\delta$H 7.36-7.38 (5H, m, Ar-CH); 5.43 (1H, dt J 6.9 Hz 14.3 Hz, 4-$^H$); 5.09 (1H, dt J 6.9 Hz 14.5 Hz, 3-$^H$); 4.04 (1H, dd J 4.0 Hz 11.2 Hz, 1-$^H$); 3.54 (2H, ddd J 2.8 Hz 6.3 Hz 11.2 Hz, O-CH$_2$); 3.45 (2H, ddd J 2.9 Hz 6.3 Hz 9.2 Hz, O-CH$_2$); 2.99-3.07 (3H, m, N-CH$_2$, 2-$^H$); 2.78 (3H, m, N-CH$_2$, 2-$^H$); 1.77-1.87 (2H, m, 5-H$_2$); 1.16-25 (2H, m, 6-H$_2$); 0.71 (3H, t J 7.4, 7-H$_3$); 13C NMR (100 MHz) $\delta$C 134.6 (4-$^CH$); 132.9 (1 x Ar-CH); 129.8 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.7 (2 x Ar-CH); 124.3 (3-$^CH$); 68.4 (1-$^CH$); 66.8 (N-(CH$_2$)$_2$); 46.1 (O-(CH$_2$)$_2$); 34.4 (5-$^CH$_2$); 33.4 (2-$^CH$_2$); 22.3 (6-$^CH$_2$); 13.4 (7-$^CH$_3$); $\nu_{\text{max}}$ (solid, cm$^{-1}$) 1106 & 1322 (sulfonamide S=O); 952 (trans alkene); m/z (ESI$^+$) calculated for C$_{18}$H$_{22}$NO$_3$S [M+Na]$^+$; 346.1447, found 346.1446.

(Z)-4-([4,8-Dimethyl-1-phenylnona-3,7-dien-1-yl]sulfonyl)morpholine (99h)

4-(Benzylsulfonyl)morpholine (120 mg, 0.5 mmol, 1 eq) and neryl acetate (118 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A, to yield (Z)-4-([4,8-dimethyl-1-phenylnona-3,7-dien-1-yl]sulfonyl)morpholine (83 mg, 45 %) as a yellow oil; $R_f = 0.30$ (95:5 Toluene:EtOAc); $^1$H NMR (400 MHz) $\delta$H 7.36-7.41 (5H, m, Ar-CH); 5.06-5.07 (1H, m, 7-$^H$); 4.84 (1H, t J 7.1, 3-$^H$); 3.98 (1H, dd J 3.8 Hz 11.2 Hz, 1-$^H$); 3.54 (3H, m, 2-$^H$); 6.4 Hz 11.5 Hz, O-(CH$_2$)$_2$); 3.45 (2H, m, 5-H$_2$); 1.77-1.87 (2H, m, 6-H$_2$); 1.16-25 (2H, m, 6-H$_2$); 0.71 (3H, t J 7.4, 7-H$_3$); 13C NMR (100 MHz) $\delta$C 138.8 (4-$^CH$); 133.2 (1 x Ar-CH); 131.9 (8-$^CH$); 129.7 (2 x Ar-CH); 129.0 (1 x Ar-CH); 128.8 (2 x Ar-CH); 123.9 (7-$^CH$); 119.2 (3-$^CH$); 68.4 (1-$^CH$); 66.8 (N-(CH$_2$)$_2$); 46.1 (O-(CH$_2$)$_2$); 32.0 (5-$^CH$_2$); 28.6 (2-$^CH$_2$); 26.3 (6-$^CH$_2$); 25.7 (-$^CH$_3$); 23.3 (-$^CH$_3$); 17.7 (4-$^CH$_3$); $\nu_{\text{max}}$ (oil, cm$^{-1}$) 1339 & 1112 (sulfonamide S=O); 702 (cis alkene); m/z (ESI$^+$) calculated for C$_{24}$H$_{29}$NO$_3$S [M+Na]$^+$; 400.1917, found 400.1919.
1-(Benzylsulfonyl)piperidine (95)

To an oven-dried 100 mL round bottom flask, piperidine (1.25 mL, 12.5 mmol, 1 eq) and triethylamine (1.8 mL, 12.5 mmol, 1 eq) was dissolved in CH$_2$Cl$_2$ (20 mL) at cooled to –20 °C. To this, phenylmethanesulfonylchloride (2.39 g, 12.5 mmol, 1 eq) was added slowly over ten minutes at –20 °C. The reaction mixture was allowed to warm to room temperature and stir for six hours, after which aqueous NH$_4$Cl (3 mL) was added. The reaction organic extracts were washed with water (3 x 25 mL) and brine (25 mL) successively, dried over MgSO$_4$ and the solvent was evaporated to dryness to yield 1-(benzylsulfonyl)piperidine as a colourless solid (1.71 g, 57 %); mp: 128 - 130 °C; $^1$H NMR (400 MHz) δ$_H$ 7.36-7.41 (5H, m, Ar-H); 4.19 (2H, s, 1-H$_2$); 3.06-3.08 (4H, m, N-(CH$_2$)$_2$); 1.51-1.54 (6H, m, (CH$_2$)$_3$); 13C NMR (100 MHz) δC 130.7 (2 x Ar-C$_H$); 129.1 (1 x Ar-C); 128.7 (2 x Ar-C$_H$); 128.6 (1 x Ar-C$_H$); 56.7 (1-C$_H$)$_2$); 46.9 (N(CH$_2$)$_2$); 25.8 (CH$_2$); $\nu_{max}$ (solid, cm$^{-1}$) 1158 & 1335 (sulfonamide S=O); m/z (ESI$^+$) calculated for C$_{12}$H$_{17}$NO$_2$S [M+H]$^+$ 240.1053, found [M-SO$_2$+H]$^+$ 176.1429.

1-[(1-Phenyl-3-en-1-yl)sulfonyl]piperidine (99i)

1-(benzylsulfonyl)piperidine (119 mg, 0.5 mmol) and allyl acetate (57 mg, 0.55 mmol) was reacted following general procedure A, to yield 1-[(1-phenylbut-3-en-1-yl)sulfonyl]piperidine as a colourless solid (107 mg, 77 %); R$_F$ = 0.42 (95:5 toluene:EtOAc); mp: 78 - 80 °C; $^1$H NMR (400 MHz, CDCl$_3$); δ$_H$ 7.34-7.41 (5H, m, Ar-H); 5.53 (1H, ddt J 6.9 Hz 10.0 Hz 13.9 Hz, 3-H); 5.00 (1H, dd J 1.4 Hz 17.0 Hz, 4-H); 4.95 (1H, d J 10.0 Hz, 4-H); 3.06-3.12 (1H, m, 2-H); 2.97-3.03 (2H, m, 2'-CH$_2$); 2.85-2.93 (1H, m, 2-H); 2.76 (2H, bs, 2'-CH$_2$); 1.39-1.44 (6H, m, 3'-CH$_2$); 4'-CH$_2$); $^{13}$C NMR (100 MHz) δC 133.4 (3-C$_H$); 133.3 (1 x Ar-C); 129.7 (2 x Ar-C$_H$); 128.8 (1 x Ar-C$_H$); 128.6 (2 x Ar-C$_H$); 118.1 (4-C$_H$); 67.7 (1-C$_H$); 46.9 (2'-CH$_2$)$_2$); 25.9 (3'CH$_2$)$_2$); 23.7 (4'-CH$_2$); $\nu_{max}$ (solid, cm$^{-1}$) 1132 & 1276 (sulfonamide S=O); m/z (ESI$^+$) calculated for C$_{15}$H$_{21}$NO$_2$S [M+K]$^+$; 318.0925, found 318.0926.
1-(Benzylsulfonyl)-1,2,5,6-tetrahydropyridine (96)

To an oven-dried 100 mL round bottomed flask, 1,2,5,6-tetrahydropyridine (1 mL, 11 mmol, 1 eq) and triethylamine (1.55 mL, 11 mmol, 1 eq) was dissolved in CH₂Cl₂ (20 mL) and cooled to −20 °C. To this, phenylmethanesulfonyl chloride (2.09 g, 11 mmol, 1 eq) in CH₂Cl₂ (10 mL) was slowly added. The reaction mixture was allowed to warm to room temperature and stir for six hours, after which aqueous NH₄Cl (3 mL) was added. The mixture was extracted with CH₂Cl₂ (50 mL), washing with water (3 x 25 mL) and brine (25 mL). The organic extracts were combined, dried over MgSO₄, filtered and the filtrate concentrated in vacuo to yield 1-(benzylsulfonyl)-1,2,5,6-tetrahydropyridine as a beige solid (2.11 g, 81 %); mp: 148 - 150 °C; ¹H NMR (400 MHz CDCl₃) δ H 7.36-7.41 (5H, m, Ar-H); 5.76-5.82 (1H, m, 4-H); 5.57-5.61 (1H, m, 3-H); 4.23 (2H, s, 1'-H); 3.65 (2H, dt J 6.6 Hz 6.8 Hz, 2-H₂); 3.21 (2H, t J 5.7 Hz, 6-H₂); 2.04-2.09 (2H, m, 5-H₂); ¹³C NMR (100 MHz) δ C 130.7 (2 x Ar-CH); 129.1 (1 x Ar-C); 128.7 (1 x Ar-CH₂); 128.6 (2 x Ar-CH); 125.4 (4-CH); 123.3 (3-CH); 57.1 (1'-CH₂); 44.7 2'-CH₂; 42.6 (6-CH₂); 25.5 (5-CH₂); vmax (solid, cm⁻¹) 1149 & 1323 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₃H₁₆NO₂S [M+H]+; 238.0896, found 238.0894.

1-[[1-Phenylbut-3-en-1-yl]sulfonyl]-1,2,5,6-tetrahydropyridine (99)

1-(Benzylsulfonyl)-1,2,5,6-tetrahydropyridine (116 mg, 0.55 mmol, 1 eq) and allyl acetate (63 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A, to yield 1-[[1-phenylbut-3-en-1-yl]sulfonyl]-1,2,5,6-tetrahydropyridine (113 mg, 82 %) as an orange oil; Rf = 0.50 (95:5 Toluene:EtOAc); ¹H NMR (400 MHz CDCl₃) δ H 7.34-7.41 (5H, Ar-H); 5.68-5.71 (1H, m, 4-H); 5.52-5.58 (1H, m, 3'-H); 5.47-5.51 (1H, m, 5-H); 5.04 (1H, dd J 1.1 Hz 17.0 Hz, 4'-H); 4.95 (1H, d J 10.0 Hz, 4'-H); 4.11 (1H, dd J 4.1 Hz 11.0 Hz, 1'-H); 3.61 (1H, dt J 2.5 Hz 5.1 Hz, 6-H); 3.35-3.36 (1H, m, 6-H); 3.06-3.14 (2H, m, 2'-H, 3'-H); 2.87-2.95 (2H, m, 2'-H, 3'-H); 2.04-2.00 (1H, m, 2-H); 1.84-1.88 (1H, m, 2-H); ¹³C NMR (100 MHz) δ C 133.3 (3'-CH₂); 133.1 (1 x Ar-C); 129.7 (2 x Ar-CH); 128.8 (1 x Ar-CH₂); 128.7 (2 x Ar-CH); 125.2 (5-CH); 123.3 (4-CH); 118.2 (4'-CH₂); 67.8 (1'-CH); 44.7 (6-CH₂); 42.7 (3-CH₂); 34.3 (2'-CH₂); 25.6 (2'-CH₂); vmax (oil, cm⁻¹) 1144 & 1309 (sulfonamide S=O); 920 (mono-substituted alkene); m/z (ESI⁺) calculated for C₁₅H₁₄NO₂S [M+Na]+; 300.1029, found 300.1029.
1-(Benzylsulfonyl)pyrrolidine (97)

To an oven-dried 100 mL round bottom flask, pyrrolidine (1.1 mL, 13.3 mmol, 1 eq) and triethylamine (1.9 mL, 13.3 mmol, 1 eq) was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to −20 °C. To this, phenylethanesulfonyl chloride (2.53 g, 13.3 mmol, 1 eq) was slowly added over ten minutes at −20 °C. The reaction mixture was allowed to warm to room temperature and stir for six hours. Aqueous NH$_4$Cl (3 mL) was added to the reaction and extracted in CH$_2$Cl$_2$ (3 x 25 mL). The organic layer was washed with water (2 x 25 mL) and brine (25 mL) successively, dried over MgSO$_4$ and the solvent was evaporated to dryness to yield 1-(benzylsulfonyl)pyrrolidine as a colourless solid (1.84 g, 61 %); mp: 82 - 84 °C; $^1$H NMR (400 MHz) δ $^H$ 7.36 - 7.41 (5H, m, Ar-H); 4.26 (2H, s, 1-C$_2$H$_2$); 3.15 (4H, t $^J$ 6.7 Hz, (N-C$_2$H$_2$)$_2$); 1.80 (4H, dt $^J$ 3.5 Hz 6.7 Hz, (C$_2$H$_2$)$_2$); 13C NMR (100 MHz) σ $^C$ 137.3 (1 x Ar-C$_H$); 130.6 (2 x Ar-C$_H$); 128.7 (1 x Ar-C$_H$); 128.6 (2 x Ar-C$_H$); 56.5 (1-C$_2$H$_2$); 48.1 (N-(C$_2$H$_2$)$_2$); 25.9 (C$_2$H$_2$)$_2$ max (solid, cm$^{-1}$) 1139 & 1323 (sulfonamide S=O); m/z (ESI+) calculated for C$_{11}$H$_{15}$NO$_2$S [M+H]$^+$ 226.0896, found [M+H-SO$_2$]$^+$ 162.1272.

1-[(1-Phenylbut-3-en-1-yl)sulfonyl]pyrrolidine (99k)

1-(benzylsulfonyl)pyrrolidine (112 mg, 0.5 mmol) and allyl acetate (57 mg, 0.55 mmol) was reacted following general procedure A to yield 1-[(1-phenylbut-3-en-1-yl)sulfonyl]pyrrolidine as a colourless solid (109 mg, 83 %); R$_f$ = 0.48 (95:5 toluene:EtOAc); $^1$H NMR (400 MHz) δ $^H$ 7.35-7.41 (5H, m, Ar-H); 5.56 (1H, ddt $^J$ 7.0 Hz 10.0 Hz 140 Hz, 3-H); 5.06 (1H, dd $^J$ 1.3 Hz 17.0 Hz, 4-H); 4.97 (1H, dd $^J$ 10.0 Hz 1.3 Hz, 4-H); 4.18 (1H, dd $^J$ 4.0 Hz 11.2 Hz, 1-H); 3.14-3.32 (2H, m, 2'-C$_2$H$_2$); 3.10 (1H, m, 2-H); 2.94 (1H, m, 2'-H); 2.79-2.84 (2H, m, 2'-CH$_2$); 1.62-1.73 (4H, m, 3'-(CH$_2$)$_2$); $^{13}$C NMR (100 MHz) σ $^C$ 133.5 (3-C$_H$); 133.4 (1 x Ar-C$_H$); 129.7 (2 x Ar-C$_H$); 128.8 (1 x Ar-C$_H$); 128.6 (2 x Ar-C$_H$); 118.1 (4-C$_2$H$_2$); 67.1 (1'-C$_H$); 48.1 (2'-(CH$_2$)$_2$); 34.0 (2-C$_2$H$_2$); 25.8 (3'-CH$_2$)$_2$; V$_{max}$ (solid, cm$^{-1}$) 1107 & 1334 (sulfonamide S=O); m/z (ESI+) calculated for C$_{14}$H$_{19}$NO$_2$S [M+K]$^+$; 304.0768, found 304.0769.
To an oven dried 150 mL round bottom flash, phenylmethanesulfonyl chloride (5.0 g, 26 mmol, 1 eq) and N,N-dimethylhydroxylamine (3.06 g, 31 mmol, 1.2 eq) was dissolved in CH₂Cl₂ (70 mL) and cooled to 0 °C. To this, triethylamine (8.0 mL, 57 mmol, 2.2 eq) was slowly added with stirring. The reaction mixture was allowed to warm to room temperature and stir for overnight before washing with H₂O (2x 50 mL), dried over MgSO₄, filtered and the filtrate evaporated to dryness to give a yellow solid. The solid was purified by column chromatography (5:1 Hexane:EtOAc) to yield N-Methoxy-N-methyl-1-phenylmethanesulfonamide as a cream solid (3.0 g, 53 %); R_F = 0.33 (5:1 Hexane:EtOAc); mp: 73 - 77 °C; ¹H NMR (400 MHz, CDCl₃); 7.38 - 7.47 (5H, m, Ar-H); 4.37 (2H, s, 1-H₂); 3.84 (3H, s, O-CH₃); 2.98 (3H, s, N-CH₃); ¹³C NMR (100 MHz) δC 131.2 (2 x Ar-C₆H); 128.9 (3 x Ar-C₆H); 127.2 (Ar-C); 63.7 (O-CH₃); 50.6 (1-C₂H₂); 39.1 (N-CH₃); v_max (solid, cm⁻¹) 1339 & 1153 (sulfonamide S=O); m/z (ESI⁺) calculated for C₉H₁₃NO₃S [M+NH₄]⁺ 233.0954, found 233.0948.

N-Methoxy-N-methyl-4-phenylhepta-1,6-diene-4-sulfonamide (99l)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (109 mg, 0.5 mmol, 1 eq) and allyl acetate (57 mg, 0.5 mmol 1.1 eq) was reacted following general procedure A to yield N-Methoxy-N-methyl-4-phenylhepta-1,6-diene-4-sulfonamide as a yellow oil ( mg, 34 %); R_F = 0.6 (toluene:EtOAc 95:5); ¹H NMR (400 MHz, CDCl₃) δH 7.69-7.72 (2H, m, Ar-H); 7.35-7.42 (3H, m, Ar-H); 5.87 (2H, ddt, J 6.9 Hz 10.2 Hz 13.9 Hz, 2-H, 6-H); 5.20 (2H, dd, J 1.5 Hz 17 Hz, 1-Htrans, 7-Htrans); 5.15 (2H, dd J 1.5 Hz 10.2 Hz, 1-Hcis, 7-Hcis); 3.66 (3H, s, O-CH₃); 3.42 (2H, dd J 6.9 Hz 15 Hz, 3-H, 5-H); 3.18 (2H, dd J 6.9 Hz 15 Hz, 3-H, 5-H); 2.23 (3H, s, N-CH₃); ¹³C NMR (100 MHz) δC 134.5 (Ar-C); 132.1 (2-C₆H, 6-C₆H); 129.7 (2 x Ar-C₆H); 128.8 (Ar-C₆H); 128.3 (2 x Ar-C₆H); 119.5 (1-C₆H, 7-C₆H); 73.1 (4-C); 63.4 (O-CH₃); 38.7 (N-CH₃); 37.5 (3-C₂H₂, 5-C₂H₂); v_max (oil, cm⁻¹) 1334 & 1150 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₅H₂₁NO₅S [M+K]⁺ 334.0874, found 334.0875.
**N-Methoxy-N-1-phenylbut-3-ene-1-sulfonamide (100a)**

![Structure](image)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (108 mg, 0.5 mmol, 1 eq) and allyl acetate (57 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure B, to yield N-methoxy-N-1-phenylbut-3-ene-1-sulfonamide (73 mg, 57 %) as a colourless oil; Rf = 0.55 (Petrol:EtOAc 95:5); 1H NMR (400 MHz CDCl₃) δ H: 7.43-7.46 (2H, m, Ar-H); 7.33-7.37 (3H, m, Ar-H); 5.51 (1H, ddt J 6.9 Hz 10.1 Hz 14.0 Hz, 3-H); 5.04 (1H, dd J 1.3 Hz 17.0 Hz, 4-Ha); 4.97 (1H, bd J 10.1 Hz, 4-Hb); 4.62 (1H, dd J 3.9 Hz 11.5 Hz, 1-H); 3.74 (3H, s, O-CH₃); 3.10-3.18 (1H, m, 2-H); 2.88-2.96 (1H, m, 2-H); 2.53 (3H, s, N-CH₃); 13C NMR (100 MHz) δ C: 132.8 (3-C); 132.2 (1 x Ar-C); 130.2 (2 x Ar-CH); 129.0 (1 x Ar-CH); 128.7 (2 x Ar-CH); 118.6 (4-CH₂); 63.7 (1-C); 63.5 (O-CH₃); 38.9 (N-CH₃); 34.5 (2-CH₂); v̇max (oil, cm⁻¹) 1341 & 1145 (sulfonamide S=O); m/z (ESI⁻) calculated for C₁₂H₁₇NO₃S [M+Na]⁻: 278.0821, found 278.0822.

**(E)-N-Methoxy-N-methyl-1-phenylpent-3-ene-1-sulfonamide (100b)**

![Structure](image)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (109 mg, 0.5 mmol) and crotyl acetate (63 mg, 0.55 mmol) was reacted following the general procedure B to yield N-methoxy-N-1-phenylbut-3-ene-1-sulfonamide (73 mg, 57 %) as a colourless oil; Rf = 0.5 (Petrol:EtOAc 95:5); 1H NMR (400 MHz CDCl₃) δ H: 7.33-7.48 (5H, m, Ar-H); 5.48 (1H, dt J 6.5 Hz 13 Hz, 4-H); 5.03-5.16 (1H, m, 3-H); 4.57 (1H, dd J 3.8 Hz 11.4 Hz, 1-H); 3.74 (3H, m, O-CH₃); 3.03-3.13 (1H, m, 2-H); 2.82-2.97 (1H, m, 2-H); 2.53 (3H, s, N-CH₃); 1.52-1.56 (3H, m, 5-H₃); 13C NMR (100 MHz) δ C: 132.4 (1 x Ar-C); 130.2 (2 x Ar-CH); 129.3 (4-CH); 129.1 (1 x Ar-CH); 128.6 (2 x Ar-CH); 125.1 (3-C); 64.2 (1-C); 63.5 (O-CH₃); 38.7 (N-CH₃); 33.4 (2-CH₂); 17.9 (5-CH₃); m/z (ESI⁻) calculated for C₁₃H₁₉NO₃S [M+Na]⁻: 292.0978, found 292.0978.

**(E)-N-Methoxy-N-methyl-1-phenylhept-3-ene-1-sulfonamide (100c)**

![Structure](image)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (109 mg, 0.5 mmol, 1 eq) and (E)-2-hexenyl acetate (78 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure B to yield N-methoxy-N-1-phenylbut-3-ene-1-sulfonamide (73 mg, 57 %) as a colourless oil; Rf = 0.6 (Petrol:EtOAc 95:5); 1H NMR (400 MHz...
(E)-N-Methoxy-N,4,8-trimethyl-1-phenylnona-3,7-diene-1-sulfonamide (100d)

\[
\begin{align*}
\text{N-Methoxy-N-methyl-1-phenylmethanesulfonamide (109 mg, 0.5 mmol, 1 eq) and neryl acetate (108 mg, 0.55 mmol, 1.1 eq) were reacted following the general procedure B to yield (E)-N-methoxy-N,4,8-trimethyl-1-phenylnona-3,7-diene-1-sulfonamide as a yellow oil (118 mg, 67 %); R_f = 0.45 (Petrol:EtOAc 95:5); } \\
\text{1H NMR (400 MHz CCl}_4) \delta 7.43-7.46 (2H, m, Ar-H); 7.34-7.36 (3H, m, Ar-H); 5.06-5.07 (1H, m, 7-H); 4.83 (1H, app t J 6.9 Hz, 3-H); 4.51 (1H, dd J 3.8 Hz 11.6 Hz, 1-H); 3.74 (3H, s, O-CH}_3; 3.09-3.15 (1H, m, 2-H); 2.83-2.89 (1H, m, 2-H); 2.53 (3H, s, N-CH}_3; 1.92-2.04 (4H, m, 5-H, 6-H); 1.70 (3H, s, 8-CH}_3; 1.57 (3H, s, 4-CH}_3; 1^3C NMR (100 MHz) \delta_c 139.0 (1 x Ar-C); 132.6 (4-C); 131.9 (8-C); 130.2 (2 x Ar-C); 128.9 (1x Ar-C); 128.6 (2 x Ar-C); 123.9 (7-C); 119.0 (3-C); 64.3 (1-C); 63.4 (O-CH}_3; 38.9 (N-CH}_3; 32.0 (5-C); 28.6 (2-C); 26.3 (6-C); 25.7 (8-C); 23.3 (4-C); 17.7 (8-C); \nu_{max} (oil, cm^{-1}) 1334 & 1143 (S=O); m/z (ESI\(^+\)) calculated for C_{19}H_{29}NO_3S [M+Na\(^+\)] \approx 369.2206, found 369.2199.
\end{align*}
\]

1-(Cyclohex-2-en-1-yl)-N-methoxy-N-methyl-1-phenylmethanesulfonamide (100e)

\[
\begin{align*}
\text{N-Methoxy-N-methyl-1-phenylmethanesulfonamide (109 mg, 0.5 mmol, 1 eq) and cyclohex-2-en-1yl acetate (147 mg, 0.5 mmol, 1 eq) was reacted following the general procedure B to yield 1-(Cyclohex-2-en-1-yl)-N-methoxy-N-methyl-1-phenylmethanesulfonamide (d.r 62:38 determined by 1H NMR) (44 mg, 30 %); R_f = 0.6 (toluene:EtOAc 95:5); } \\
\text{1H NMR (400 MHz CCl}_4) \delta 7.34-7.48 (5H, m, Ar-H); 5.76 (2H, app bs, 2-H, 3-H); 4.56 (1H, d J 6.7 Hz, 1-H); 3.73 (3H, s, O-CH}_3; 3.31-3.34 (1H, m, 1-H); 2.39 (3H, s, N-CH}_3; 1.89-1.99 (2H, m, 4-H, 6-H); 1.47-1.88 (3H, m, 4-H, 5-H); 1.36-1.45 (1H, m, 6-H); 1^3C NMR (100 MHz) \delta_c 131.9 (1 x Ar-C); 130.7 (2 x Ar-C); 130.3 (3-C); 129.3 (1 x Ar-C); 128.9 (2 x Ar-C); 126.5 (2-C); 67.8 (1-C); 63.6 (O-}
\end{align*}
\]
N-Methoxy-N,3-dimethyl-1-phenylbut-3-ene-1-sulfonamide (100f)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (108 mg, 0.5 mmol, 1 eq) and 2-methyl allyl acetate (63 mg, 0.5 mmol, 1 eq) was reacted following the general procedure B to yield N-Methoxy-N,3-dimethyl-1-phenylbut-3-ene-1-sulfonamide as a yellow oil (91 mg, 67 %); Rf = 0.58 (Petrol:EtOAc 95:5); 1H NMR (400 MHz CDCl3) δH 7.44-7.46 (2H, m, Ar-H); 7.34-7.36 (3H, m, Ar-H); 4.79 (1H, dd J 3.5 Hz 12.2 Hz, 1-H); 4.67 (1H, d J 1.1 Hz, 3'-'H); 4.61 (1H, app s, 3'-'H); 3.76 (3H, O-CH3); 3.09 (1H, dd J 3.5 Hz 14 Hz, 2-H); 2.92 (1H, dd J 12.2 Hz 14 Hz, 2-H); 2.52 (3H, s, N-CH3); 1.62 (3H, s, 4-CH2); 13C NMR (100 MHz) δc 139.8 (3-CH); 132.2 (1 x Ar-C); 130.2 (Ar-CH); 129.0 (Ar-CH); 128.6 (Ar-CH); 114.7 (3'-CH2); 63.5 (O-CH3); 62.7 (1-CH); 38.9 (N-CH3); 37.8 (2-CH2); 22.2 (4-CH2); m/z (ESI+) calculated for C13H19NO3S [M+Na]+; 292.0978, found 292.0981.

(E)-N-Methoxy-N-methyl-1,4-diphenylbut-3-ene-1-sulfonamide (100g)

N-Methoxy-N-methyl-1-phenylmethanesulfonamide (108 mg, 0.5 mmol) and cinnamyl acetate (88mg, 0.5 mmol, 1 eq) was reacted following the general procedure B to yield (E)-N-methoxy-N-methyl-1,4-diphenylbut-3-ene-1-sulfonamide as a yellow oil (98 mg, 60 %); 1H NMR (400 MHz CDCl3) δH 7.19-7.50 (10H, m, Ar-H); 6.43 (1H, d J 15.7 Hz, 4-H); 5.91 (1H, dt J 7.3 Hz 15.7 Hz, 3-H); 4.71 (1H, dd J 3.8 Hz 11.2 Hz, 1-H); 3.77 (3H, s, O-CH3); 3.27-3.34 (1H, m, 2-H); 3.06-3.14 (1H, m, 2-H); 2.56 (3H, s, N-CH3); 13C NMR (100 MHz) δc 136.9 (1 x Ar-C); 133.6 (4-CH); 132.2 (1 x Ar-C); 130.2 (2 x Ar-CH); 129.2 (1 x Ar-C); 128.8 (2 x Ar-CH); 128.4 (2 x Ar-CH); 127.4 (1 x Ar-CH); 126.2 (2 x Ar-CH); 124.3 (3-CH); 63.9 (O-CH3); 63.5 (1-CH); 38.9 (N-CH3); 33.9 (2-CH2); m/z (ESI+) calculated for C18H21NO3S [M+Na]+; 354.1134, found 354.1141.
**N-Methyl-1-phenylmethanesulfonamide (101)**

Methylamine solution (5.25 mL, 2M, 10.5 mmol, 1 eq) was added slowly to a solution of phenylmethanesulfonyl chloride (2.0 g, 10.5 mmol, 1 eq) and triethylamine (1 mL, 10.5 mmol, 1 eq) in CH₂Cl₂ (50 mL) at 0 °C. The reaction was allowed to warm to room temperature and left for overnight. The organic layer was subsequently extracted from the aqueous, washing the organic layer with water (3 x 50 mL). The organic extracts were combined, dried over MgSO₄ and evaporated to dryness to yield N-Methyl-1-phenylmethanesulfonamide as a colourless solid (980 mg, 50 %); ¹H NMR (400 MHz CDCl₃) δ= 7.39-7.40 (5H, m, Ar-H); 4.26 (2H, s, 2'-H₂); 4.00 (1H, bs, N-H); 2.71 (3H, s, N-CH₃); ¹³C NMR (100 MHz) δ= 130.5 (2 x Ar-C=H); 129.4 (1 x Ar-CH); 128.9 (1 x Ar-CH); 128.3 (1 x Ar-CH); 128.7 (2 x Ar-CH₂); 29.8 (N-CH₃); νmax (solid, cm⁻¹) 3289 (broad, N-H) 1298 & 1090 (sulfonamide S=O); m/z (ESI⁺) calculated for C₈H₁₁NO₂S [M+Na]+ 208.0403, found 208.0404.

**N-Allyl-N-methyl-1-phenylbut-3-ene-1-sulfonamide (102)**

N-Methyl-1-phenylmethanesulfonamide (516 mg, 2.8 mmol, 1 eq) and allyl acetate (600 mg, 5.6 mmol, 2 eq) was reacted following general procedure A to yield N-Allyl-N-methyl-1-phenylbut-3-ene-1-sulfonamide as a yellow oil (690 mg, 93 %); Rf = 0.3 (petrol:EtOAc 9:1); ¹H NMR (400 MHz CDCl₃) δ= 7.36-7.41 (5H, m, Ar-H); 5.48-5.59 (2H, m, 3-H, 3'-H); 5.10-5.13 (2H, m, 4'-H₂); 4.95-5.10 (2H, m, 4-H₂); 4.12 (1H, dd J 4.10 Hz 11.2 Hz, 1-H); 3.45 (1H, dd J 6.2 Hz 15.2 Hz, 2'-H); 3.22-3.25 (1H, m, 2'-H); 3.06-3.13 (1H, m, 2-H); 2.88-2.96 (1H, m, 2-H); 2.51 (3H, s, 1'-CH₃); ¹³C NMR (100 MHz) δ= 133.3 (3'-CH); 133.2 (3'-CH); 129.7 (2 x Ar-CH); 128.9 (Ar-CH); 128.7 (2 x Ar-CH₂); 118.5 (4'-CH₂); 118.2 (4'-CH₂); 67.7 (1'-CH); 53.0 (2'-CH₂); 34.3 (2'-CH₂, 1'-CH₃); m/z (ESI⁺) calculated for C₁₄H₁₉NO₂S [M+Na]+ 288.1029, found 288.1020.

**2-Methyl-7-phenyl-2,3,6,7-tetrahydro-1,2-thiazepene 1,1-dioxide (103)**

To an oven dried 10 mL round bottom flask, N-allyl-N-methyl-1-phenylbut-3-ene-1-sulfonamide (44 mg, 0.17 mmol) was added to a solution of Grubbs 2nd generation catalyst (7 mg, 0.09 mmol, 0.05 eq) in CH₂Cl₂ (5 mL).
The reaction was allowed to stir at room temperature for 16 hours, after which the reaction mixture was evaporated to dryness. The crude mixture was purified by column chromatography to yield 2-Methyl-7-phenyl-2,3,6,7-tetrahydro-1,2-thiazepene 1,1-dioxide (40 mg, 55 %); R<sub>f</sub> = 0.5 (petrol:EtOAc 9:1); <sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ<sub>H</sub> 7.33-7.42 (5H, m, Ar-H); 6.17-6.23 (1H, m, 4-H); 6.00-6.07 (1H, m, 5-H); 4.28 (1H, dd J 5.2 Hz 16.3 Hz, 3-H); 3.90 (1H, dd J 1.2 Hz 12 Hz, 7-H); 3.53 (1H, dd J 6.6 Hz 16.3 Hz, 3-H); 3.11-3.19 (1H, m, 6-H); 2.89 (3H, s, 2-CH<sub>3</sub>); 2.59 (1H, ddd J 1.2 Hz 9.0 Hz 10.2 Hz, 6-H); <sup>13</sup>C NMR (100 MHz) δ<sub>C</sub> 133.9 (Ar-C); 132.9 (4-C); 130.0 (5-C); 129.4 (2 x Ar-C); 128.7 (2 x Ar-C); 128.5 (Ar-C); 63.2 (7-C); 35.2 (2-CH<sub>3</sub>); 29.8 (6-CH<sub>2</sub>); m/z (ESI<sup>+</sup>) calculated for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>S [M+NH<sub>4</sub>]<sup>+</sup> 255.1162, found 255.1162.

1-(3-Fluorobenzyl)piperazine<sup>168</sup>

3-Fluorobenzyl bromide (1.23 mL) was reacted following general procedure C.1 to yield tert-butyl 4(3-fluorobenzyl)piperazine-1-carboxylate as an orange oil (1.43 g, 74 %); <sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ<sub>H</sub> 7.24-7.30 (1H, m, Ar-H); 7.05-7.09 (2H, m, Ar-H); 6.95 (1H, td J<sub>HF</sub> 2.0 Hz 8.3 Hz, 2-H); 3.49 (2H, s, 1'-CH<sub>2</sub>); 3.43 (4H, t J 4.8 Hz, N-(CH<sub>2</sub>)<sub>2</sub>); 2.38 (4H, t J 4.8 Hz, N-(CH<sub>2</sub>)<sub>2</sub>); 1.45 (9H, s, C-(CH<sub>3</sub>)<sub>3</sub>).

Tert-butyl 4(3-fluorobenzyl)piperazine-1-carboxylate (1.43 g, 4.8 mmol) was reacted following general procedure C.2 to yield 1-(3-fluorobenzyl)piperazine as an orange solid (0.93 g, 65 %); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.07-7.13 (1H, Ar-H); 6.39-6.95 (2H, m, Ar-H); 6.78 (1H, td J 1.6 Hz 8.3 Hz, 2-H); 3.32 (2H, s, 1'-H<sub>2</sub>); 2.73 (4H, t J 4.8 Hz, N-(CH<sub>2</sub>)<sub>2</sub>); 2.26 (4H, bs, N-(CH<sub>2</sub>)<sub>2</sub>); 2.03 (1H, bs, NH).
1-(4-Methoxybenzyl)piperazine$^{168}$

![Chemical Structure](attachment:image1.png)

4-Methoxybenzyl chloride (1.35 mL) was reacted following general procedure C.1 to yield tert-butyl 4-(4-methoxybenzyl)piperazine-1-carboxylate as a yellow oil (1.64 g, 82 %); $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.22 (2H, app d J 8.5 Hz, Ar-H); 6.85 (2H, app d J 8.5 Hz, Ar-H); 3.80 (3H, s, O-C$_3$H$_3$); 3.45 (2H, s, 1'-H$_2$); 3.40-3.43 (4H, m, N-(C$_2$H$_5$)$_2$); 2.35-2.38 (N-(C$_2$H$_5$)$_2$); 1.45 (9H, s, C-(C$_3$H$_3$)$_3$).

Tert-butyl 4-(4-methoxybenzyl)piperazine-1-carboxylate (1.5 g, 8.1 mmol) was reacted following general procedure C.2 to yield 1-(4-methoxybenzyl)piperazine as a yellow oil (0.84 g, 50 %); $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.23 (2H, app d J 8.5 Hz, Ar-H); 6.85 (2H, app d J 8.5 Hz, Ar-H); 3.80 (3H, s, O-C$_3$H$_3$); 3.43 (2H, s, 1'-H$_2$); 2.88 (4H, t J 4.9 Hz, N-(C$_2$H$_5$)$_2$); 2.39 (4H, bs, N-(C$_2$H$_5$)$_2$); 1.72 (1H, bs, NH).

1-(3-Methylbenzyl)piperazine$^{168}$

![Chemical Structure](attachment:image2.png)

3-Methylbenzyl bromide (1.35 mL) was reacted following general procedure C.1 to yield tert-butyl 4-(3-methylbenzyl)piperazine-1-carboxylate as a yellow oil (1.48 g, 77 %); $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.19-7.23 (1H, m, Ar-H); 7.06-7.13 (3H, m, Ar-H); 3.47 (2H, s, 1'-H$_2$); 3.43 (4H, t J 4.9 Hz, N-(C$_2$H$_5$)$_2$); 2.38 (4H, t J 4.9 Hz, N-(C$_2$H$_5$)$_2$); 2.34 (3H, s, Ar-C$_3$H$_3$); 1.45 (9H, s, C-(C$_3$H$_3$)$_3$).

4-(3-Methylbenzyl)piperazine-1-carboxylate (1.48 g, 5.1 mmol) was reacted following general procedure C.2 to yield 1-(3-methylbenzyl)piperazine as a colourless solid (0.97 g, 77 %); $^1$H NMR (400 MHz CDCl$_3$) $\delta$H 7.20 (1H, t J 7.5 Hz, Ar$_{ortho}$-H); 7.05-7.14 (3H, m, Ar-H); 3.45 (2H, s, 1'-H$_2$); 2.89 (4H, t J 4.9 Hz, N-(C$_2$H$_5$)$_2$); 2.41 (2H, bs, N-H, N-(C$_2$H$_5$)$_2$); 2.34 (3H, s, Ar-C$_3$H$_3$); 2.19 (2H, bs, N-(C$_2$H$_5$)$_2$).
1-Benzyl-4-(benzylsulfonfonyl)piperazine (64a)

1-benzylpiperazine (1 g, 5.7 mmol, 1 eq) was reacted following general procedure D to yield 1-benzyl-4-(benzylsulfonfonyl)piperazine as a colourless solid (1.45 g, 77 %); mp: 125 - 129 °C; 1H NMR (400 MHz CDCl₃) δH 7.36-7.40 (5H, m, Ar-H); 7.26-7.32 (5H, m, Ph-H); 4.20 (2H, s, 1-H₂); 3.49 (2H, s, 4'-H₂); 3.15 (4H, t J 4.7 Hz, 2'-H₂); 2.41 (4H, t J 4.7 Hz, 3'-H₂); 13C NMR (100 MHz) δC 137.4 (1 x Ar-C); 131.6 (1 x Ar-C); 130.8 (2 x Ar-CH); 129.1 (2 x Ar-CH); 128.8 (2 x Ar-CH); 128.7 (1 x Ar-CH); 128.3 (2 x Ar-CH); 127.3 (1 x Ar-CH); 62.7 (4'-CH₂); 56.7 (1'-CH₂); 52.7 (2'-(CH₂)₂); 46.0 (3'-(CH₂)₂); νmax (solid, cm⁻¹) 1147 & 1340 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₈H₂₆N₂O₂S [M+H]⁺: 331.1475, found 331.1476.

1-Benzyl-4-[[1-phenylbut-3-en-1-yl]sulfonfonyl]piperazine (104a)

1-Benzyl-4-(benzylsulfonfonyl)piperazine (165 mg, 0.5 mmol, 1 eq) and allyl acetate (57 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A, to yield 1-benzyl-4-[[1-phenylbut-3-en-1-yl]sulfonfonyl]piperazine (141 mg, 76 %) as a colourless solid; Rf = 0.45; mp: 74 - 78 °C; 1H NMR (400 MHz) δH 7.36-7.39 (5H, m, Ar-H); 7.23-7.31 (5H, m, Ar-H); 5.53 (1H, ddt J 7.0 Hz 10.0 Hz 14.0 Hz, 3'-H); 4.96 (1H, d J 10.2 Hz, 4'-H₂); 4.07 (1H, dd J 4.0 Hz 11.2 Hz, 1'-H); 3.44 (2H, bs, 1-H₂); 3.05-3.13 (3H, m, 2'-H,3-H₂); 2.85-2.94 (3H, m, 2'-H,3-H₂); 2.22-2.36 (4H, m, 2'-H₂); 13C NMR (100 MHz) δC 137.4 (1 x Ar-C); 133.2 (3'-CH); 132.9 (1 x Ar-C); 129.8 (2 x Ar-CH); 129.1 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.7 (2 x Ar-CH); 128.3 (2 x Ar-CH); 127.3 (1 x Ar-CH); 118.2 (4'-CH₂); 68.0 (1'-CH); 62.7 (1'-CH₂); 52.9 (2'-CH₂); 46.0 (3'-CH₂); νmax (solid, cm⁻¹) 1147 & 1340 (sulfonamide S=O); 959 (mono-substituted alkene); m/z (ESI⁺) calculated for C₂₁H₂₆N₂O₂S [M+H]⁺: 371.1788, found 371.1799.

(E)-1-Benzyl-4-[[1-phenylhept-3-en-1-yl]sulfonfonyl]piperazine (104b)

1-Benzyl-4-(benzylsulfonfonyl)piperazine³ (165 mg, 0.5 mmol) and E-2-hexenyl acetate acetate (60 mg, 0.55 mmol) was reacted following the general method, to yield (E)-1-Benzyl-4-[[1-phenylhept-3-en-1-
1-(Benzylsulfonyl)-4-(3-fluorobenzyl)piperazine\(^{26}\) (64b)

Fluorobenzyl)piperazine (0.42 g, 2.1 mmol, 1 eq) was reacted following general procedure D to yield 1-(benzylsulfonyl)-4-(3-fluorobenzyl)piperazine as a colourless solid (0.60 g, 90 %); mp: 125 - 129 °C; 7.36-7.39 (5H, m, Ph-H); 7.25-7.30 (1H, m, Ar-H); 7.03-7.07 (2H, m, Ar-H); 6.94-6.99 (1H, m, Ar-H); 4.19 (2H, s, Ph-H); 3.54 (2H, s, 4-H); 3.17-3.19 (4H, m, N-(CH\(_2\))\(_2\)); 2.46 (4H, bs, N-(CH\(_2\))\(_2\)); \(^{13}\)C NMR (100 MHz) \(\delta_\text{C} 162.9 (3'\text{-CF}, d J_{CF} 246 Hz); 130.8 (2 x Ph-OH); 130.0 (5'\text{-CH}, d J_{CF} 8.2 Hz); 128.9 (2 x Ph-OH); 128.8 (1 x Ph-H); 128.6 (Ph-O); 124.9 (6'\text{-CH}, 1'\text{-Q}); 116.0 (2'\text{-CH}, d J_{CF} 21.5 Hz); 114.6 (4'\text{-CH}, d J_{CF} 21.5 Hz); 61.7 (4'\text{-CH}); 56.8 (Ph-OH); 52.5 (N-(CH\(_2\))\(_2\)); 45.6 (N-(CH\(_2\))\(_2\)); \(v_{\text{max}}\) (solid, cm\(^{-1}\)) 1317 & 1155 (sulfonamide S=O); \(m/z\) (ESI\(^{+}\)) calculated for C\(_{19}\)H\(_{21}\)FN\(_2\)O\(_2\)S [M+H]\(^{+}\); 349.1381, found 349.1381.

1-(3-Fluorobenzyl)-4-[[1-phenylbut-3-en-1-yl]sulfonyl]piperazine (104c)

1-(Benzylsulfonyl)-4-(3-fluorobenzyl)piperazine (174 mg, 0.5 mmol) and allyl acetate (60 mg, 0.55 mmol) was reacted following the general procedure A to yield 1-(3-fluorobenzyl)-4-[[1-phenylbut-3-en-1-yl]sulfonyl]piperazine (130 mg, 67 %) as an orange oil; \(R_f = 0.20\) (95:5 toluene:EtOAC); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_\text{H} 7.38-7.39 (5H, m, Ph-H); 7.17-7.27 (1H, m, Ar-H); 6.91-7.00 (3H, m, Ar-H); 5.54 (1H, ddt J 7.0 Hz 9.9 Hz 17.0 Hz 3'-H); 5.0 (1H, d J 17 Hz, 4'-H); 4.96 (1H, d J 10.0 Hz, 4'-H); 4.08 (1H, dd J 3.9 Hz 11.0 Hz, 1'-H); 3.47 (2H, s, 1'-H); 3.06-3.16 (3H, m, 2'-H, N-CH\(_2\)); 2.86-2.94 (2H, m, 2'-CH, N-CH\(_2\)); 2.22-2.40 (4H, m, N-(CH\(_2\))\(_2\)); \(^{13}\)C NMR (100 MHz) \(\delta_\text{C} 164.1 (3''\text{-CF}, d J_{CF} 248 Hz); 161.7 (1 x Ph-C); 140.3 (4''\text{-CH}, d J_{CF} 6.7 Hz);
133.2 (2 x Ph-CH); 130.8 (1 x Ph-C); 129.0 (1 x Ph-CH); 128.7 (2 x Ph-CH); 124.5 (6''-CH, d JCF 2.7 Hz); 118.3
(4''-CH); 115.7 (2''-CH, d JCF 21.2); 114.3 (4''-CH, d JCF 21.2); 68.1 (1''-CH); 62.1 (1''-CH); 52.9 (N-(CH2)2); 45.9
(N-(CH2)2); 34.2 (2''-CH2); vmax (oil, cm⁻¹) 1486 (C-F); 1340 & 1140 (sulfonamide S=O); m/z (ESI⁺) calculated
for C21H22FN2O2S [M+H⁺]; 389.1694, found 389.1695.

1-(Benzylsulfonyl)-4-(3-methylbenzyl)piperazine¹²¹ (64d)

1-(3-methylbenzyl)piperazine (0.80 g, 4.2 mmol, 1 eq) was reacted following general procedure D to yield 1-
(benzylsulfonyl)-4-(3-methylbenzyl)piperazine (1.40 g, 57 %) as a yellow oil; ¹H NMR (400 MHz CDCl₃) δH
7.37-7.43 (5H, m, Ph-H); 7.20-7.28 (1H, m, Ar-H); 7.09-7.13 (2H, m, Ar-H); 4.02 (2H, s, Ph-H2); 3.48 (2H, s, 4-
H2); 3.18 (4H, t J 4.4 Hz, N-(CH2)2); 2.42-2.45 (4H, m, N-(CH2)2); 2.36 (3H, bs, 3'-H3); ¹³C NMR (100 MHz) δC
138.0 (1''-C); 130.8 (2 x Ph-CH); 130.0 (2 x Ar-CH); 128.8 (2 x Ph-CH); 128.7 (1 x Ph-CH); 128.3 (3''-C); 128.2
(2 x Ar-CH); 126.5 (Ph-C); 126.4 (1 x Ar-CH); 62.6 (4-CH2); 56.6 (Ph-CH2); 52.7 (N-(CH2)2); 45.9 (N-(CH2)2); 21.4
(3''-CH3); m/z (ESI⁺) calculated for C19H₂₄N₂O₂S [M+H⁺]; 345.1631, found 345.1635.

1-(3-Methylbenzyl)-4-((1-phenylbut-3-en-1-yl)sulfonyl)piperazine (104g)

1-(Benzylsulfonyl)-4-(3-fluorobenzyl)piperazine (174 mg, 0.5 mmol, 1 eq) and allyl acetate (60 mg, 0.55 mmol,
1.1 eq) was reacted following the general procedure A to yield 1-(3-methylbenzyl)-4-((1-phenylbut-3-en-1-
yl)sulfonyl)piperazine (100 mg, 53 %) as an orange oil; Rf = 0.35 (CH₂Cl₂:EtOAc 95:5); ¹H NMR (400 MHz
CDCl₃) δH 7.36-7.39 (5H, m, Ar-H); 7.20 (1H, t J 7.4 Hz, 3''-H); 7.04-7.09 (3H, m, Ar-H); 5.54 (1H, ddt J 7.0 Hz
10.0 Hz 13.9 Hz, 3''-H); 5.05 (1H, dd J 1.2 Hz 17.0 Hz, 4''-H); 4.96 (1H, bd J 10.5 Hz, 4''-H); 4.07 (1H, dd J 3.9
Hz 11.2 Hz, 1''-H); 3.40 (2H, s, 1-H2); 3.05-3.12 (3H, m, 2''-H, N-H2); 2.85-2.93 (3H, m, 2-H, N-H2); 2.32-2.35
(5H, s, Ar-CH3, N-H2); 2.23-2.28 (2H, m, N-H₂); ¹³C NMR (100 MHz) δC 137.9 (1''-C); 137.2 (3''-C); 133.2 (3-
CH); 129.9 (1 x Ar-CH); 129.7 (Ph-CH); 128.9 (Ph-CH); 128.7 (Ph-CH); 128.1 (1 x Ar-CH); 128.0 (1 x Ar-CH);
126.3 (1 x Ar-CH); 118.2 (4-CH2); 68.1 (1-CH); 62.7 (Ar-CH2); 52.9 (N-(CH2)2); 45.9 (N-(CH2)2); 34.2 (2-CH2);
21.4 (Ar-CH3); vmax (oil, cm⁻¹) 1341 & 1145 (sulfonamide S=O); m/z (ESI⁺) calculated for C₂₂H₂₈N₂O₂S [M+H⁺];
385.1944, found 385.1943.
1-(Benzylsulfonyl)-4-(4-methoxybenzyl)piperazine (1\textsuperscript{21}) (64c)

4-(methoxybenzyl)piperazine (0.62 g, 3.72 mmol, 1 eq) was reacted following general procedure D to yield 1-(benzylsulfonyl)-4-(4-methoxybenzyl)piperazine (0.81 g, 75\%) as a colourless solid; m.p: 122 – 125 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta t 7.34-7.39\) (5H, m, Ph-\(\text{H}\)); 7.19 (2H, app d \(J 8.4\) Hz, Ar-\(\text{H}\)); 6.85 (2H, app d \(J 8.4\) Hz, Ar-\(\text{H}\)); 4.18 (2H, s, Ph-\(\text{H}\)); 3.78 (3H, s, O-\(\text{C}\)-\(\text{H}\)_3)); 3.43 (2H, s, 4-\(\text{H}\)_2)); 3.14 (4H, t \(J 4.3\) Hz, N-(\(\text{CH}_2\)_2)); 2.39 (4H, t \(J 4.3\) Hz, N-(\(\text{CH}_2\)_2)); \(^13\)C NMR (100 MHz) \(\delta c 158.9\) (4'-\(\text{C}\)); 130.8 (2 x Ph-\(\text{C}\)_H)); 130.4 (2 x Ar-\(\text{C}\)_H)); 128.8 (2 x Ph-\(\text{C}\)_H)); 62.0 (4-\(\text{C}\)-\(\text{H}\)_2)); 56.5 (Ph-\(\text{C}\)_H)); 55.3 (O-\(\text{C}\)-\(\text{H}\)_3)); 52.6 (N-(\(\text{C}\)-\(\text{H}\)_2)); 45.9 (N-(\(\text{C}\)-\(\text{H}\)_2)); \(m/z\) (ESI\(^{+}\)) calculated for C\(_{19}\)H\(_{24}\)NO\(_3\)S [M+H]\(^{+}\) 361.1580, found 361.1567.

1-(4-Methoxybenzyl)-4-[(1-phenylbut-3-en-1-yl)sulfonyl]piperazine (104h)

1-(Benzylsulfonyl)-4-(4-methoxybenzyl)piperazine (180 mg, 0.5 mmol, 1 eq) and allyl acetate (58 mg, 0.55 mmol, 1.1 eq) was reacted following the general procedure A to yield 1-(4-Methoxybenzyl)-4-[(1-phenylbut-3-en-1-yl)sulfonyl]piperazine (71 mg, 37\%) as an orange oil; \(R_f = 0.25\) (CH\(_2\)_Cl\(_2\):MeOH 98:2); \(^1\)H NMR (400 MHz) \(\delta t 7.34-7.43\) (5H, m, Ph-\(\text{H}\)); 7.13 (2H, app d \(J 8.6\) Hz, Ar-\(\text{H}\)); 6.83 (2H, dd \(J 1.9\) Hz 6.7 Hz, Ar-\(\text{H}\)); 5.52 (1H, ddt \(J 7.1\)Hz 10.0 Hz 13.9 Hz, 3'-\(\text{H}\)); 5.02 (1H, dd \(J 1.7\) Hz 17.1 Hz, 4'-\(\text{H}\)); 4.96 (1H, dd \(J 1.2\) Hz 10.4 Hz, 4'-\(\text{H}\)); 3.78 (3H, s, -O\(\text{C}\)-\(\text{H}\)_3)); 3.36 (2H, s, 1-\(\text{H}\)_2)); 3.03-3.14 (2H, m, 2'-\(\text{H}\), 3'-\(\text{H}\)); 2.84-2.92 (2H, m, 2'-\(\text{H}\), 3'-\(\text{H}\)); 2.19-2.32 (4H, m, 2-(\(\text{H}\)_2)); \(^13\)C NMR (100 MHz) \(\delta c 158.8\) (O-\(\text{O}\)-\(\text{Me}\)); 133.2 (3'-\(\text{CH}\)); 132.9 (1 x Ph-\(\text{Q}\)); 130.3 (2 x Ar-\(\text{Q}\)); 129.7 (2 x Ph-\(\text{Q}\)); 129.4 (1 x Ar-\(\text{Q}\)); 128.9 (2 x Ph-\(\text{Q}\)); 128.7 (1 x Ph-\(\text{Q}\)); 118.2 (4'-\(\text{CH}\)_2)); 113.5 (2 x Ar-\(\text{Q}\)); 68.0 (1'-\(\text{CH}\)); 62.1 (1'-\(\text{CH}\)); 55.3 (-O\(\text{C}\)-\(\text{H}\)_3)); 52.7 (2-(\(\text{CH}\)_2)); 46.0 (2-(\(\text{CH}\)_2)); 34.5 (2'-\(\text{CH}\)); \(\nu_{max}\) (oil, \(cm^{-1}\)) 1339 & 1150 (sulfonamide S=O).
Synthesis of 6-Oxabicyclo[3.2.1]oct-3-en-6-one\textsuperscript{69} (5)

To an oven dried 500 mL round bottom flask, 3-cyclohexene carboxylic acid (15.3 g, 121 mmol, 1 eq) and NaHCO\textsubscript{3} (30.2 g, 363 mmol, 3 eq) was added to H\textsubscript{2}O (100 mL) and stirred until homogenous and protected from light. After 20 minutes potassium iodide (120 g, 724 mmol, 6 eq) and iodine (32.1 g, 127 mmol, 1.05 eq) in H\textsubscript{2}O (300 mL) was added to the mixture in one portion. The reaction was allowed to stir at room temperature for overnight, after which the mixture was extracted with CHCl\textsubscript{3} (3 x 500 mL), washed with 10 % Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (500 mL), 10 % NaHCO\textsubscript{3} (500 mL) and water (300 mL). The organic extracts were combined, dried over MgSO\textsubscript{4}, filtered and the filtrate was concentrated in vacuo to yield 4-iodo-6-oxabicyclo[3.2.1]octan-7-one (5) as a beige solid (28.4 g, 94 %). The product was used without further purification in the next step.

To an oven dried 500 mL round bottom flask, 4-iodo-6-oxabicyclo[3.2.1]octan-7-one (22.5 g, 90 mmol, 1 eq) and DBU (20.1 mL, 135 mmol, 1.5 eq) was dissolved in dry benzene (250 mL). The reaction mixture was then heated to reflux for 16 hours, after which the mixture was cooled, filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by column chromatography (CH\textsubscript{2}Cl\textsubscript{2}) to yield 6-oxabicyclo[3.2.1]oct-3-en-6-one as a colourless oil (8.7 g, 78 %); R\textsubscript{f} = 0.4; \textsuperscript{1}H NMR (400 MHz CDCl\textsubscript{3}) \textdelta\textsubscript{H} 6.22-6.26 (1H, m, 2-H); 5.84-5.87 (1H, m, 3-H); 4.76 (1H, t J 5.4 Hz, 1-H); 2.90 (1H, bs, 5-H); 2.42-2.56 (3H, m, 5'-H\textsubscript{2}); 2.10 (1H, d J 11.2 Hz, 4-H); \textsuperscript{13}C NMR (100 MHz) \textdelta\textsubscript{C} 179.4 (6-C); 130.3 (3-C\textsubscript{H}); 129.3 (2-C\textsubscript{H}); 73.3 (1-C\textsubscript{H}); 38.0 (5-C\textsubscript{H}); 34.5 (4-C\textsubscript{H}); 29.1 (5'-C\textsubscript{H}2); \textnu\textsubscript{max} (oil, cm\textsuperscript{-1}) 1770.6 (C=O); 720 (cis alkene); m/z (ESI\textsuperscript{+}) calculated for C\textsubscript{7}H\textsubscript{8}O\textsubscript{2} [M+Na]\textsuperscript{+}; 124.0524, found 124.0524.

Synthesis of Methyl cis-5-acetoxycyclohex-3-ene-1-carboxylate\textsuperscript{39} (7a)

To an oven dried 250 mL round bottom flask, bicyclo[3.2.1]oct-2-en-6-one (2.1 g, 18 mmol, 1 eq) and sodium metal (55 mg, 2.4 mmol, 0.13 eq) was added to freshly distilled methanol (100 mL) at room temperature. The reaction mixture was left to stir at room temperature for 9 hours, after which the solvent was removed. The residual oil was partitioned between ether and water, subsequently extracting with Et\textsubscript{2}O (3 x 50 mL).
organic extracts were combined, dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to yield methyl (1S,5S)-5-hydroxycyclohex-3-ene-1-carboxylate (7a) as a colourless oil (1.7 g, 61 %). The crude oil was used without further purification in the next step.

To an oven dried 50 mL round bottom flask, acetyl chloride (1.08 mL, 15.2 mmol, 1.3 eq) was slowly added to a mixture of methyl (1S,5S)-5-hydroxycyclohex-3-ene-1-carboxylate (1.64 g, 11.7 mmol, 1 eq) and pyridine (1.7 mL) in CH₂Cl₂ (10 mL) at 0 °C. The mixture was stirred for 15 minutes, neutralised with aqueous NaHCO₃ (2 mL) and diluted with Et₂O (30 mL). The organic phase was successively washed with NaHCO₃ solution (3 x 25 mL), 10 % HCl (2 x 25 mL), NaHCO₃ solution (25 mL) and brine (25 mL). The organic extracts were combined, dried over MgSO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (98:2 CHCl₃:Et₂O) to yield methyl (1S,5S)-5-acetoxy-cyclohex-3-ene-1-carboxylate (cis:trans 98:2) as a colourless oil (1.03 g, 45 %); Rf = 0.38; 1H NMR (400 MHz CDCl₃) δH 5.87 (1H, ddt J 1.9 Hz 3.6 Hz 9.8 Hz, 3-H); 5.53 (1H, d J 9.8 Hz, 4-H); 5.26-5.32 (1H, m, 5-H); 3.58 (3H, s, CO₂CH₃); 2.73 (1H, ddt J 2.3 Hz 7.8 Hz 11.4 Hz, 1-H); 2.22-2.27 (1H, m, 6-H); 2.17-2.20 (2H, m, 2-H); 1.93 (3H, s, O-C₃H₃); 13C NMR (100 MHz) δC 174.3 (C=O₂Me); 170.3 (C=O); 129.0 (3-C₆H); 126.6 (4-C₆H); 68.9 (5-C₆H); 51.7 (O-C₆H); 37.5 (1-C₆H); 30.3 (6-C₆H₂); 27.0 (2-C₆H₂); 21.0 (CO₂-CH₃); vmax (oil, cm⁻¹) 1770.6 (C=O); m/z (ESI⁺) calculated for C₁₀H₁₄O₄[M+Na⁺]; 198.0892, found 198.0889.


To an oven dried 500 mL round bottom flask, bicyclo[3.2.1]oct-2-6-one (2.10 g, 17 mmol, 1 eq) was dissolved in dry THF (40 mL) and cooled to 0 °C. LiAlH₄ (1.02 g, 26 mmol, 1.5 eq) in dry THF (30 mL) was slowly added to the reaction mixture and stirred for two hours at 0 °C. 1M solution of Rochelle’s salt (20 mL) was added slowly to quench the reaction, once quenched the mixture was stirred for one hour. The reaction mixture was extracted with EtOAc (3 x 150 mL), washing with water (100 mL) and brine (100 mL). The organic phase was dried over MgSO₄ and evaporated to dryness to yield cis-5-(hydroxymethyl)cyclohex-2-en-1-ol as a yellow oil (2.18 g, 86 %). The crude product was used without further purification in the next reaction.

To an oven dried 50 mL round bottom flask, crude cis-5-(hydroxymethyl)cyclohex-2-en-1-ol (1.51 g, 11.8 mmol, 1 eq) and imidazole (1.61 g, 23.6 mmol, 2 eq) was added to dry DMF (15 mL) and cooled to 0 °C. To this mixture, tert-butyldimethylsilyl chloride (1.77 g, 11.8 mmol, 1 eq) was added slowly, stirring at 0 °C for one hour. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with ice cold water (20 mL) and extracted with Et₂O (3 x 25 mL), washing with brine (100 mL). The organic phase
was dried over MgSO₄ and evaporated to dryness to yield cis-5-((tert-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-ol (2.85 g, 83 %).

To an oven dried 25 mL round bottom flask, acetyl chloride (0.18 ml, 2.6 mmol, 1.3 eq) was added to a solution cis-5-((tert-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-ol (0.49 g, 2.0 mmol, 1 eq) in CH₂Cl₂ (3 mL) and pyridine (0.24 mL) at 0°C. The slurry was stirred for 15 minutes and quenched with aqueous NaHCO₃ (1 mL) at 0 °C. The resultant mixture was extracted with Et₂O (3 x 25 mL), washed successively with saturated NaHCO₃ (2 x 20 mL), 10 % HCl (10 mL), aqueous NaHCO₃ (20 mL) and brine (20 mL), dried over MgSO₄ and the solvent was evaporated to dryness. The crude product was purified by column chromatography (9:1 CHCl₃:Et₂O) to yield cis-5-((tert-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-yl acetate (0.34 g, 70 %) as a colourless oil; Rf = 0.80; ¹H NMR (400 MHz) δH 5.86 (1H, ddt J 2.0 Hz 4.7 Hz 7.1 Hz, 2-H); 5.57 (1H, m, 3-H); 5.26 (1H, m, 1-H); 3.51 (2H, d J 5.9 Hz, 5'-H₂); 2.09-2.14 (2H, m, 4-H, 6-H); 2.05 (3H, s, COCH₃); 1.85-1.95 (1H, m, 4-H); 1.79-1.84 (1H, m, 5-H); 1.32 (1H, dt J 9.9 Hz 12.0 Hz, 6-H); 0.89 (9H, s, (CH₃)₃Si); 0.06 (6H, s, Si-(CH₃)₂); ¹³C NMR (100 MHz) δC 170.8 (C=O); 130.2 (2-C₂H₃); 128.6 (3'-C₂H₃); 127.1 (3-CH); 70.5 (1-CH); 67.3 (5'-CH₂); 35.6 (5-C₂H₃); 31.4 (6-C₂H₂); 28.0 (4-C₂H₂); 25.9 (C-(CH₃)₃); 21.3 (COCH₃); 18.2 (C-(CH₃)₃); -5.4 (Si-(CH₃)₂); vmax (oil, cm⁻¹) 2953 (CH=CH, sp² stretch); 1741.2 (C=O); m/z (ESI⁺) calculated for C₁₅H₂₆O₃Si [M+Na⁺]; 307.1700, found 307.1712.

cis-Dimethyl 2-(5-((tert-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-yl)malonate (112)

To an oven-dried 25 mL round bottomed flask, a solution of dimethylmalonate (0.2 mL, 1.95 mmol, 3.5 eq) was sodium hydride, 60 % dispersed in mineral oil (65 mg, 1.63 mmol, 2.5 eq) in anhydrous THF (6 mL) was prepared and stirred at room temperature. To this, a solution of Pd(PPh₃)₄ (29 mg, 0.022 mmol, 0.033 eq), PPh₃ (50 mg, 0.19 mmol, 0.29 eq) in THF (1 mL) was added. The reaction mixture was heated to reflux and left stirring for 7.5 hours, after which the reaction was cooled to room temperature, quenched with H₂O (1 mL) and concentrated in vacuo. The crude product was purified using column chromatography (pentane:acetone 95:5) to yield cis-Dimethyl 2-(5-((tert-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-yl)malonate (130 mg, 56 %) as a colourless oil and single diastereomer; Rf = 0.6; ¹H NMR (400 MHz) δH 5.77-5.82 (1H, m, 3'-H); 5.50-5.45 (1H, m, 2'-H); 3.76 (3H, s, O-CH₃); 3.75 (3H, s, O-CH₃); 3.49 (2H, m, 7'-H₂); 3.28 (1H, d J 8.8 Hz, 1-H); 2.95-3.02 (1H, m, 1'H); 2.08-2.13 (1H, m, 4'-H); 1.79-1.89 (2H, m, 6'-H₂, 5'-H); 1.66-1.76 (1H, m, 4-H); 1.04 (1H, dt J 11.6 Hz 12.6 Hz, 6'-H₂); 0.91 (9H, s, Si-(CH₃)₃); 0.05 (6H, s, Si-(CH₃)₂); ¹³C NMR (100 MHz) δC 168.9 (C=O); 168.8 (C=O); 128.6 (3'-CH); 127.5 (2'-CH); 67.8 (7'-CH₂); 56.9 (1'-CH); 52.4 (O-(CH₃)₂); 36.6 (5'-CH); 36.5 (1'-CH); 30.1 (6'-CH₂); 28.3 (4'-CH₂); 25.9 (Si-(CH₃)₃); -5.35 (Si-(CH₃)₂); vmax (oil, cm⁻¹) 1736 (C=O). m/z (ESI⁺) calculated for C₁₅H₂₆O₃Si [M+Na⁺]; 379.1911, found 379.1919.
cis-[[Tert-butyldimethylsilyl]oxy]methyl)cyclohex-2-en-1-yl]-N,N-dimethyl-1-phenylmethanesulfonamide (113)

N,N-Dimethyl-1-phenylmethanesulfonamide (212 mg, 1.0 mmol, 1 eq) and (1S, 5S)-5-[[tert-butyldimethylsilyl]oxy]methyl)cyclohex-2-en-1-yl acetate (310 mg, 1.1 mmol, 1.1 eq) were reacted following general procedure A to yield 1-((R)-[[Tert-butyldimethylsilyl]oxy]methyl)cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide as a mixture of diastereomers (d.r 1:0.5) (0.37 g, 85 %); This was further purified to obtain the pure major diastereomer (71 mg) as a colourless oil; R_f = 0.51 (major isomer) 0.47 (minor isomer) (pentane:acetone 98:2); data for major diastereomer 113a: ^1H NMR (400 MHz MeOD) δ_H 7.47-7.49 (2H, m, Ar-H); 7.36-7.39 (3H, m, Ar-H); 5.70-5.74 (1H, m, 4-H); 5.65-5.67 (1H, m, 3-H); 4.21 (1H, d J 7.2, 1-H); 3.45-3.51 (2H, m, 6'-H2); 3.19-3.23 (1H, m, 2-H); 2.45 (6H, s, N-(CH3)2); 2.11-2.14 (1H, m, 7-Hex); 1.97-2.00 (1H, m, 5-H); 1.77-1.84 (1H, m, 6-H); 1.57-1.64 (1H, m, 5-H); 1.00 (1H, dt J 11.6, 12.5, 7-Hex); 0.86 (9H, s, C-(CH3)3); -0.03 (6H, d J 2.4, Si-(CH3)2); ^13C NMR (100 MHz) δ_C 134.5 (Ar-C); 131.7 (Ar-C); 129.9 (Ar-CH); 129.6 (4-C'CH); 128.2 (3-C'CH); 72.2 (1-C'H); 69.0 (6-C'CH2); 39.8 (2'-C'CH3); 38.0 (6-C'H); 37.8 (N-(CH3)2); 32.7 (7-C'H2); 29.2 (5-C'CH2); 26.4 (C-(CH3)3); 19.2 (C-(CH3)3); -5.3 (Si-(CH3)2); data for minor diastereomer 113b: ^1H NMR (500 MHz CDCl3); 7.36-7.44 (5H, m, Ar-H); 6.27 (1H, dd J 0.8 Hz 10.2 Hz, 3-H); 5.82 (1H, ddd J 2.2 Hz 4.9 Hz 7.5 Hz, 4-H); 4.00 (1H, d J 9.3 Hz, 1-H); 3.40 (1H, dd J 6.4 Hz 10.0 Hz, 6'-H); 3.33 (1H, dd J 6.4 Hz 10.0 Hz, 6'-H); 3.25-3.27 (1H, m, 2-H); 2.46 (6H, N-(CH3)2); 2.03-2.08 (1H, m, 7-Hex); 1.76-1.79 (1H, m, 5-H); 1.60-1.66 (2H, m, 5-H, 6-H); 0.81 (9H, s, C-(CH3)3); 0.75 (1H, q J 12.1 Hz, 7-Hex); -0.063 (6H, d J 9.1 Hz, Si-(CH3)2); ^13C NMR (100 MHz) δ_C 133.3 (Ar-C); 129.9 (Ar-C); 128.7 (Ar-C); 128.6 (4-C); 128.8 (Ar-C); 128.2 (3-C); 72.6 (1-C'); 67.7 (6-C'H2); 37.8 (2-C'); 37.5 (N-(CH3)2); 36.8 (6-C'H); 31.0 (7-C'H2); 28.3 (5-C'H2); 25.8 (C-(CH3)3); 18.2 (C-(CH3)3); -5.5 (Si-(CH3)2); m/z (ESI^+) calculated for C26H37NO3Si [M+H]^+: 424.2336, found 424.2342.
(1R,5R)-5-[[[(R)-N,N-dimethylsulfamoyl]phenyl]methyl]cyclohex-3-en-1-yl)methyl 4-bromobenzoate (116)

A solution of the pure major diastereomer 1-(5R)-[[[Tert-butyldimethylsilyl]oxy]methyl]cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (41 mg, 0.1 mmol, 1 eq) and TBAF (50 mg, 0.19 mmol, 1.9 eq) in THF (2 mL) was stirred at 0 °C for 15 minutes. The reaction mixtures was warmed to room temperature for overnight and passed through a silica plug to yield a crude mixture of the corresponding alcohol.

The crude alcohol 110 (29 mg, 0.09 mmol, 1 eq) was added to a solution of CH$_2$Cl$_2$ (5 mL), triethylamine (9 mg, 0.09 mmol, 1 eq) and p-bromobenzoyl chloride (10 mg, 0.45 mmol, 5 eq) at room temperature. The reaction mixture was stirred for 2 hours, prior to the addition of H$_2$O (10 mL) and DCM (10 mL). The organic phase was extracted and washed with H$_2$O (3 x 10 mL), dried over MgSO$_4$ and evaporated to dryness to yield (1R,5R)-5-[[[(R)-N,N-dimethylsulfamoyl]phenyl]methyl]cyclohex-3-en-1-yl)methyl 4-bromobenzoate (42 mg, 95%) as a brown crystalline solid. $^1$H NMR (400 MHz CDCl$_3$) δH 7.88 (2H, app d J 8.5 Hz, Ar-H); 7.57 (2H, app d J 8.5 Hz, Ar-H); 7.36-7.42 (5H, m, Ph-H); 5.71-5.75 (1H, m, 4-H); 5.62-5.64 (1H, m, 3-H); 4.18 (2H, d J 6'-'H$_2$); 3.97 (1H, d J 7.9 Hz, 1-H); 3.34 (1H, app bs, 2-H); 2.45 (6H, s, N-(CH$_3$)$_2$); 2.30-2.33 (1H, m, 7-H); 2.11-2.20 (2H, m, 5-H, 6-H); 1.69-1.76 (1H, m, 5-H); 1.16-1.22 (1H, m, 7-H); $^{13}$C NMR (100 MHz) δC 170.3; 165.8; 133.0; 131.9; 131.7 (2 x Ar-H); 131.1 (2 x Ar-H); 130.2 (2 x Ph-H); 128.8 (Ph-H); 128.7 (2 x Ph-H); 128.2 (4-H); 127.2 (3-H); 71.7 (1-H); 69.4 (6'-H$_2$); 38.2 (2-H); 37.5 (N-(CH$_3$)$_2$); 33.6 (6-H); 31.6 (7-H); 28.3 (5-H); m/z (ESI$^+$) calculated for C$_{23}$H$_{26}$BrNO$_4$S [M+K]$^+$; 530.0416.

3.2 Alternative Methods for α-Alkylation

3.2.1 General Procedures

General Procedure E: Alkylation of sulfonamides via nucleophilic substitution method

\[ \text{LDA (2.2 eq) THF, -20 °C, 1 hr} \]
\[ \text{then:} \]
\[ \text{R-X} \]
\[ \text{-20 °C, 3 hr} \]
To an oven-dried 25 mL round-bottomed flask, flushed with nitrogen, dry diisopropylamine (0.32 mL, 2.2 mmol, 2.2 eq) in anhydrous THF (8 mL) was added, stirring at −78 °C. To this solution n-BuLi (1.6M in hexanes, 1.38 mL, 2.2 mmol, 2.2 eq) was slowly added and the reaction mixture stirred at −78 °C for 10 min followed by 0 °C for a further 10 min to generate LDA. The LDA solution was cooled to −20 °C and N,N-dimethyl-1-phenylmethanesulfonamide (0.20 g, 1 mmol, 1 eq) dissolved in anhydrous THF (2 mL) was added dropwise. The reaction mixture was left to stir for 1 hour after which time a solution of allylic bromide (1 mmol, 1 eq) in anhydrous THF (1 mL) was added dropwise. The reaction mixture was left to stir for a further 3 hours at −20 °C. The resultant mixture was quenched by addition of saturated aqueous NH₄Cl solution (2 mL) and separated between CH₂Cl₂ (25 mL) and H₂O (25 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL) and the combined organic layers were dried over MgSO₄ and concentrated in vacuo. The solid mixture was purified by column chromatography to yield the titled compound.

**General Procedure F: Synthesis of arylmethane sulfonamides**

To an oven-dried 100 mL round bottomed flask, substituted-benzylsulfonyl chloride (2 mmol, 1 eq) was dissolved in CHCl₃ (50 mL). To this, dimethylamine (8M, 10 eq) was slowly added at room temperature and allowed to stir for overnight, after which the organic layer was extracted from the aqueous. The organic extracts were washed with H₂O (2 x 100 mL) and brine (25 mL) successively, dried over MgSO₄ and evaporated to dryness to yield the titled compound.

### 3.2.2 Experimental Data

**N,N-Dimethyl-1-phenylbut-3-en-1-sulfonamide (90a)**

Allyl bromide (120 mg, 1 mmol, 1 eq) was reacted following the general method E to yield N,N-dimethyl-1-phenylbut-3-ene-1-sulfonamide (220.4 mg, 92% yield) as a colourless solid; all data matches that of general procedure A.
(E)-N,N-Dimethyl-1-phenylpent-3-ene-1-sulfonamide (90b)

Crotyl bromide (135 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield N,N-dimethyl-1-phenylpent-3-ene-1-sulfonamide as a mixture of isomers (E:Z 6:1, determined by ¹H NMR) (218 mg, 86 %) as a colourless solid; all data matches that of general procedure A.

N,N-4-Trimethyl-1-phenylpent-3-ene-1-sulfonamide (90c)

Prenyl bromide (150 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield N,N,4-trimethyl-1-phenylpent-3-ene-1-sulfonamide 187 mg, 70 %) as a colourless solid; all data matches that of general procedure A.

(E)-N,N-Dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (90e)

Cinnamyl bromide (202 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield (E)-N,N-dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (195 mg, 61 %) as a colourless solid; all data matches that of general procedure A.
(E)-N,N-Dimethyl-1-phenylhex-3-ene-1-sulfonamide (117)

1-bromo-2-pentene (153 mg, 1 mmol) was reacted following the general procedure E to yield (E)-N,N-dimethyl-1-phenylhex-3-ene-1-sulfonamide (237 mg, 88%) as a colourless solid (E:Z ratio = 90:10 by 1H NMR); Rr = 0.53 (9:1 toluene:EtOAc); mp: 75 - 76 °C; 1H NMR (400 MHz, CDCl3) δH 7.34-7.41 (5H, m, Ar-H); 5.46-5.53 (1H, m, 3'-H); 5.07-5.15 (1H, m, 4'-H); 4.10 (1H, dd J 4.0 Hz 11.0 Hz, 1-H); 2.98-3.04 (1H, m, 2'-H); 2.80-2.88 (1H, m, 2-H); 2.54 (6H, s, N- (CH3)3); 1.87 (2H, quint J 7.25 Hz, 5'-H); 0.82 (3H, t J 7.44 Hz, 6'-H); 13C NMR (100 MHz) δC 136.1 (4'-CH); 133.4 (1 x Ar-C); 129.6 (2 x Ar-CH); 128.8 (1 x Ar-CH); 128.6 (2 x Ar-CH); 123.4 (3'-CH); 67.5 (1'-CH); 37.6 (N-(CH3))2; 33.2 (2'-CH2); 25.5 (5'-CH2); 13.6 (6'-CH3); vmax (solid, cm⁻¹) 1314 & 1133 (sulfonamide S=O); m/z (ESI+) calculated for C14H11NO3S [M+Na]⁺: 290.1185, found 267.1295.

1-(Cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (90g)

3-Bromocyclohexene (167 mg, 1 mmol. 1 eq) was reacted following the general procedure E to yield 1-(cyclohex-2-en-1-yl)-N,N-dimethyl-1-phenylmethanesulfonamide (d.r: 71:29, determined by 1H NMR) (248 mg, 89%) as a colourless solid; Rr = 0.42 (95:5 toluene:EtOAc); mp: 104 - 106 °C; data for major diastereomer: 1H NMR (400 MHz, CDCl3) δH 7.34-7.40 (5H, m, Ar-H); 6.19 (1H, dd J 2.2 Hz 10.5 Hz, 2'-H); 5.76-5.80 (1H, m, 3'-H); 4.05 (1H, d J 9.8 Hz, 1-H); 3.10-3.15 (1H, m, 1'-H); 2.40 (6H, s, N-(CH3))2; 1.71-1.94 (2H, m, 4'-H); 1.54-1.61 (2H, m, 6'-H, 5'-H); 1.41-1.48 (1H, m, 5'-H); 1.07-1.14 (1H, m, 6'-H); 13C NMR (100 MHz) δC 133.5 (1 x Ar-C); 130.1 (2 x Ar-CH); 129.8 (3'-CH); 128.8 (1 x Ar-CH); 128.7 (2 x Ar-CH); 127.3 (2'-CH); 72.6 (1'-CH); 37.4 (N-(CH3))2; 26.7 (6'-CH2); 25.0 (4'-CH2); 20.6 (5'-CH2). Data for minor diastereomer: 1H NMR (400 MHz, CDCl3) δH 7.34-7.40 (5H, m, Ar-CH); 5.66-5.69 (1H, m, 3'-H); 5.45-5.48 (1H, m, 2'-H); 3.97 (1H, d J 8.4 Hz, 1'-H); 3.16-3.19 (1H, m, 1'-H); 2.42 (6H, s, N-(CH3))2; 2.07-2.13 (1H, m, 6'-H); 1.66-1.73 (2H, m, 5'-H); 1.51-1.61 (1H, m, 6'-H); 13C NMR (100 MHz) δC 133.3 (1 x Ar-C); 129.9 (2'-CH); 129.8 (2 x Ar-CH); 128.7 (1 x Ar-CH); 128.6 (2 x Ar-CH); 127.0 (3'-CH); 71.8 (1'-CH); 36.6 (N-(CH3))2; 28.0 (6'-CH2); 24.9 (4'-CH2); 21.2 (5'-CH2); vmax (solid, cm⁻¹) 1320 & 1130 (sulfonamide S=O); m/z (ESI+) calculated for C15H13NO3S [M+Na]⁺: 302.1185, found 302.1192.
**N,N-3-Trimethyl-1-phenylbut-3-ene-1-sulfonamide (90i)**

3-bromo-2-methylpropene (273 mg, 1 mmol, 1 eq) was used following the general procedure E to yield N,N-3-Trimethyl-1-phenylbut-3-ene-1-sulfonamide (253 mg, 99 %) as a colourless solid; all data matches that of general procedure A.

**N,N,N,4,8-Tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (90j)**

Geranyl bromide (219 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield (E)-N,N,N,4,8-tetramethyl-phenylnona-3,7-diene-1-sulfonamide (296 mg, 88 %) as a colourless solid; all data matches that of general procedure A.

**3-Bromo-N,N-dimethyl-1-phenylbut-3-ene-1-sulfonamide (118)**

2,3-Dibromopropene (200 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield 3-bromo-N,N-dimethyl-1-phenylbut-3-ene-1-sulfonamide (245 mg, 77 %) as an orange solid; R_f = 0.59 (90:10 toluene:EtOAc); mp: 100 - 102 °C; ^1H NMR (400 MHz, CDCl_3) δH 7.37-7.44 (5H, m, Ar-H); 5.46 (1H, s, 4-H); 5.30 (1H, d J 1.0 Hz, 4-H); 4.53 (1H, dd J 4.0 Hz 11.0 Hz, 1-H); 3.37 (1H, dd J 4.0 Hz 14 Hz, 2-H); 3.26 (1H, dd J 11 Hz 14 Hz, 2-H); 2.57 (6H, s, N-(CH_3)_2); ^13C NMR (100 MHz) δC 132.2 (1 x Ar-C); 129.6 (2 x Ar-CH); 129.1 (1 x Ar-CH); 128.8 (2 x Ar-CH); 128.5 (3-CH); 120.6 (4-CH); 110.5 (1-CH); 41.8 (2-CH); 37.7 (N-(CH_3)_2); V_{max} (solid, cm^{-1}) 1324 & 1133 (sulfonamide S=O); m/z (ESI+) calculated for C_{12}H_{17}BrNO_2S [M+Na]^+; 339.9977, found 339.9978.
(E)-4-Bromo-N,N-dimethyl-1-phenylbut-3-ene-1-sulfonamide (119)

1,3-Dibromopropene (200 mg, 1 mmol, 1 eq) was reacted following the general procedure E to yield (E)-4-bromo-N,N-dimethyl-1-phenylbut-3-ene-1-sulfonamide (Z:E 66:44, determined by $^1$H NMR) (251 mg, 79 %) as a colourless solid; $R_f = 0.50$ (90:10 toluene:EtOAc); mp: 90 - 92 °C; data for E-isomer; $^1$H NMR (400 MHz, CDCl$_3$) δH 7.36-7.43 (5H, m, Ar-H); 6.10 (1H, d J 7.1 Hz, 4-H); 5.92 (1H, ddt J 4.0 Hz 7.3 Hz 11.0 Hz, 3-H); 4.22 (1H, dd J 5.1 Hz 10.6 Hz, 1-H); 3.17-3.23 (1H, m, 2-H); 3.02-3.09 (1H, m, 2-H); 2.57 (6H, s, N-(CH$_3$)$_2$); $^{13}$C NMR (100 MHz) δC 132.9 (1 x Ar-C); 132.5 (3-CH); 129.5 (2 x Ar-CH); 129.4 (1 x Ar-CH); 128.9 (2 x Ar-CH); 110.7 (4-C); 65.6 (1-C); 37.7 (N-(CH$_3$)$_2$); 30.6 (2-CH$_2$). Data for Z-isomer; $^1$H NMR (400 MHz, CDCl$_3$) δH 7.36-7.34 (5H, m, Ar-H); 6.09 (1H, d J 13.5 Hz, 4-H); 5.92 (1H, ddt J 4.1 Hz 7.3 Hz 11 Hz, 3-H); 4.12 (1H, dd J 4.1 Hz 10.8 Hz, 1-H); 3.02-3.19 (1H, m, 2-H); 2.84-2.92 (1H, m, 2-H); 2.52 (6H, s, N-(CH$_3$)$_2$); $^{13}$C NMR (100 MHz) δC 132.6 (1 x Ar-C); 129.9 (3-CH); 129.3 (2 x Ar-CH); 129.1 (1 x Ar-CH); 128.8 (2 x Ar-CH); 107.8 (4-C); 66.6 (1-C); 37.6 (N-(CH$_3$)$_2$); 33.6 (2-CH$_2$); $\nu_{\text{max}}$ (solid, cm$^{-1}$) 1317 & 1134 (sulfonamide S=O); m/z (ESI+) calculated for C$_{12}$H$_{16}$BrNO$_2$S [M+Na]$^+$; 339.9977, found 339.9980.

4-[(4-Methyl-1-phenylpent-3-en-1-yl)sulfonyl]morpholine (124a)

4-(Benzylsulfonyl)morpholine (121 mg, 0.5 mmol, 1 eq) and prenyl bromide (75 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield 4-[(4-Methyl-1-phenylpent-3-en-1-yl)sulfonyl]morpholine (115 mg, 74 %) as a colourless solid; $R_f = 0.41$; mp: 98 - 100 °C; $^1$H NMR (400 MHz, CDCl$_3$) δH 7.35-7.40 (5H, m, Ar-H); 4.84 (1H, t J 7.3 Hz, 3-H); 3.99 (1H, dd J 3.9 Hz 11.3 Hz, 1-H); 3.54 (2H, ddd J 3.0 Hz 6.5 Hz 11.5 Hz, O-H$_2$); 3.44 (2H, ddd J 3.0 Hz 6.3 Hz 11.4 Hz, O-H$_2$); 3.01-3.08 (3H, m, 2-H, N-H$_2$); 2.76-2.85 (3H, m, 2-H, N-H$_2$); 1.56 (6H, 4-(CH$_3$)$_2$); $^{13}$C NMR (100 MHz) δC 135.1 (4-C); 133.3 (1 x Ar-C); 129.7 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.7 (2 x Ar-CH); 118.7 (3-C); 68.2 (1-C); 66.7 (O-C$_2$H$_2$); 46.1 (N-CH$_3$); 28.9 (2-CH$_2$); 25.7 (4-CH$_3$); 17.9 (4-CH$_3$); $\nu_{\text{max}}$ (solid, cm$^{-1}$) 1335 & 1106 (sulfonamide S=O); m/z (ESI+) calculated for C$_{16}$H$_{23}$NO$_2$S [M+Na]$^+$; 332.1291, found 332.1295.
1-(Benzyloxysulfonyl)pyrrolidin (113 mg, 0.5 mmol, 1 eq) and cinnamyl bromide (99 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield (E)-1-[(1,4-diphenylbut-3-en-1-yl)sulfonyl]pyrrolidine (98 mg, 57 %); Rf = 0.33; mp: 118 - 121 °C; 1H NMR (400 MHz, CDCl3) δH 7.44-7.36 (5H, Ar-H); 7.15-7.24 (5H, Ar-H); 6.43 (1H, d J 15.8 Hz, 4-H); 5.94 (1H, dt J 7.4 Hz 14.9 Hz, 3-H); 4.24 (1H, dd J 4.1 Hz 11.7 Hz, 1-H); 3.05-3.13 (2H, m, 2-H); 2.81-2.86 (2H, m, 2'-H2); 1.63-1.74 (4H, m, (3'-H2)2); 13C NMR (100 MHz) δC 137.0 (1 x Ar-C); 133.6 (1 x Ar-C); 133.1 (4-C); 129.7 (2 x Ar-C); 128.9 (1 x Ar-C); 128.7 (2 x Ar-C); 128.4 (2 x Ar-C); 127.3 (1 x Ar-C); 126.1 (2 x Ar-C); 125.1 (3-C); 67.4 (1-C); 48.2 (2'-C(2'H)2); 33.4 (2-C); 25.8 (3'-C(2'H)); v max (solid, cm⁻¹) 1315 & 1137 (sulfonamide S=O); m/z (ESI+) calculated for C20H23NO2S [M+K]+ 380.1081, found 380.1091.

1-[(3-Bromo-1-phenylbut-3-en-1-yl)sulfonyl]pipерidine (124c)

1-[(3-Bromo-1-phenylbut-3-en-1-yl)sulfonyl]pipерidine (120 mg, 0.5 mmol, 1 eq) and 2,3-dibromoprop-1-ene (99 mg, 0.5 mmol, 1 eq) was reacted following the general procedure A to yield 1-[(3-bromo-1-phenylbut-3-en-1-yl)sulfonyl]pipерidine (133 mg, 71 %); Rf = 0.55 (toluene:EtOAc 95:5); mp: 77 - 79 °C; 1H NMR (400 MHz, CDCl3) δH 7.35-7.41 (5H, Ar-H); 5.42 (1H, s, 4-H); 5.27 (1H, d J 1.3 Hz, 4-H); 4.42 (1H, dd J 4.0 Hz 11.4 Hz, 1-H); 3.37 (1H, dd J 4.0 Hz 14.4 Hz, 2-H); 3.23 (1H, dd J 11.4 Hz 14.4 Hz, 2-H); 2.81 (2H, bs, 2'-H2); 1.39-1.46 (6H, m, 3'-H2, 4'-H2); 13C NMR (100 MHz) δC 132.3 (1 x Ar-C); 129.7 (2 x Ar-C); 129.0 (1 x Ar-C); 128.7 (2 x Ar-C); 128.6 (3-C); 120.5 (4-C); 65.8 (1-C); 46.9 (2'-C(2'H)2); 42.1 (2-C); 25.8 (3'-C(2'H)); v max (solid, cm⁻¹) 1315 & 1137 (sulfonamide S=O); m/z (ESI+) calculated for C13H20BrNO2S [M+Na]+ 380.0290, found 380.0288.
1-Benzyl-4-[(1-phenylbut-3-en-1-yl)sulfonyl]piperazine (104a)

A: 1-Benzyl-4-(benzylsulfonyl)piperazine (165 mg, 0.5 mmol, 1 eq) and crotyl bromide (67.5 mg, 0.5 mmol, 1 eq) was reacted following the general procedure A to yield (E)-1-benzyl-4-([(1-phenylpent-3-en-1-yl)sulfonyl]piperazine (107.6 mg, 56%).

1-[(1-Phenylbut-3-en-1-yl)sulfonyl]-1,2,5,6-tetrahydropyridine (99)

1-(benzylsulfonyl)-1,2,3,6-tetrahydropyridine (116 mg, 0.5 mmol, 1 eq) and allyl bromide (61 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E, to yield 1-[(1-phenylbut-3-en-1-yl)sulfonyl]-1,2,3,6-tetrahydropyridine (113 mg, 82%) as an orange oil; all data in accordance with general procedure A.

N,N-Dimethyl-[1-(4-trifluoromethyl)phenyl]methanesulfonamides (120)

(4-Trifluoromethyl)benzylsulfonyl chloride (0.50 g, 1.9 mmol, 1 eq) was reacted with dimethylamine 2.4 mL, 8M, 10 eq) following general procedure F, yielding yielding N,N-dimethyl-[1-(4-trifluoromethyl)phenyl]methanesulfonamide as a colourless solid (0.42 g, 82%); mp: 174 - 176 °C; 1H NMR (400 MHz, CDCl3) δH 7.66 (2H, d, J 8.2 Hz, Ar-H); 7.54 (2H, d, J 8.2 Hz, Ar-H); 4.26 (2H, s, 1-H2); 2.78 (6H, s, N-(C6H5)2); 13C NMR (100 MHz) δc: 131.9 (q, J 33 Hz, C-CF3); 131.0 (app s, 2 x Ar-C); 126 (q J 271 Hz, CF3); 125.7 (q J 3.8 Hz, 2 x Ar-CH); 55.2 (2-CH2); 37.8 (N-(CH3)2); νmax (solid, cm⁻¹) 1329 & 1117 (sulfonamide S=O); m/z (ESI+) calculated for C_{10}H_{12}F_{3}NO_{2}S [M+Na]^+ 290.0433, found 290.0417.
(E)-N,N-Dimethyl-4-phenyl-1-[4-(trifluoromethyl)phenyl]but-3-ene-1-sulfonamide (124d)

N,N-Dimethyl-1-[4-(trifluoromethyl)phenyl]methanesulfonamide (130 mg, 0.5 mmol) and cinnamyl bromide (99 mg, 0.5 mmol) was reacted following the general method E to yield (E)-N,N-dimethyl-4-phenyl-1-[4-(trifluoromethyl)phenyl]but-3-ene-1-sulfonamide (119 mg, 63 %) as a colourless solid and (1E,6E)-N,N-dimethyl-1,7-diphenyl-4-[4-(trifluoromethyl)phenyl]hepta-1,6-diene-3-sulfonamide as a colourless oil (65 mg, 13 %); R_f = 0.18 (monallyl), 0.57 (diallyl); data for mono-allylated product; mp: 100 - 102 °C; ^1H NMR (400 MHz, CDCl_3) δ_H 7.67 (2H, d J 8.2 Hz, Ar-H); 7.59 (2H, d J 8.2 Hz, Ar-H); 7.19-7.27 (5H, m, Ph-H); 6.42 (1H, d J 15.6 Hz, 4-H); 5.89 (1H, dt J 4.1 Hz 10.9 Hz, 3-H); 3.23-3.29 (1H, m, 2-H); 3.03-3.11 (1H, m, 2-H); 2.61 (6H, s, N-(C_H_3)_2); ^13C NMR (100 MHz) δ_C 137.4 (1 x Ar-C); 136.6 (1 x Ph-C); 133.7 (4 x C_H); 131.2 (q J 33 Hz, C_F_3); 130.0 (app s, 2 x Ar-CH); 128.6 (2 x Ph-CH); 127.6 (2 x Ph-CH); 126.1 (1 x Ph-CH); 125.5 (q J 3.6 Hz, 2 x Ar-CH); 124.0 (3-CH); 123.9 (q, J 273 Hz, C_F_3); 66.9 (1-CH); 37.7 (N-(C_H_3)_2); 33.8 (2-CH2); v_max (solid, cm^-1) 1320 & 1113 (sulfonamide S=O); m/z (ESI+) calculated for C_19H_20F_3NO_2S [M+Na]^+ 406.1059, found 406.1066.

N,N-Dimethyl-1-(p-tolyl)methanesulfonamides (121)

p-Tolyl-methanebenzylsulfonyl chloride (0.50 g, 2.3 mmol, 1 eq) and dimethylamine (2.85 mL, 8M) was reacted following general procedure F, yielding N,N-Dimethyl-1-(p-tolyl)methanesulfonamide as a colourless solid (0.46 g, 96 %); mp: 81 - 83 °C; ^1H NMR (400 MHz, CDCl_3) δ_H 7.28 (2H, d J 7.9 Hz, Ar-H); 7.19 (2H, d J 7.9 Hz, Ar-H); 4.19 (2H, s, 1-H_2); 2.72 (6H, s, N-(C_H_3)_2); 2.36 (3H, s, p-CH_3); ^13C NMR (100 MHz) δ_C 138.6 (1 x Ar-C); 130.5 (2 x Ar-CH); 129.5 (2 x Ar-CH); 125.9 (1 x Ar-C); 55.7 (1-CH_3); 38.8 (N-(C_H_3)_2); 21.2 (p-CH_3); v_max (solid, cm^-1) 1317 & 1139 (sulfonamide S=O); m/z (ESI+) calculated for C_10H_15NO_2S [M+Na]^+ 236.0716, found 236.0717.
$N,N$-4-Trimethyl-1-(p-tolyl)pent-3-ene-1-sulfonamide (124e)

\[
\begin{align*}
\text{N,N-Dimethyl-1-}(p\text{-tolyl})\text{methanesulfonamide (106 mg, 0.5 mmol, 1 eq) and prenyl bromide (74 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield } N,N-4-Trimethyl-1-(p-tolyl)-pent-3-ene-1-sulfonamide \text{ as a colourless solid (69 mg, 49 %); R} & = 0.4 (95:5 \text{ toluene: EtOAc); mp: 45 - 47 °C; } \text{H NMR (400 MHz, CDCl}\_3 \text{)} \delta H 7.28 (2H, d J 7.9 Hz, Ar-H); 7.16 (2H, d J 7.9 Hz, Ar-H); 4.85 (1H, t J 7.3 Hz, 3-H); 4.03 (1H, dd J 3.9 Hz 11.2 Hz, 1-H); 3.00-3.06 (1H, m, 2-H); 2.76-2.85 (1H, m, 2-H); 2.54 (6H, s, N-(CH\_3)\_2); 2.36 (3H, s, Ar-CH\_3); 1.58 (6H, bs, 4-(CH\_3)\_2); 13C NMR (100 MHz) \delta C 138.6 (4-C); 134.8 (Ar-C-CH\_3); 130.5 (1 x Ar-C); 129.5 (2 x Ar-CH\_3); 129.3 (2 x Ar-CH\_3); 119.0 (3-CH); 67.1 (1-CH); 37.7 (N(CH\_2)\_2); 28.2 (2-CH\_2); 25.7 (4-CH\_3); 21.2 (Ar-CH\_3); 17.9 (4-CH\_3); v\text{max (solid, cm}^{-1}) 1321 \text{ & 1130 (sulfonamide S=O); m/z (ESI+) calculated for } C\text{\textsubscript{15}H\textsubscript{30}NO\textsubscript{2}S [M+K]\textsuperscript{+} 320.1081, \text{found 320.1082.}
\end{align*}
\]

$1-(4\text{-Chlorophenyl})-N,N$-dimethanesulfonamide (122)

\[
\begin{align*}
(4\text{-Chlorophenyl})\text{sulfonyl chloride (0.50 g, 2.22 mmol, 1 eq) and dimethylamine (2.8 mL, 8M) was reacted following general procedure F, yielding } 1-(4\text{-chlorophenyl})-N,N\text{-dimethanesulfonamide as a colourless solid (343 mg, 66 %); mp: 108 - 110 °C; } \text{H NMR (400 MHz, CDCl}\_3 \text{)} \delta H 7.32-7.38 (4H, m, Ar-H); 4.18 (2H, s, 1-H); 2.76 (6H, s, N-CH\_3)\_2); 13C NMR (100 MHz) \delta C 134.9 (1 x Ar-C); 131.9 (2 x Ar-CH\_3); 129.0 (2 x Ar-CH\_3); 127.6 (1 x Ar-C); 55.1 (2-CH\_2); 37.8 (N(CH\_2)\_2); v\text{max (solid, cm}^{-1}) 1329 \text{ & 1140 (sulfonamide S=O); m/z (ESI+) calculated for } C\text{\textsubscript{9}H\textsubscript{12}ClNO\textsubscript{2}S [M+H]\textsuperscript{+} 234.0350, \text{found 234.0353.}
\end{align*}
\]
3-Bromo-1-(4-chlorophenyl)-N,N-dimethylbut-3-ene-1-sulfonamide (124f)

1-(4-Chlorophenyl)-N,N-dimethylmethanesulfonamide (117 mg, 0.5 mmol, 1 eq) and 2,3-dibromoprop-1-ene (100 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield 3-bromo-1-(4-chlorophenyl)-N,N-dimethylbut-3-ene-1-sulfonamide as a colourless oil (89 mg, 53 %); Rf = 0.4 (toluene:EtOAc 95:5); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37 (4H, s, Ar-\(H\)); 5.46 (1H, bs, 4-\(H\)); 5.31 (1H, d \(J\) 1.7 Hz, 4-\(H\)); 4.50 (1H, dd \(J\) 3.9 Hz 14.5 Hz, 1-\(H\)); 3.34 (1H, dd \(J\) 3.9 Hz 14.5 Hz, 2-\(H\)); 3.20 (1H, dd \(J\) 11.3 Hz 14.5 Hz, 2-\(H\)); 2.62 (6H, s, N-(\(CH_3\))\(_2\)); \(^1\)C NMR (100 MHz) \(\delta\) C 135.1 (C-Cl); 130.9 (2 x Ar-\(C\)); 130.7 (1 x Ar-\(C\)); 129.1 (2 x Ar-\(C\)); 128.1 (3-\(C\)); 120.9 (4-\(CH_2\)); 64.5 (1-\(CH\)); 41.8 (2-\(CH_2\)); 37.78 (N-(\(CH_3\))\(_2\)); \(\nu\)max (solid, cm\(^{-1}\)) 1330 & 1138 (sulfonamide S=O); m/z (ESI+) calculated for C\(_{12}\)H\(_{15}\)BrClNO\(_2\)S [M+Na]\(^+\) 373.9588, found 373.9601.

1-(4-Bromophenyl)-N,N-dimethylmethanesulfonamide (123)

(4-Bromomethyl)sulfonyl chloride (0.5 g, 1.85 mmol) and dimethylamine (2.3 mL, 8M) was reacted following general procedure F, yielding 1-(4-bromophenyl)-N,N-dimethylmethanesulfonamide as a colourless solid (440 mg, 86 %); mp: 147 - 149 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (1H, bs, Ar-\(H\)); 7.51 (1H, d \(J\) 7.8 Hz, Ar-\(H\)); 7.35 (1H, d \(J\) 7.8 Hz, Ar-\(H\)); 7.24-7.28 (1H, m, Ar-\(H\)); 4.17 (2H, s, 1-\(H\)); 2.77 (6H, s, N-(\(CH_3\))\(_2\)); \(^1\)C NMR (100 MHz) \(\delta\) C 133.5 (1 x Ar-\(CH\)); 131.8 (1 x Ar-\(CH\)); 131.3 (1 x Ar-\(C\)); 130.3 (1 x Ar-\(CH\)); 129.3 (1 x Ar-\(CH\)); 122.7 (C-Br); 55.2 (1-\(CH_2\)); 37.8 (N-(\(CH_3\))\(_2\)); \(\nu\)max (solid, cm\(^{-1}\)) 1329 & 1138 (sulfonamide S=O); m/z (ESI+) calculated for C\(_{9}\)H\(_{12}\)BrClNO\(_2\)S [M+Na]\(^+\) 299.9664, found 299.9653.

(E)-1-(4-Bromophenyl)-N,N-dimethylpent-3-ene-1-sulfonamide (124g)

133
1-(4-Bromophenyl)-N,N-dimethylmethanesulfonamide (139 mg, 0.5 mmol, 1 eq) and crotyl bromide (68 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield (E)-1-(4-bromophenyl)-N,N-dimethylpent-3-ene-1-sulfonamide as a yellow oil (cis:trans 1:2 as determined by ¹H NMR) (64.2 mg, 38 %); Rf = 0.38 (toluene:EtOAc 95:5); Data for major trans isomer; ¹H NMR (400 MHz, CDCl₃) δH 7.49-7.56 (2H, m, 2 x Ar-H); 7.34-7.38 (1H, m, Ar-H); 7.24-7.28 (1H, m, Ar-H); 5.45-5.54 (1H, m, 4-H); 5.08-5.17 (1H, m, 3-H); 4.05 (1H, dd J 3.9 Hz 11.2 Hz, 1-H); 2.95-3.07 (1H, m, 2-H); 2.75-2.91 (1H, m, 2-H); 2.59 (6H, s, N-(CH₃)₂); 1.54-1.59 (3H, m, 5-CH₃); ¹³C NMR (100 MHz) δC 135.8 (Ar-C); 132.6 (Ar-CH); 131.9 (Ar-CH); 130.2 (Ar-CH); 129.4 (4-CH); 128.3 (Ar-CH); 125.1 (3-CH); 122.6 (C-Br); 67.0 (1-CH); 37.7 (N-(CH₃)₂); 32.2 (2-CH₂); 17.9 (5-CH₃); vmax (solid, cm⁻¹) 1329 & 1138 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₃H₁₃NO₃S [M+Na]⁺ 354.0134, found 354.0174.

N,N-Dimethyl-1-phenylethane-1-sulfonamide (125a)

N,N-Dimethyl-1-phenylmethanesulfonamide (0.15g, 1.5 mmol, 1 eq) and iodomethane (0.71g, 5 mmol, 4 eq) was reacted following general procedure E, for an extended reaction time of 16 hours at room temperature, to yield N,N-dimethyl-1-phenylethane-1-sulfonamide as a colourless oil (0.18g, 86 %); Rf = 0.6 (95:5 toluene:EtOAc); ¹H NMR (400 MHz, CDCl₃) δH 7.35-7.45 (5H, m, Ar-H); 4.28 (1H, q J 7.1 Hz, 1-H); 2.59 (6H, s, N-(CH₃)₂); 1.77 (3H, d J 7.1 Hz, 2-CH₃); ¹³C NMR (100 MHz) δC 135.3 (1 x Ar-C); 128.9 (2 x Ar-CH); 128.8 (1 x Ar-CH); 128.7 (2 x Ar-CH); 62.1 (1-CH); 37.7 (N-(CH₃)₂); 16.2 (2-CH₃); vmax (oil, cm⁻¹) 1321 & 1137 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₀H₁₅NO$_2$S [M+Na]$^+$ 236.0716, found 236.0722.

N,N-Dimethyl-1-phenylpropane-1-sulfonamide (125b)

N,N-Dimethyl-1-phenylmethanesulfonamide (99.6 mg, 0.5 mmol, 1 eq) and iodoethane (78 mg 0.5 mmol, 1 eq) was reacted following the general procedure E to yield N,N-dimethyl-1-phenylpropane-1-sulfonamide (43 mg, 40 %); Rf = 0.47; ¹H NMR (400 MHz, CDCl₃) δH 7.36-7.40 (5H, m, Ar-H); 4.00 (1H, dd J 3.9 Hz 11.2 Hz, 1-H); 2.53 (6H, s, N-(CH₃)₂); 2.33-2.45 (1H, m, 2-H); 2.11-2.21 (1H, m, 2-H); 0.85 (3H, t J 7.5 Hz, 3-H₂); ¹³C MR (100 MHz) δC 133.5 (1 x Ar-C); 129.5 (2 x Ar-CH); 128.9 (1 x Ar-CH); 128.7 (2 x Ar-CH); 69.1 (N-(CH₃)₂); 37.6 (1-CH); 23.3 (2-CH₂); 11.4 (3-CH₃); vmax (solid, cm⁻¹) 1319 & 1139 (sulfonamide S=O); m/z (ESI⁺) calculated for C₁₁H₁₇NO₃S [M+Na]$^+$ 250.0872, found 250.0870.
N,N-2-Trimethyl-1-phenylbutane-1-sulfonamide (125c)

\[
\begin{array}{c}
\text{N, N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol, 1 eq) and 2-bromobutane (343 mg, 0.5 mmol, 1 eq) was reacted following the general procedure E to yield N,N-2-trimethyl-1-phenylbutane-1-sulfonamide as a colourless oil and mixture of diastereomers (77:23, determined by } ^1\text{H NMR) (101 mg, 80 %); R}_{\text{F}} = 0.63; ^1\text{H NMR (400 MHz, CDCl}_3) \, \delta_\text{H} 7.34-7.44 (5\text{H, m, Ar-H}); 4.05 (1\text{H, d J 6.6 Hz, 1-H}); 2.47-2.52 (1\text{H, m, 2-H}); 2.46 (6\text{H, s, N-C(H}_3)_2); 1.60-1.70 (1\text{H, m, 3-H}); 1.27-1.30 (1\text{H, m, 3-H}); 0.93-0.97 (5\text{H, m, 4-H}_3, 2'-H_2); ^13\text{C NMR (100 MHz) } \delta_\text{C} 132.9 (\text{Ar-C}); 130.3 (2 \times \text{Ar-CH}); 128.6 (2 \times \text{Ar-CH}); 71.1 (1-CH); 37.6 (N-(C(H)_3)_2); 36.1 (2-CH); 27.7 (3-CH_2); 16.3 (2'-CH_3); 11.1 (4-CH_3); \nu_{\text{max}} (\text{solid, cm}^{-1}) 1320 & 1140 (\text{sulfonamide S=O}); m/z (ESI+) calculated for C_{13}H_{21}NO_2S [M+Na]^+ 278.1185, found 278.1180.\\
\end{array}
\]

N,N-Dimethyl-1,2-diphenylethane-1-sulfonamide (125d)

\[
\begin{array}{c}
\text{N,N-Dimethyl-1-phenylmethanesulfonamide (99.6 mg 0.5 mmol, 1 eq) and benzyl bromide (86 mg, 0.5 mmol, 1 eq) was reacted following the general procedure A to yield N,N-dimethyl-1,2-diphenylethane-1-sulfonamide as a yellow oil (101.7 mg, 70 %); R}_{\text{F}} = 0.39; ^1\text{H NMR (400 MHz, CDCl}_3) \, \delta_\text{H} 7.31-7.39 (5\text{H, m, Ar-H}); 7.11-7.17 (3\text{H, m, Bn-H}); 6.98-7.00 (2\text{H, m, Bn-H}); 4.32 (1\text{H, dd J 3.2 Hz 11.4 Hz, 1-H}); 3.71 (1\text{H, dd J 3.3 Hz 14.2 Hz, 2-H}); 3.40 (1\text{H, dd J 11.4 Hz 14.2 Hz, 2-H}); 2.54 (6\text{H, s, N-(CH}_3)_2); ^13\text{C NMR (100 MHz) } \delta_\text{C} 137.2 (\text{Bn-C}); 133.0 (\text{Ar-C}); 129.7 (2 \times \text{Ar-CH}); 129.0 (2 \times \text{Bn-CH}); 128.9 (1 \times \text{Ar-CH}); 128.7 (2 \times \text{Ar-CH}); 128.3 (2 \times \text{Bn-CH}); 126.6 (\text{Bn-CH}); 68.9 (1-CH); 37.7 (N-(CH}_3)_2); 36.4 (2-CH_2); \nu_{\text{max}} (\text{solid, cm}^{-1}) 1328 & 1141 (\text{sulfonamide S=O}); m/z (ESI+) calculated for C_{16}H_{19}NO_2S [M+Na]^+ 312.1029, found 312.1031.\\
\end{array}
\]

1-Cyclopentyl-N,N-dimethyl-1-phenylmethanesulfonamide (125e)

\[
\begin{array}{c}
\text{N,N-Dimethyl-1-phenylmethanesulfonamide (99.6 mg 0.5 mmol, 1 eq) and bromocyclobutane (373 mg, 0.5 mmol, 1 eq) was reacted following the general procedure A, for an extended reaction time of 16 hours at room temperature, to yield 1-cyclopentyl-N,N-dimethyl-1-phenylmethanesulfonamide as a colourless oil and single diastereomer (55 mg, 41 %) R}_{\text{F}} = 0.65; ^1\text{H NMR (400 MHz, CDCl}_3) \, \delta_\text{H} 7.34-7.39 (5\text{H, m, Ar-H}); 3.92 (1\text{H, d J}
\end{array}
\]
10.2 Hz, 1-H); 2.68-2.79 (1H, m, 2-H); 2.43 (6H, s, N-(CH₃)₂); 2.21-2.58 (1H, m, 3-H); 1.60-1.72 (2H, m, 4-H, 5-H); 1.51-1.59 (2H, m, 4-H, 5-H); 1.43-1.49 (2H, m, 3-H, 6-H); 0.95-1.0 (1H, m, 6-H); ¹³C NMR (100 MHz) δ C 134.9 (1 x Ar-C); 129.5 (1 x Ar-CH); 128.6 (4 x Ar-CH); 72.9 (1-CH); 41.7 (2-CH); 37.5 (N-(CH₃)₂); 32.2 (3-CH₂); 31.9 (4-CH₂); 25.3 (5-CH₂); 23.9 (6-CH₂); \( \nu_{max} \) (solid, cm⁻¹) 1339 & 1131 (sulfonamide S=O); m/z (ESI+) calculated for C₁₄H₂₁NO₂S [M+Na]⁺ 290.1185, found 290.1180.
CHAPTER 4 REFERENCES

CHAPTER 5 APPENDIX

5.1 NMR Data

Compound 90a
Compound 90b

[Chemical structure image]

[Graphical representation of NMR spectra with ppm scale]
Compound 90c
Compound 90d
Compound 90f
Compound 90g
Compound 90h
Compound 90i
Compound 90j
Compound 90k
Compound 91

1H NMR spectrum

13C NMR spectrum
Compound 92
Compound 99f

[Diagram of the compound 99f]
Compound 99g
Compound 99h
Compound 99j
Compound 99k
Compound 99I
Compound 100b
Compound 100c
Compound 100d
Compound 100e

[Chemical structure diagram]

[1D NMR spectrum]

[2D NMR spectrum]
Compound 100g
Compound 104a
Compound 104b
Compound 104c

Chemical structure and spectra.
Compound 104h
Compound 7a
Compound 111
Compound 112
Compound 113a
Compound 116
Compound 117
Compound 124a
Compound 124b
Compound 124c
Compound 124d
Compound 124f
Compound 124g
Compound 125a
Compound 125b
Compound 125c
Compound 125e
5.2 Crystal Data

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5.3 HPLC Data

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Compound 90a

Enantiomer 1:

![Graph of Enantiomer 1](image_url)

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<th>[min]</th>
<th>[mAU·s]</th>
<th>[mAU]</th>
<th>%</th>
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<td>1</td>
<td>0.376</td>
<td>0.164</td>
<td>7856.93164</td>
<td>796.88593</td>
<td>100.0000</td>
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Totals: 7856.93164 796.88593
Enantiomer 2:

![Chemical Structure Image]

Signal 1: DAD1 C, Sig=220,4 Ref=360,100

<table>
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<tr>
<th>#</th>
<th>Ret Time [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
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<tbody>
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<td>1</td>
<td>8.505 BB</td>
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<td>124.28360</td>
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<td>1.09814e4</td>
<td>966.55383</td>
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Totals: 1.11057e4 980.68726
Compound 100a

L19a & L19b = 4 % ee

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<tbody>
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L19f = 8 % ee

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<tbody>
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<td>400.97998</td>
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Totals: 753.01828 112.43892