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# Elucidating the Mechanism of the Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation of α-Sulfonyl Anions

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## Declaration

I confirm that this thesis, presented for the degree of MSc Chemistry (by research), has been composed entirely by myself and it is the result of my own work. This thesis has not been submitted for any other degree or professional qualification.

Eleanor Bowen, Lancaster University

## Abstract

This research project focused on the investigation of the palladium-catalysed decarboxylative asymmetric allylic alkylation (Pd-DAAA) reaction of α-anions of a 5-membered sulfone, sulfolane, bearing a range of ketone and ester anion stabilising substituents, in the presence of the (*S*,*S*)-ANDEN Phenyl Trost ligand. In the first instance, the synthesis of the prerequisite substrates for the Pd-DAAA reaction, namely a sulfone bearing allyl ester and phenyl ester substituents, and a sulfone bearing allyl ester and phenyl ketone substituents, was optimised.

A mechanistic study followed, and it was discovered that substrates containing a 2-methyl substituted allyl ester were less reactive than their non-substituted counterparts, making these intermediates unsuitable for enolate crossover studies. Instead, $^{2}$H-labelling of the allylic ester was achieved in good yield with 93% deuterium incorporation at the terminal alkene position. Enolate crossover reactions of both ester and ketone deuterated and non-deuterated substrates showed significant crossover, suggesting that an outer-sphere alkylation mechanism operates for both ester and ketone substrates.

Relative stereochemistry determination experiments were attempted to conclusively establish the mechanism of the Pd-DAAA of cyclic sulfones, using *cis*-5-phenyl-2-cyclohexen-1-ol as the allylic stereochemical label. Although benzyl ester and phenyl ketone precursors were successfully prepared, they were found to be unreactive in the Pd-DAAA process, even over an extended reaction time with temperatures up to 120 °C.

Optimisation of the Pd-DAAA of cyclic sulfones was explored by testing the use of additives, in an effort to increase the observed enantioselectivity. Ultimately, no increase in enantioselectivity was observed as compared to previously optimised additive-free conditions. Using these conditions, the substrate scope of the Pd-DAAA reaction was substantially broadened for a range of not only 5- but also 6-membered cyclic sulfones with varying ester and ketone substituents, affording novel enantioenriched alkylated products with 10-94% ee.

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## Acknowledgements

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## Abbreviations

| | |
|---|---|
| AAA | asymmetric allylic alkylation |
| Ac | acetyl |
| acac | acetylacetonate anion |
| Ad | adamantyl |
| Ar | unspecified aryl group |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| BSA | bis(trimethylsilyl)acetamide |
| Bu | butyl |
| C | celsius |
| CDI | 1,1'-carbonyldiimidazole |
| cod | 1,5-cyclooctadiene |
| CSA | camphorsulfonic acid |
| DAA | decarboxylative allylic alkylation |
| DAAA | decarboxylative asymmetric allylic alkylation |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | 1,2-dichloroethane |
| DFT | density functional theory |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| ee | enantiomeric excess |
| Et | ethyl |
| HPLC | high performance liquid chromatography |
| L | ligand |
| LDA | lithium diisopropylamide |
| LG | unspecified leaving group |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| $M^+$ | unspecified metal cation |

| | |
|---|---|
| Me | methyl |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| n.d. | not determined |
| NMR | nuclear magnetic resonance |
| Nu | unspecified nucleophile |
| *o* | *ortho* |
| o/n | overnight |
| OTf | trifluoromethanesulfonate |
| P | product |
| *p* | *para* |
| Ph | phenyl |
| PHOX | phosphinooxazoline |
| pmdba | 4,4'-methoxydibenzylideneacetone |
| Pr | propyl |
| R | unspecified alkyl group |
| rt | room temperature |
| SM | starting material |
| *t* | *tertiary* |
| TBA | tetrabutylammonium cation |
| TBME | *tert*-butyl methyl ether |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| Tol | tolyl |
| TS | transition state |
| Ts | tosyl |
| $X^-$ | unspecified counterion |

## Chapter 1: Literature Review

## 1. Introduction

Ring systems are the fundamental building blocks of the majority of small molecule drugs on the market currently.[1] Rings provide rigidity to the drug molecule, and affect its pharmacokinetic and pharmacodynamics properties. Every year, on average 28% of newly developed drugs contain one novel ring system. However, in 2014, 40% of drugs did not contain $sp^3$-hybridised carbon atoms in any ring system. This widespread use of aromatic systems ($sp^2$-hybridised) could be attributed to the overuse of highly efficient cross-coupling methods for carbon-carbon bond formation.[2]

It has been shown, however, that increasing the complexity of a drug molecule by introducing more $sp^3$ and chiral centres correlates with success as the compound passes through development and clinical testing phases,[3] and there is a decrease in the average number of aromatic rings per molecule in going from preclinical drug candidates to candidates that are successful in clinical trials.[2] A potential reason for this phenomenon could be that a high 'aromatic proportion' in a molecule can negatively affect aqueous solubility, a factor that must be carefully controlled in drug development.[4] This suggests that limiting the number of aromatic rings per molecule could make the drug candidate statistically more developable.

Conversely, increased saturation in a molecule is more likely to enhance its aqueous solubility whilst maximising the interrogation of three-dimensional chemical space.[3] Since Lipinski developed the Rule of 5,[5] a set of criteria that describe the physical properties of most oral small molecule drugs, the pharmaceutical industry is more conscious of the impact of the physical properties of a drug candidate prior to, and during, development.[4] The increased complexity that saturated molecules offer may also enable the discovery of new binding sites by disrupting protein-protein interactions.[6]

Additionally, toxicity is a leading cause of attrition during all phases of drug development, and is often due to off-target effects within the body.[7] It has been shown that compounds with greater saturation possess lower toxicity, and it has been hypothesised that this is due to more complementary binding between a more three-dimensional molecule and the three-dimensional binding sites in drug targets, limiting off-target effects.[8]

The synthesis of novel saturated three-dimensional molecules is challenging, particularly those containing a chiral quaternary all-carbon centre. Indeed, the majority of drug molecules bearing this feature are derived from natural products comprising the quaternary centre, thus highlighting the lack of reliable synthetic methods for their construction.[9] More efficient

assembly of quaternary stereogenic centres could significantly enhance the diversity of three-dimensional building blocks, substantially expanding beyond the structures that natural products can offer. For example, most natural products have limited nitrogen incorporation, yet nitrogen is extremely common in medicinal chemistry, particularly for building heterocycles and fused compounds, as well as in cross-coupling reactions.[10]

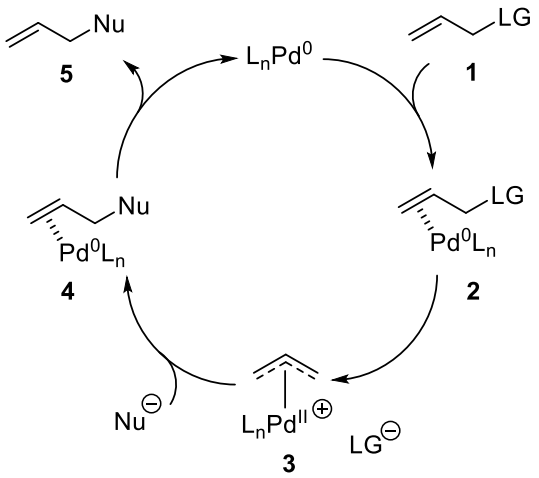
In a push towards unprecedented ring systems, spirocyclic compounds were popularised as novel building blocks for drug discovery in 2010 as alternatives to flat aromatic rings.[11] Spiro rings are represented in numerous natural products,[12] and they offer a high degree of three-dimensionality, which enables more efficient use of chemical space in order to maximise hydrogen bonding, lipophilic, and π-stacking interactions, allowing for more complementary binding between the drug and its binding site.[13] The rigidity of spirocycles also imposes well-defined spatial orientation on exit vectors, leading to a larger set of vectors being accessible in three-dimensional space.[14] It has also been found that molecules containing a small ring bearing a chiral quaternary centre are less subject to oxidative metabolism within the body than analogous molecules containing simple $sp^3$-chains, potentially lowering toxicity.[15] Additionally, many emerging spiro building blocks for drug discovery are structurally novel, thus with potential for patent protection.[12]

Because of the apparent benefits of incorporating spirocyclic building blocks into drug molecules, they are of increasing interest in the pharmaceutical industry, yet remain a rarity in fragment libraries.[16] This is likely due to limitations in the current methods available for the synthesis of novel spirocyclic compounds, particularly in enantiopure form. Spirocycles necessarily contain a quaternary centre, and despite significant advances by Carreira *et al*. in this area,[14] the stereoselective construction of chiral spirocycles remains an underdeveloped area.

## 1.2 A Comparison of Direct and Decarboxylative Allylic Alkylation

Over the years, asymmetric allylic alkylation (AAA) and decarboxylative asymmetric allylic alkylation (DAAA) methodologies have been developed to allow for reliable formation of chiral quaternary centres by carbon-carbon bond formation. In particular, by using chiral ligands, these quaternary centres can be installed with high enantioselectivity. These reactions can proceed under mild reaction conditions, making this method attractive to industry.[17] AAA and DAAA allow for the desired increased complexity in molecules as they can impart stereochemistry at quaternary centres. AAA and DAAA are unique in that they allow for a variety of bond types, both carbon-carbon and many carbon-heteroatom bonds, to form in the presence of a single catalyst.[18]

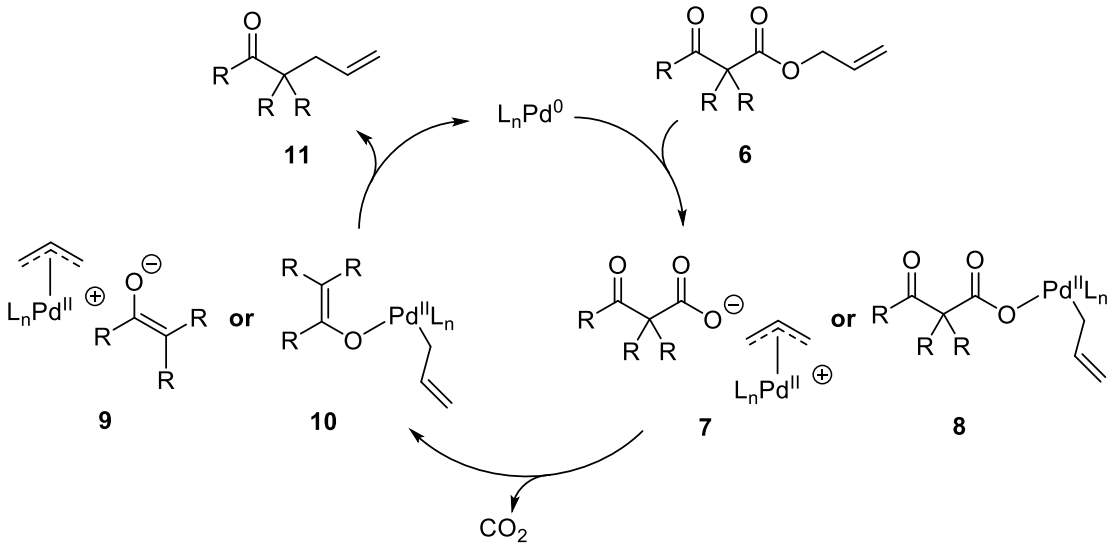
Direct allylic alkylation occurs between an allylic electrophile and a nucleophile as two independent species. The catalytic cycle of direct allylic alkylation involves four elementary steps (Scheme 1). The first is complexation of a palladium catalyst to the alkene of allyl electrophile **1** to give palladium(0) complex **2**. This is followed by the ionisation step, which involves an oxidative addition of palladium(0) to give π-allylpalladium(II) system **3**. An incoming nucleophile then attacks this intermediate to form a new allylated product **4**. The final step is decomplexation, where allylated product **5** dissociates from the palladium catalyst, which is then regenerated.




**Scheme 1**

A process similar to direct allylic alkylation is the decarboxylative allylic alkylation reaction in which the allylic electrophile and latent nucleophile are tethered *via* an ester or carbonate motif, such as in **6** (Scheme 2). The catalytic cycle of decarboxylative allylic alkylation begins with complexation of the palladium(0) catalyst to the alkene of allyl substrate **6**, followed by an oxidative addition to give a π-allylpalladium(II) system, where the nucleophile and electrophile

exist as an ion pair **7**, or as a covalently-bonded σ-allylpalladium(II) species **8**. **7** or **8** can then undergo decarboxylation to give rise to enolate **9** as an ion pair, or covalently-bonded **10**. The enolate nucleophile generated *in situ* then undergoes allylic alkylation to form allylated product **11**, after decomplexation.



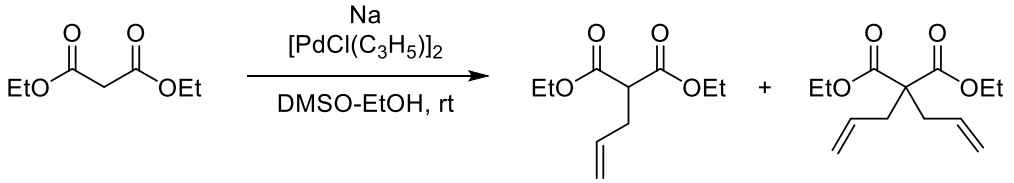

**Scheme 2**

While direct and decarboxylative allylic alkylation reactions can afford the same products, they differ in a number of ways. Decarboxylative allylic alkylation reactions are unimolecular as the nucleophilic and electrophilic species form simultaneously *in situ*, and therefore high-energy intermediates are formed in catalytic concentrations, minimising unwanted side-reactions.[19] On the other hand, direct asymmetric allylic alkylation reactions are intermolecular processes, requiring stoichiometric nucleophile addition.

A further benefit of decarboxylative allylic alkylation is the ability to regiospecifically alkylate non-symmetrical ketones, more specifically an enolate that is generated by decarboxylation is rapidly trapped by the allylic electrophile even in the presence of other enolisable positions without enolate scrambling.[19] Conversely, direct allylic alkylation of non-symmetrical ketones typically requires the use of a strong base or specific enol equivalent to regioselectively form either the kinetic or thermodynamic enolate. This often limits the process to ketones with a single enolisable position, or ketones where the difference in p$K_a$ between possible enolisable positions is substantial. The use of mild, neutral conditions gives the decarboxylative process utility over a wider range of substrates.[20]

## 1.3 The Development of Palladium-Catalysed AAA

The first allylic alkylation reaction was reported in 1965, in which the coupling of π-allylpalladium(II) chloride and diethyl malonate (**12**) afforded ethyl allyl malonate (**13**) in 37% yield as well as ethyl diallylmalonate (**14**) in 39% yield, with metallic palladium(0) as the by-product (Scheme 3).[21]

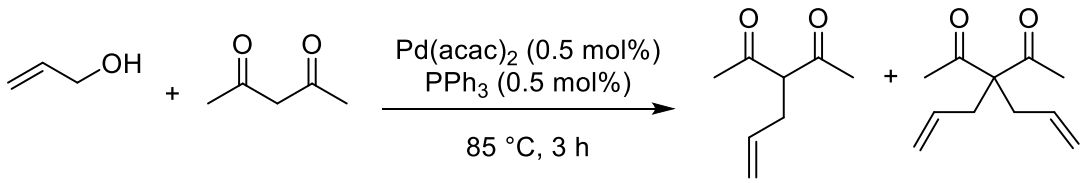



**12** **13** 37% **14** 39%

**Scheme 3**

The use of stoichiometric palladium would cause this first iteration of the allylic alkylation process to be very expensive and would prevent both the scale-up and the utility of the reaction. Therefore, attention turned to converting this reaction into a catalytic process. In 1970, two research groups reported the development of catalytic allylic alkylation reactions.[22,23] The scope of palladium catalysts that could be used for allylic alkylation was demonstrated, including palladium(0) complexes, such as tetrakis (triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride in the presence of sodium phenoxide, and palladium(II) acetate in the presence of triphenylphosphine.[22]

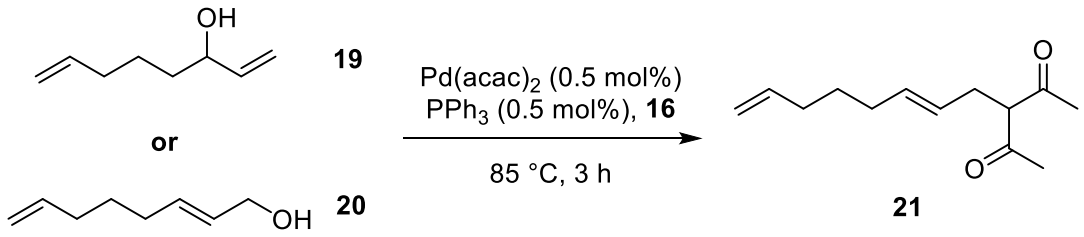
The utility of this process was demonstrated in the reaction of allylic alcohols, such as **15**, with acetylacetone (**16**), using palladium(II) acetylacetonate in the presence of triphenylphosphine as the catalyst, to give allylated products **17** and **18** (Scheme 4).[23] Subsequently, the scope of this method was extended to the alkylation of allylic esters and amines.




**15** **16** **17** 70% **18** 26%

**Scheme 4**

Interestingly, it was discovered that isomeric allylic alcohols **19** and **20** both yielded the same allylated product **21**, suggesting that both reactions proceeded *via* a common intermediate (Scheme 5).

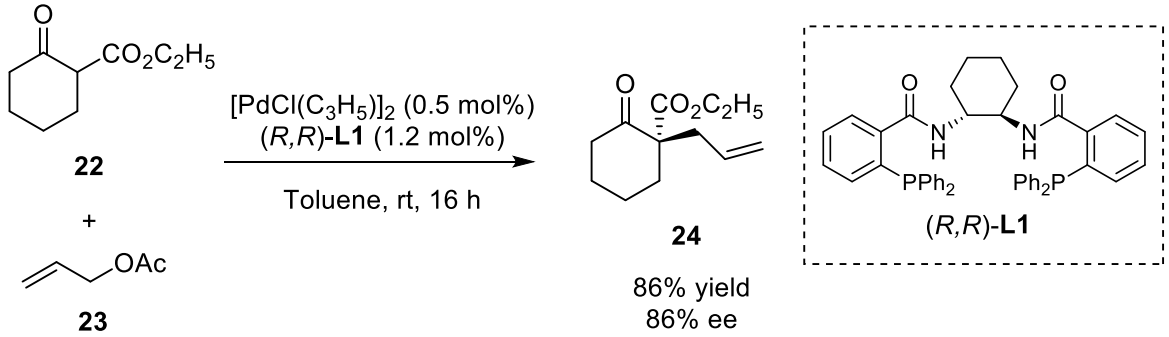



**Scheme 5**

In order to increase the utility of the allylic alkylation reaction, attention turned to the investigation of enantioselective variants of the allylic alkylation reaction using chiral ligands.

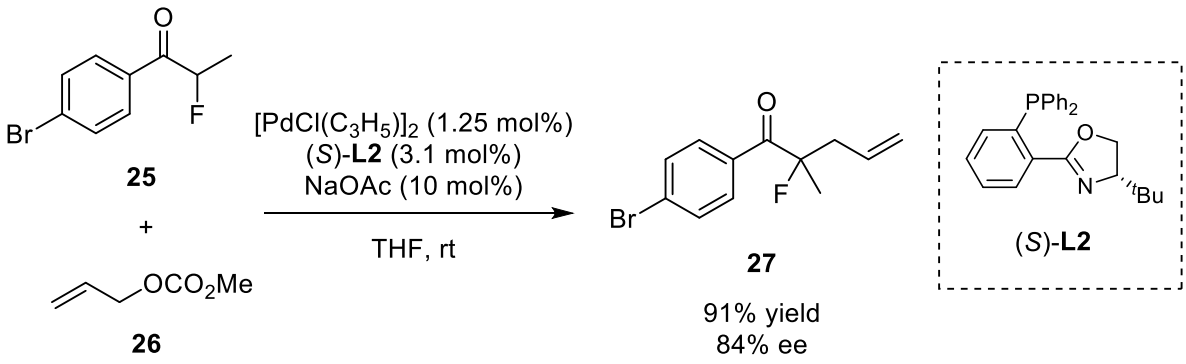
Palladium-catalysed allylic alkylation reactions were originally unresponsive to asymmetric induction, until 1992, when a variety of bidentate ligands were synthesised, leading to the disclosure of the first enantioselective allylic alkylation reaction.[24] Two factors in particular influenced the design of these ligands: first, the hypothesis that increasing the bite angle, θ, by altering the tether lengths in a bidentate ligand, could enhance asymmetric induction by pushing the chiral environment closer towards the allyl moiety; and second, the knowledge that the use of $C_2$ symmetric ligands has been key for successfully inducing asymmetry in other reaction processes.[25]

The two main groups of ligands used for allylic alkylation are Trost ligands, such as the (*R,R*)-DACH phenyl Trost ligand (*R,R*)-**L1** (Scheme 6), and phosphinooxazolines (PHOX) ligands, such as the (*S*)-*t*-Bu-PHOX ligand (*S*)-**L2** (Scheme 7). An example of an allylic alkylation reaction using (*R,R*)-**L1** was the AAA of a cyclohexanone derivative **22** and allyl acetate (**23**) with allylpalladium(II) chloride dimer as a source of palladium (Scheme 6), to afford **24**, bearing an all-carbon quaternary centre, in 86% yield and 86% ee.[26]




**Scheme 6**

An example of allylic alkylation using PHOX ligand (*S*)-**L2** was the AAA reaction of acyclic fluorinated ketones (Scheme 7), such as **25**, using allyl methyl carbonate (**26**) and allylpalladium(II) chloride dimer as the palladium source, to give α-quaternary ketone **27** in 91% yield and 84% ee.[27]

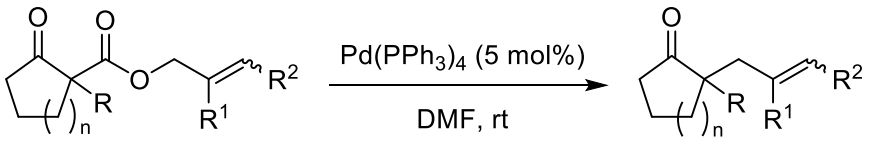



**Scheme 7**

This research area has undergone substantial development since these original discoveries to the asymmetric allylic alkylation of a broad variety of functional groups.[17]

## 1.4 The Development of Palladium-Catalysed Decarboxylative AAA

Two research groups reported the first decarboxylative palladium-catalysed allylic alkylation reaction in quick succession in 1980.[28,29] The conversion of allylic cyclic β-ketoesters **28** to α-allylic ketones **29** was reported to proceed in moderate to high yields by means of decarboxylative allylic alkylation (Scheme 8), using tetrakis (triphenylphosphine)palladium(0) in catalytic quantities.[28]




**28**

n = 1,2
R = Et, allyl; $R^1$= Me; $R^2$= alkyl

**29**
10 examples
31-96%

**Scheme 8**

While products **29** contain a quaternary all-carbon centre and therefore do not posses a second acidic α-proton, there were issues with dialkylation of simpler malonate systems (Scheme 9), such as **30**, leading to lower yield of the desired monoalkylated product **31** for these reactions.

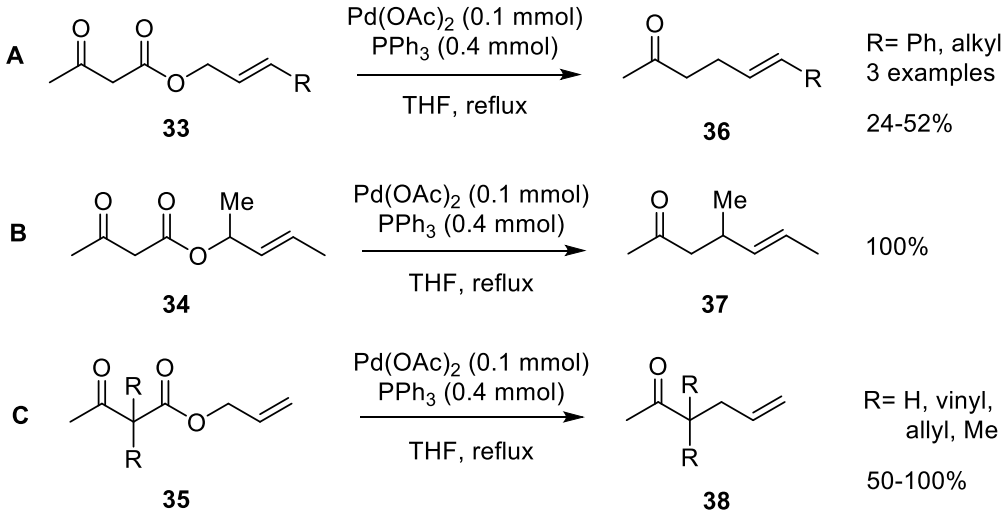

**30**

**31**
37%

**32**
16%

**Scheme 9**

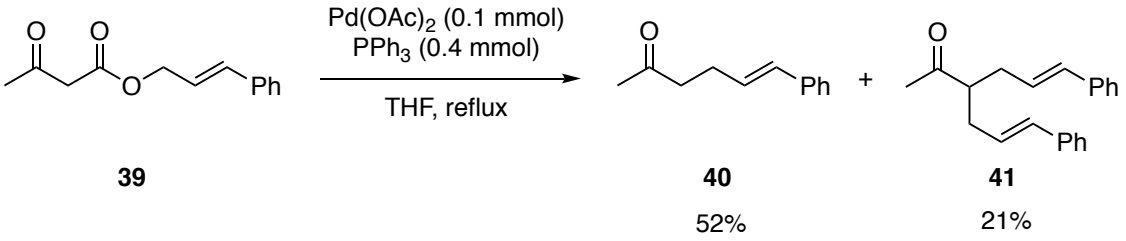
Almost simultaneously, the decarboxylative allylic alkylation of allylic esters **33-35** to give ɣ,δ-unsaturated methyl ketones **36-38** under mild conditions was reported in up to 100% yield (Scheme 10).[29]




**Scheme 10**

Reaction A afforded the linear product **36** exclusively, with no observed branched product formation. The use of disubstituted allylic electrophile **34** successfully afforded **37**, which presumably proceeded *via* a symmetrical π-allylpalladium(II) intermediate. Reactions A and B are analogous to the Carroll rearrangement but can take place at much lower temperatures, highlighting one of the benefits of decarboxylative allylic alkylation. Importantly, allylic alkylation reaction C provided a route to products **38** containing a quaternary all-carbon centre.

Once again, there was formation of unwanted dialkylated products, such as **41**, formed from simpler malonate systems, such as **39**, leading to decreased yields of the desired monoalkylated product in some cases (Scheme 11).

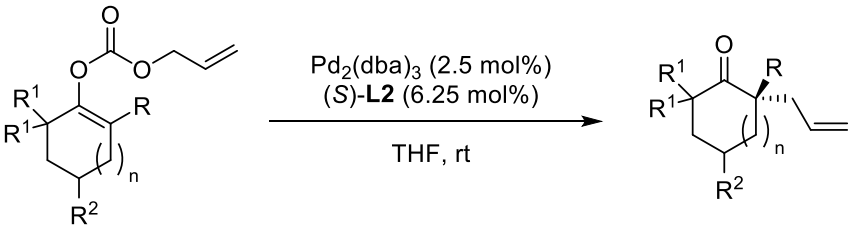



**Scheme 11**

Although this reaction was successful in forming quaternary carbon centres under extremely mild conditions, the utility of the reaction was limited until enantioselective versions of the reaction emerged.

The first enantioselective decarboxylative allylic alkylation processes were reported in 2004.[30] The use of decarboxylative asymmetric allylic alkylation of ketone enolates **42** to generate α-chiral ketones **43** bearing quaternary all-carbon centres was demonstrated (Scheme 12),

giving good to excellent yields and high enantioselectivity. In this process, allyl enol carbonates were utilised which revealed the latent ketone enolate upon decarboxylation.




**42**

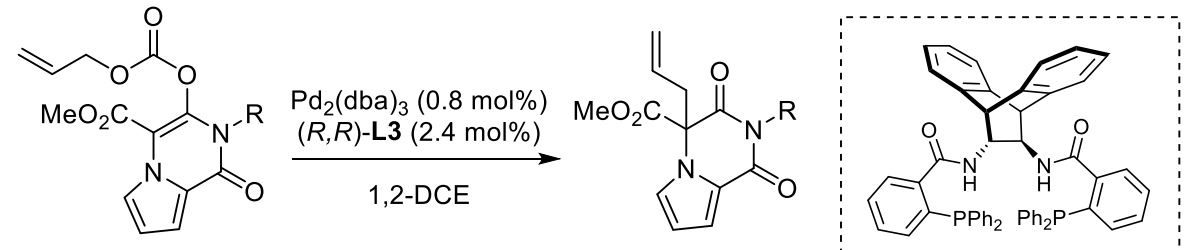
n= 1,2,3
R= Me, Et, Bn, $^{t}$Bu; $R^1$= Me;
$R^2$= ethylene ketal

**43**

13 examples
55-96% yield
79-92% ee

**Scheme 12**

DAAA reactions of a wide range of other functionalities have also been reported since then. In 2011, the first decarboxylative asymmetric allylic alkylation of β-imidoester derived carbonate **44** was disclosed (Scheme 13), with **44** undergoing DAAA in the presence of (*R,R*)-**L3** and tris(dibenzylideneacetone)dipalladium(0) to form alkylated product **45** in moderate yield and good ee.[31]




**44**

R=4-bromo-2-fluorobenzyl

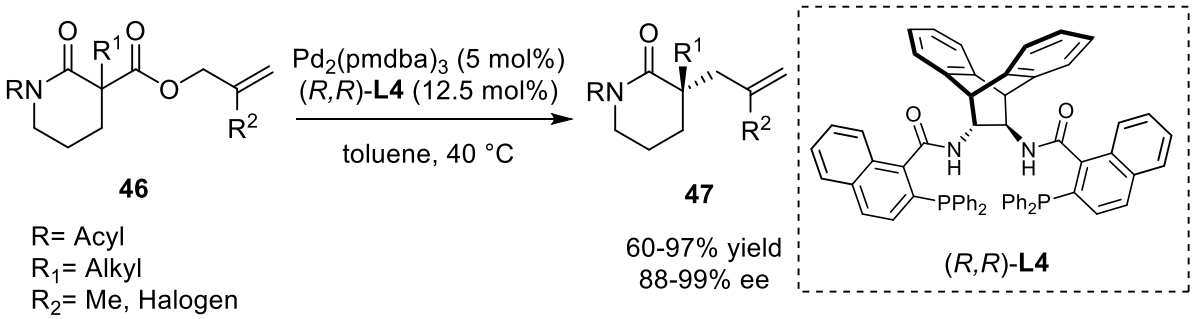
**45**

65% yield
80% ee

*(R,R)*-**L3**

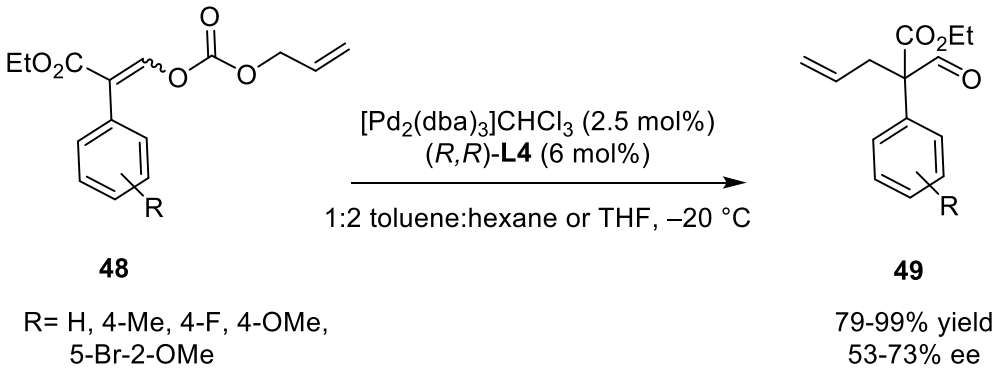
**Scheme 13**

An important example of DAAA was the synthesis of a variety of α-quaternary-δ-lactams **47**, in good to excellent yield and ee, from lactams **46** using tris(4,4'-methoxydibenzylidene acetone)dipalladium(0) and (*R,R*)-**L4** (Scheme 14).[32] The ability to construct a quaternary stereogenic centre in nitrogen-containing substrates was key for expanding reaction scope beyond the structures offered by natural products and entering chemical space relevant to medicinal chemistry.



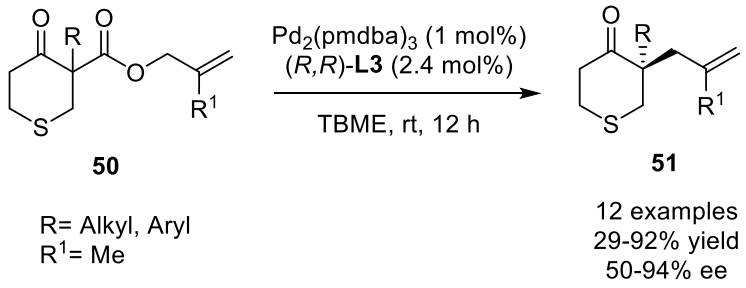

**Scheme 14**

The first DAAA reaction of aldehydes was not reported until 2015, despite aldehydes offering higher reactivity than ketones.[33] Allyl enol carbonates **48** underwent decarboxylative allylic alkylation in the presence of tris(dibenzylideneacetone) dipalladium(0) and (*R,R*)-**L4** to afford α-quaternary aldehydes **49** in excellent yields and moderate to good ee (Scheme 15).




**Scheme 15**

A further interesting example of DAAA was disclosed in 2017, using 4-thiopyranones **50** to form α-quaternary 4-thiopyranones **51** in moderate to high ee (Scheme 16).[34] α-Quaternary 4-thiopyranones were traditionally difficult to synthesise using standard enolate alkylation methods due to issues with ring-opening *via* β-sulfur elimination. The 4-thiopyranones formed in this reaction have potential as building blocks for drug discovery, however, the carbon-sulfur bond can also be reduced to form acyclic α-quaternary ketones which, again, have been difficult to access using traditional methods.

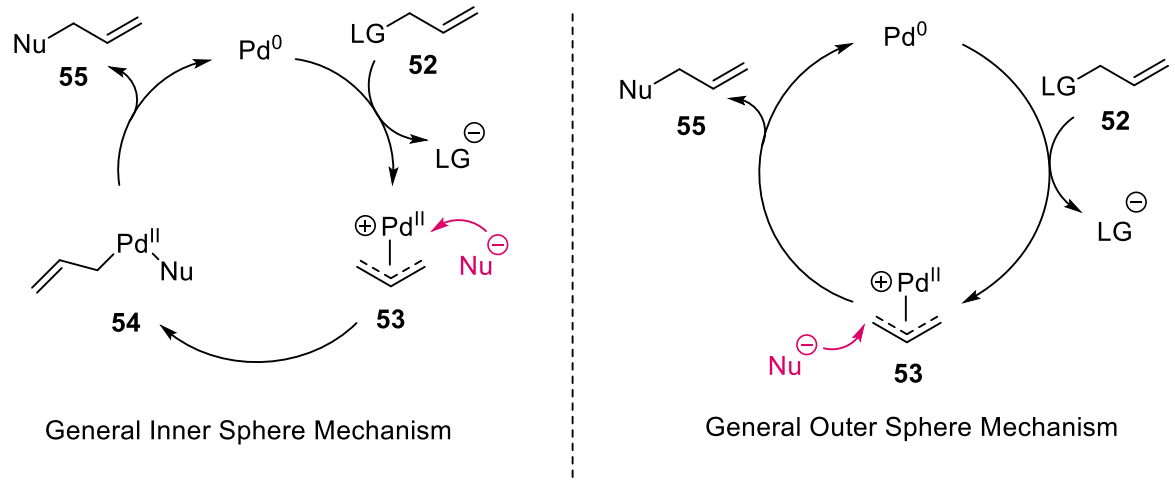



**Scheme 16**

Having reviewed the discovery and development of enantioselective variants of palladium-catalysed allylic alkylation reactions, methods for elucidating the mechanism of the reactions as well as the origins of enantioselectivity are discussed in the next two sections.

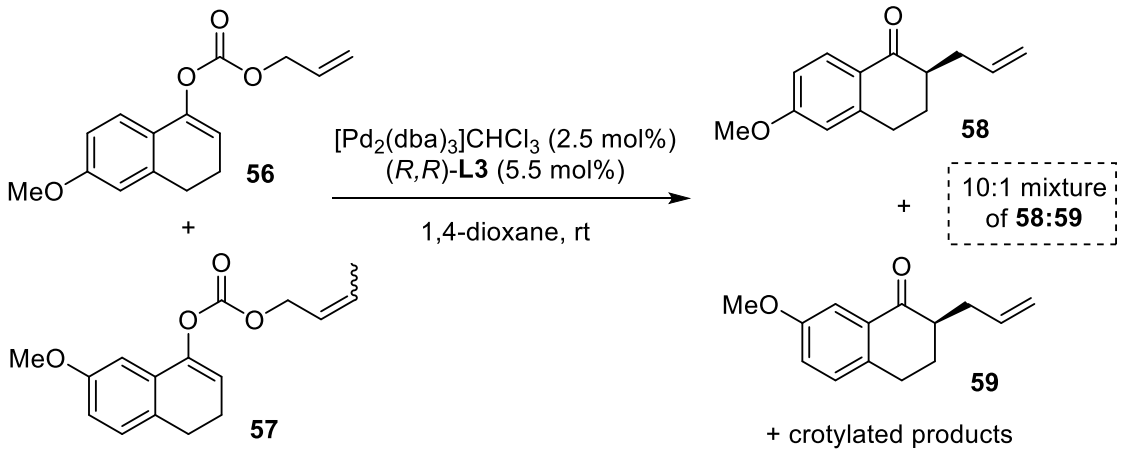
## 1.5 Elucidating the Mechanism of Allylic Alkylation Reactions

There are two potential mechanisms that the palladium-catalysed allylic alkylation reaction can proceed by, which differ in the nucleophilic addition step (Scheme 17). The first is the inner-sphere mechanism, whereby the nucleophile first binds to π-allylpalladium(II) complex **53** catalyst to form **54**, and the subsequent reductive elimination occurs within the metal coordination sphere to afford product **55**. Alternatively, the reaction can proceed *via* an outer-sphere mechanism, where the nucleophile attacks π-allyl system in **53** directly from the outside of the coordination sphere and substitutes the palladium complex to afford product **55**. Whether the reaction mechanism is inner or outer-sphere is highly dependent on the p$K_{aH}$ of the nucleophile employed. Although there are exceptions, stabilised nucleophiles, with a p$K_{aH}$ of <25, typically undergo the reaction *via* the outer-sphere mechanism, whereas unstabilised nucleophiles, with a p$K_{aH}$ of >25, are typically alkylated *via* an inner-sphere mechanism.[35] In addition, the mechanism can also be dependent on the chiral ligand used.



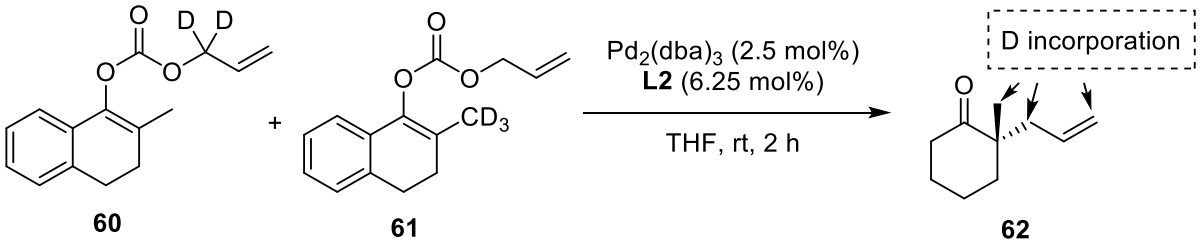

**Scheme 17**

There are a number of strategies that can be used to provide evidence for which mechanism is in operation. One such approach is to perform enolate crossover experiments. In 2005, crossover experiments using a 1:1 mixture of allyl and crotyl enol carbonates, **56** and **57**, respectively, were conducted and minimal crossover was observed, with a 10:1 ratio of the expected allylated product **58** to the crossover allylated product **59**, in addition to crotylated products (Scheme 18).[36] The lack of crossover was attributed to the rate of alkylation surpassing the rate of diffusion of the enolate and π-allylpalladium(II) cation generated upon decarboxylation from the solvent cage, as 1,4-dioxane is better at forming solvent-caged ion pairs than tetrahydrofuran, for example.




**Scheme 18**

In the same year, crossover experiments using a 1:1 mixture of deuterated allyl enol carbonates **60** and **61** using tetrahydrofuran, benzene and 1,4-dioxane as solvents were performed (Scheme 19).[37] In addition to observing deuterium scrambling by NMR spectroscopy, high resolution mass spectrometry indicated the presence of all four potential crossover products in approximately equal amounts, which, in addition to observed deuterium scrambling by NMR spectroscopy, gave rise to a mixture of 6 isomers of **62**. This experiment indicated that the π-allylpalladium(II) complex and the enolate readily dissociate from one another under the reaction conditions, strongly suggesting that alkylation proceeds *via* an outer-sphere mechanism.



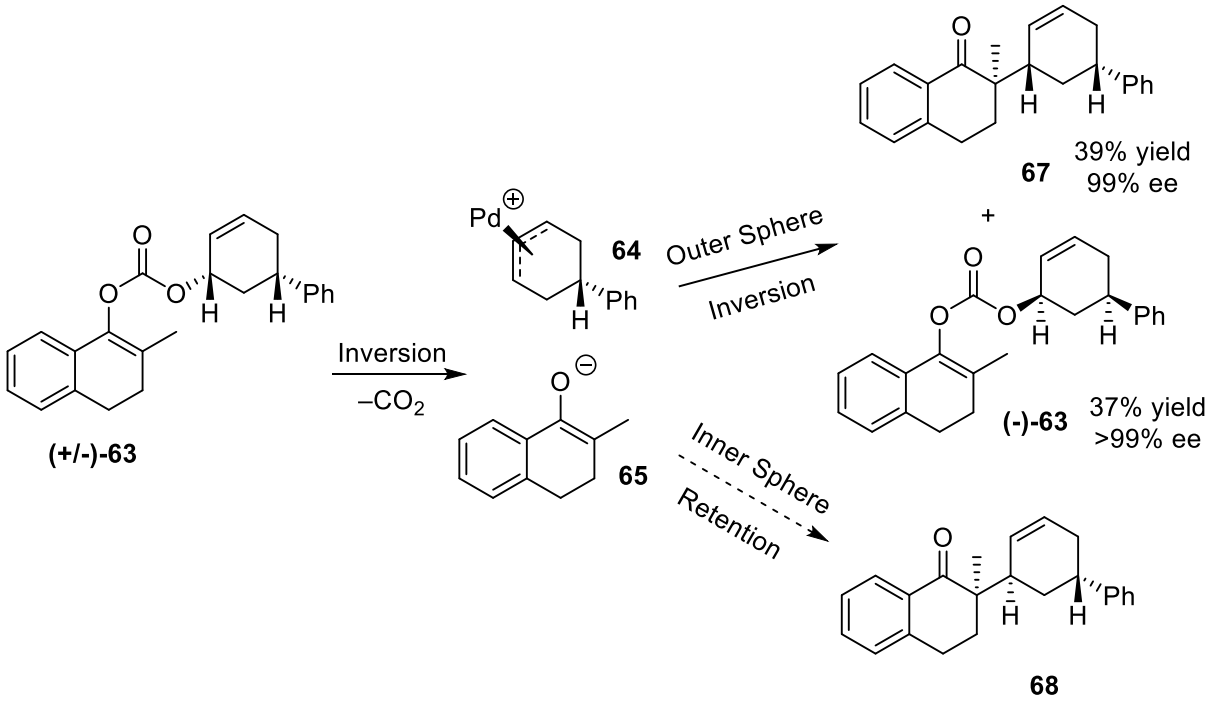

Mixture of 6 isomers, 88%, 87% ee

**Scheme 19**

Both crossover experiments yielded contrasting results. On one hand, this could be due to the use of two different ligands and slight structural differences in substrate. On the other hand, it could suggest that further evidence to corroborate the observed results is required. Furthermore, the presence or lack of crossover gives insight into whether the π-allylpalladium(II) complex and the enolate remain associated during the course of the reaction but cannot provide conclusive evidence of an inner- or outer-sphere alkylation. Species that readily dissociate, giving rise to crossover products, may strongly indicate towards an outer-sphere alkylation; however, lack of crossover gives no indication of whether the π-

allylpalladium(II) complex and the enolate are covalently-bound or exist as a tight ion pair, making the conclusion whether inner- or outer-sphere alkylation operates more tentative.

A more conclusive approach to gaining mechanistic evidence for inner- and outer-sphere alkylation is to perform the DAAA of a chiral allylic substrate, such as **63** (Scheme 20), and then determine the relative stereochemistry of product **67**, as was demonstrated in 2009.[20] Overall, inner- and outer-sphere mechanisms should lead to different stereochemical outcomes. The oxidative addition of the allylic electrophile in **63** to the palladium catalyst proceeds by inversion to afford symmetrical π-allylpalladium(II) unit **64** and enolate **65** after decarboxylation. Then, in the case of an outer-sphere mechanism, alkylation should take place by displacement of palladium with inversion, leading to a net retention of stereochemistry in **67**. In the inner-sphere mechanism, reductive elimination would lead to retention of stereochemistry in **68**. Therefore, the inner-sphere process results in a net inversion of stereochemistry. It was determined by $^{1}$H NMR spectroscopy and X-ray crystallography that the product formed was **67**, where the phenyl group and the nucleophile were *cis*, and therefore the mechanism was concluded to be outer-sphere.

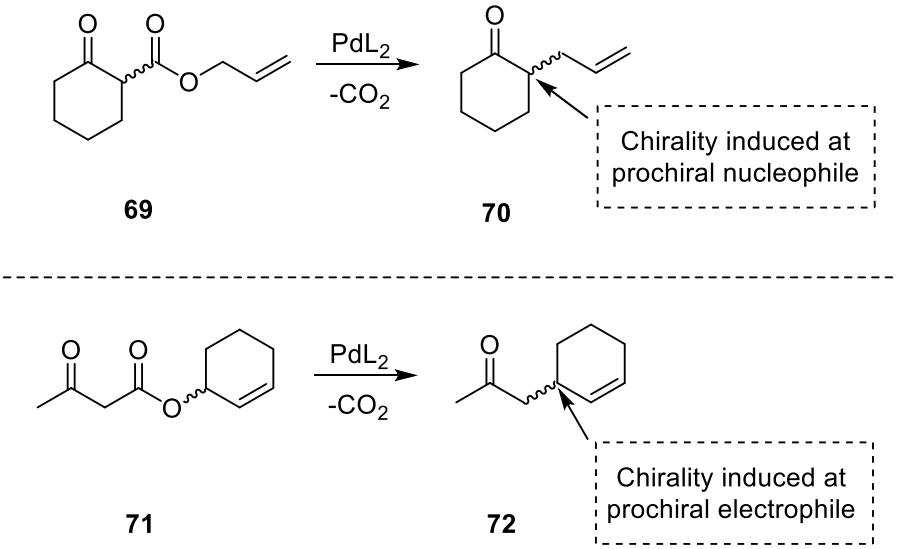



**Scheme 20**

In addition, a nearly perfect kinetic resolution was observed, where one enantiomer of **63** did not react and was recovered in 37% yield (74% based on 50% theoretical yield), and >99% ee, and the other enantiomer of **63** afforded **67** as a single diastereoisomer in 39% yield (79% yield based on 50% theoretical yield) and 99% ee.

## 1.6 The Origin of Enantioselectivity

In both direct and decarboxylative palladium-catalysed asymmetric allylic alkylation reaction processes, enantioselectivity can be imparted either on the nucleophilic centre, as in **70** (Scheme 21), or on the electrophilic centre, as in **72**, or potentially on both, depending on the structure of each.




**Scheme 21**

Inducing asymmetry at the prochiral nucleophile remains more challenging than at the prochiral electrophile. In particular, for systems that proceed *via* an outer-sphere mechanism, specifically if the reaction rate allows for diffusion outside of the coordination sphere, the chiral environment generated by the metal-ligand complex may not be efficiently relayed to the nucleophile, resulting in a lack of differentiation between the enantiotopic faces of the nucleophile.[38] If the reaction proceeds *via* an inner-sphere mechanism, it could be argued that the chiral environment will have a greater effect on the prochiral nucleophile. Imparting asymmetry using prochiral nucleophiles and non-prochiral electrophiles can be extremely useful, as for example, it can allow for the formation of α-quaternary stereocentres of carbonyl compounds.[39]

The origin of the enantioselectivity of allylic alkylation reactions has been a matter of debate. In 1999, Trost proposed a cartoon model used to describe the chiral pocket of the palladium-ligand complex for Trost ligands, named the 'Wall-and-Flap' model (Figure 1).[40]

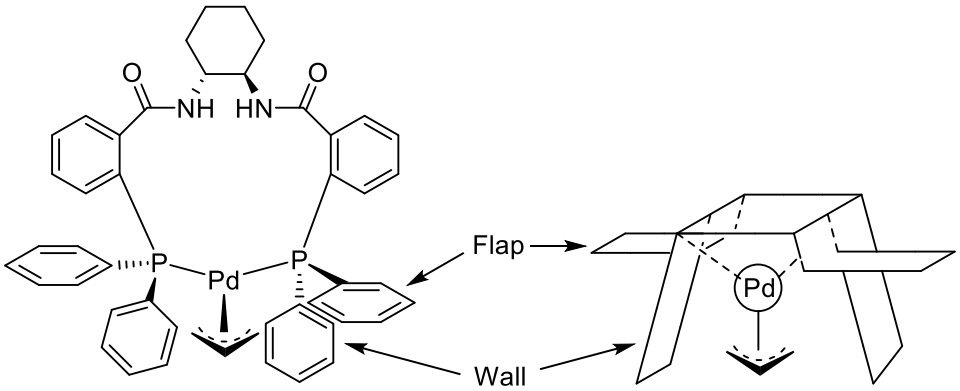



**Figure 1**

The lowest energy conformation of the complex was determined, where two phenyl rings, which act as the 'walls', point approximately perpendicular to the allyl moiety, and two phenyl rings that are parallel to the allyl moiety and act as the 'flaps'.

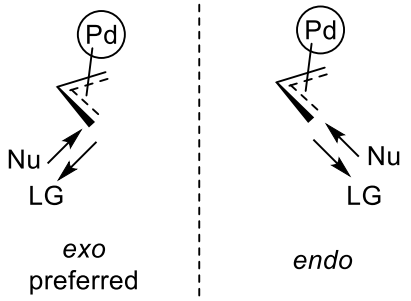



**Figure 2**

Both *exo* ionisation and nucleophilic attack are preferred over the *endo* processes due to stereoelectronic effects (Figure 2), and the 'walls' sterically block two quadrants. As such, path B (Figure 3), *via* the least hindered '*exo*' quadrant, is favoured for both ionisation and nucleophilic addition, in order to minimise steric interactions with the ligand.[41]

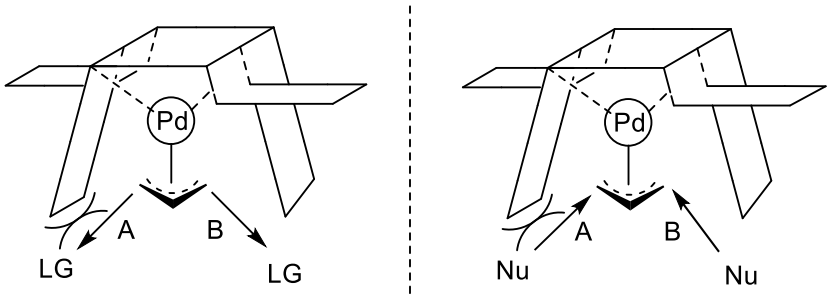
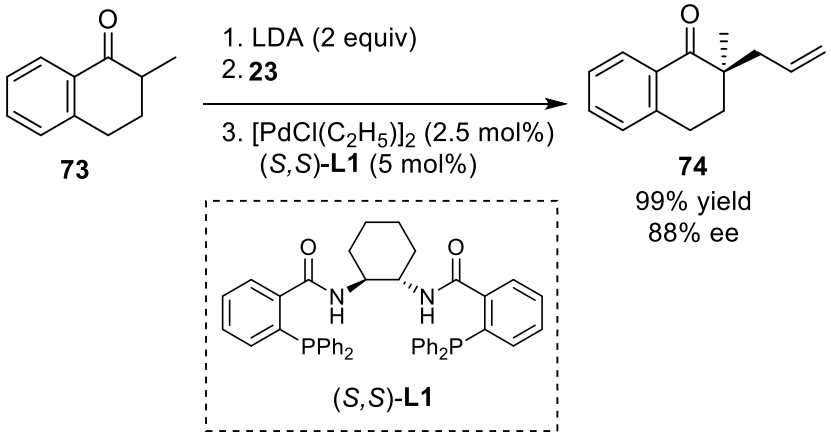



**Figure 3**

The 'Wall-and-Flap' model has been shown to be broadly applicable to accurately rationalise the stereochemical outcome of most AAA reactions catalysed by palladium bearing Trost

ligands. As an example, the observed enantioselectivity of asymmetric allylic alkylation of 2-methyl-1-tetralone (**73**) with allyl acetate (**23**), using an allylpalladium(II) chloride dimer with an (*S,S*)-DACH phenyl Trost ligand (*S,S*)-**L1** as the catalyst (Scheme 22),[41] can be described using the 'Wall-and-Flap' model.




**Scheme 22**

Three potential 'Wall-and-Flap' transition states for this reaction were proposed (Figure 4). The preferred transition state should minimise steric interactions with the ligand. For this reason, **TS-3** was postulated to be the preferred transition state as the bulky aryl group is positioned under the flap, as opposed to under the allyl group, as in **TS-1**, or under the ligand wall, as in **TS-2**. A reaction *via* **TS-3** would afford the (*S*)-enantiomer, as was observed experimentally (Scheme 22).

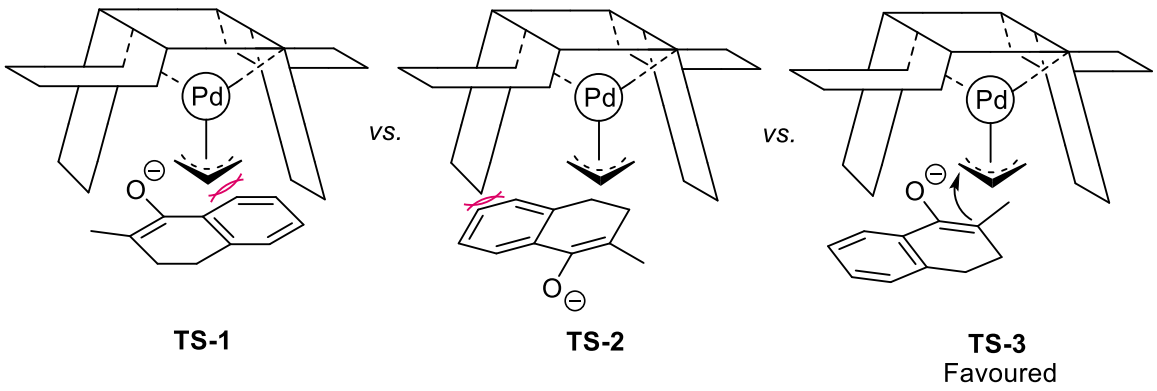
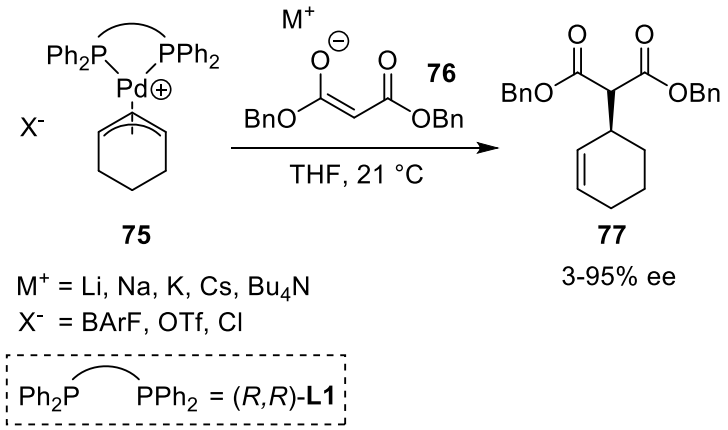



**Figure 4:** Possible transition states for AAA of **73** using an (*S,S*)-DACH phenyl Trost ligand

However, in 2008, further DFT calculations provided evidence that a conformation where the phenyl rings of a Trost ligand are close enough to have a sufficient interaction with the allyl moiety and the incoming nucleophile would be very high in energy due to sterics, and therefore, steric interactions alone could not describe the observed stereoselectivity.[42] It was postulated that other factors that affect the observed stereochemistry must be involved.




**Scheme 23**

More specifically, the asymmetric allylic alkylation of dibenzyl malonate enolate **76** and π-allylpalladium(II) complex **75**, bearing Trost ligand (*R,R*)-**L1**, was performed, where the asymmetric centre is installed at the allylic position in **77** (Scheme 23). It was concluded that three interactions dictated the observed selectivity of the reaction. The first factor is nucleophilic attack, directed by hydrogen bonding of the nucleophile with the concave amide proton, promoting pro-*S* selectivity when using an (*R,R*)-ligand. The second factor is nucleophilic attack, directed by the metal escort ion of the enolate, $M^+$, which coordinates to the concave amide carbonyl, and promotes pro-*R* selectivity. These interactions oppose one another, and therefore, the selectivity is highly dependent on the nature of both counterions, $M^+$ and $X^-$. The final interaction is a pro-*R* torquoselective bias, as described by the 'Wall-and-Flap' model, where one of the phenyl rings interacts with the allyl moiety (Figure 5).

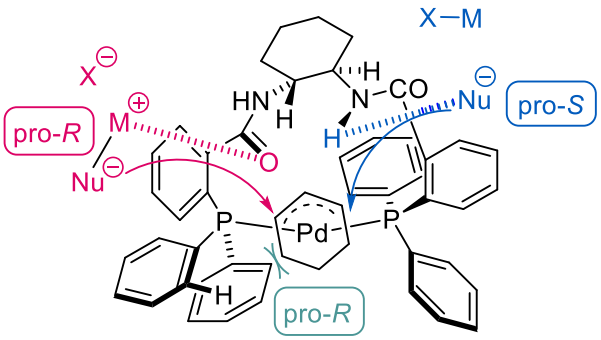
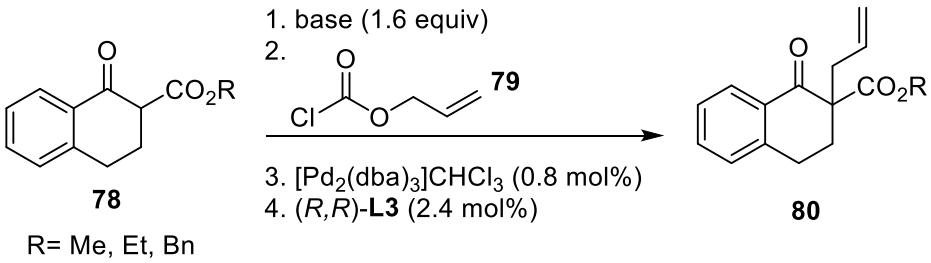



**Figure 5**

Indeed, it was found that the identity of the counterion, $X^-$, and the escort metal ion, $M^+$, had a large impact on the observed selectivity. More specifically, it was shown that the larger the escort metal ion, the higher the selectivity of alkylation. It was hypothesised that smaller cations, such as lithium, are able to strongly coordinate to the enolate nucleophile, preventing the nucleophile from efficiently hydrogen bonding to the concave amide proton by making the

lone pair less available. In addition, smaller cations coordinate more strongly to the concave amide carbonyl than larger cations. Overall, this leads to the erosion of enantioselectivity. In contrast, the greater the dissociation of the metal cation, $M^+$, from the enolate nucleophile, as well as the greater the affinity of the metal cation, $M^+$, for the counter anion, $X^-$, the greater the pro-*S* selectivity and, therefore, the higher the observed enantioselectivity. The range of ees observed was vast, from near racemic with a lithium cation to 95% ee with the non-coordinating tetrabutylammonium cation.

Another interesting counterion effect on the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction of 1,3-dicarbonyl compounds **78** with allyl chloroformate (**79**) was discovered in 2011, where a carbonate is formed *in situ* and subsequently undergoes Pd-DAAA to afford **80** (Table 1).[31]




| Entry | Solvent | Base | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | THF | LiHMDS | 93 | 63 (*S*) |
| 2 | 1,2-DCE | LiHMDS | 99 | 88 (*R*) |
| 3 | THF | $Cs_2CO_3$ | 90 | 75 (*S*) |
| 4 | 1,2-DCE | $Cs_2CO_3$ | 36 | 66 (*S*) |

**Table 1**

In certain solvents, a switch of enantioselectivity from *R* to *S* was observed, depending on the base used. When lithium bis(trimethylsilyl) amide was used in tetrahydrofuran, the *S* enantiomer of **80** was formed in 63% ee (Table 1, entry 1); however, when using 1,2-dichloroethane as the solvent (entry 2), the *R* enantiomer was formed in 88% ee. Conversely, in both 1,2-dichloroethane and tetrahydrofuran, caesium carbonate gave the *S* enantiomer of **80** in 66% and 75% ee, respectively (entries 3 and 4).

In order to gain further insight into the switch in enantioselectivity, 'lithium scavengers' such as 12-crown-4 were utilised. As such, the addition of three equivalents of 12-crown-4, when using lithium bis(trimethylsilyl)amide as the base, gave a significant decrease in enantiopurity, as well as a reversal of the sense of stereoinduction. The same experiment had no effect on the

enantioselectivity for the reactions utilising caesium carbonate as the base, suggesting the lithium cation was responsible for the reversal of enantioselectivity. It was reasoned that tetrahydrofuran, a strongly coordinating solvent, could act as a lithium scavenger, accounting for the apparent solvent dependency.

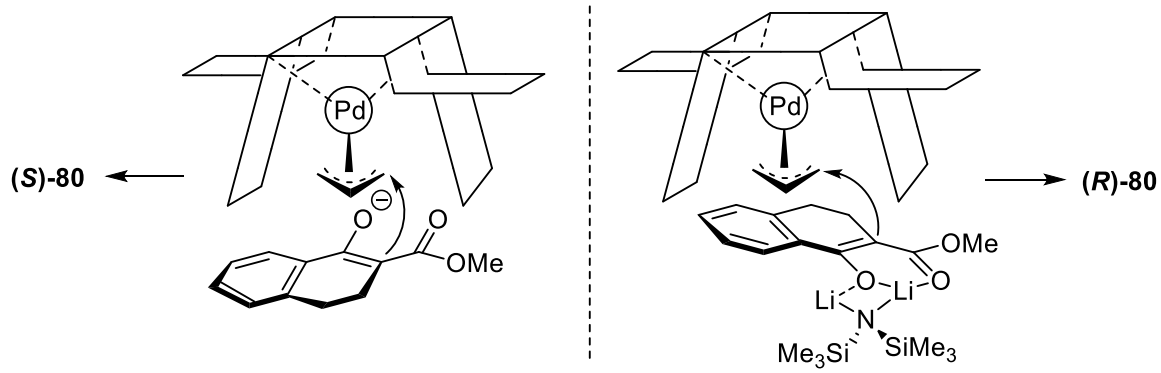
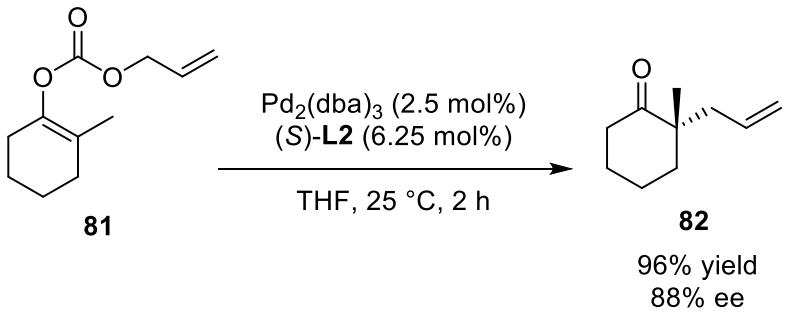



**Figure 6**

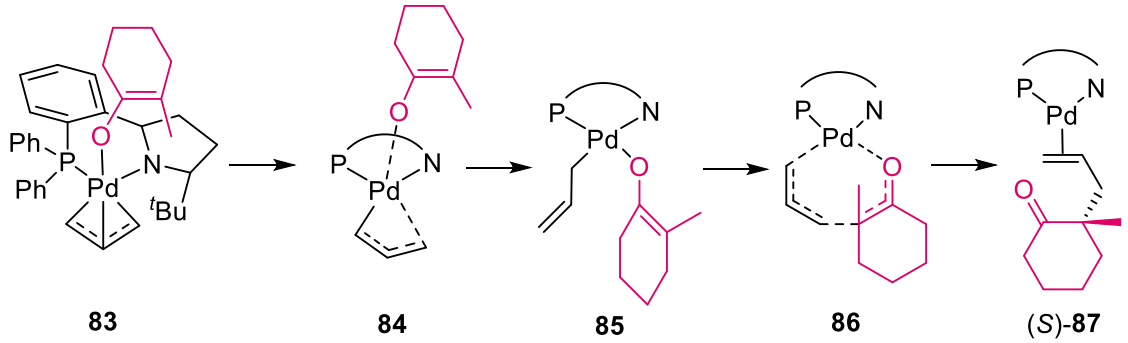
It was proposed that the aggregation states of the lithium cations employed affect which face of the prochiral nucleophile attacks the chiral π-allylpalladium(II) intermediate as when the amount of LiHMDS added was decreased from 1.6 equivalents to one equivalent, the enantioselectivity of **80** was found to be lower, suggesting that multiple lithium cations were aggregating (Figure 6). This caused a reverse in facial selectivity as the conformation where the bulky aggregates are underneath the 'wall' would be unfavourable due to steric interactions leading to the *R* enantiomer. Conversely, in the absence of aggregation, it is less favourable for the naphthyl group to interact with the 'wall', hence the *S* enantiomer is favoured (Table 1, entries 1, 3 and 4).

In 2012, DFT calculations were used to further elucidate the mechanism of a decarboxylative asymmetric allylic alkylation of prochiral nucleophiles.[39] The reaction investigated was the enantioselective DAAA of allyl enol carbonate **81** in the presence of tris(dibenzylideneacetone)dipalladium(0) and PHOX ligand (*S*)-**L2** to give allylcyclohexanone **82** in 96% yield and 88% ee (Scheme 24).




**Scheme 24**

It was found that an inner-sphere alkylation pathway that proceeds *via* a 5-coordinate palladium(II) complex **83** could best account for the observed enantioselectivity of the reaction (Scheme 25). After ligand rearrangement, 4-coordinate complex **85** was formed *via* transition state **84**. Notably, the calculations suggested that the ensuing reductive elimination step occurs *via* seven-membered transition state **86** to afford complex **87** which, after decomplexation, gives allylcyclohexanone **82**. The internal rearrangement process that affords **85** was determined to be enantiodetermining, with the pathway leading to the formation of *S*-**82**, the major enantiomer formed, found to be lower energy than the pathway to form *R*-**82**. The transition state **84** for *R*-**82** is higher energy due to increased steric interactions between the PHOX ligand and the methyl group on the enolate, whereas the transition state for *S*-**82** avoids these interactions, hence the observed enantioselectivity.




**83** **84** **85** **86** (*S*)-**87**

**Scheme 25**

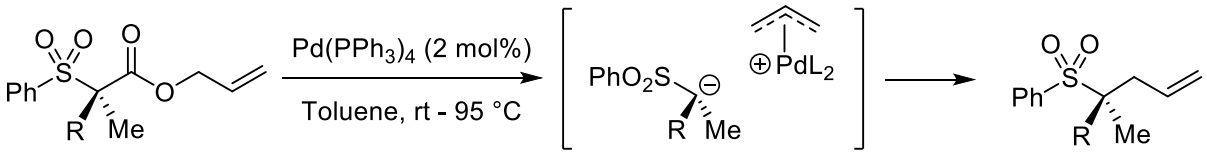
Since the reaction was determined to occur *via* an inner-sphere mechanism, it is an exception to the general rule that stabilised nucleophiles, with a p$K_{aH}$ of <25, typically undergo the reaction *via* the outer-sphere mechanism. However, the ketone enolate generated from **81** has a p$K_{aH}$ of approximately 20, evidencing that the mechanistic pathway for a particular substrate can be more nuanced, depending on other factors such as the chiral ligand used.

## 1.7 The Allylic Alkylation of α-Sulfonyl Anions

Given our interest in constructing novel three-dimensional building blocks, we are keen to investigate the enantioselective allylic alkylation of α-sulfonyl anions, and gain insight into the mechanism of the reaction. As such, a brief discussion of allylic alkylation reactions of sulfones is warranted.

Sulfones are versatile substrates due to the nature of their electronic and steric properties. α-Sulfonyl carbon atoms can act as both a nucleophile and an electrophile, and sulfones can act as directing groups for reactions occurring at the adjacent carbon atom.[43] Sulfones are commonly found as scaffolds in drug molecules,[44] and the development of methodologies for the synthesis of α-chiral sulfones in an enantiomerically pure form is becoming increasingly important.[43]

The first highly stereospecific palladium-catalysed decarboxylative allylic alkylation of allyl sulfonyl esters **88** to afford allyl phenyl sulfones **90**, was reported in 2010 (Scheme 26).[45] The reaction occurs under neutral conditions, which is an improvement over previous methodologies for the alkylation of sulfones, which typically require the use of basic organolithium reagents that are hazardous, particularly on large scale. Enantioenriched starting materials were utilised with 2 mol% tetrakis (triphenylphosphine)palladium(0) as the catalyst, varying the temperature between room temperature and 95 °C depending on the substrate. The scope of the reaction included both α-aryl and α,α-dialkyl sulfones, and all reactions occurred with high levels of conservation of enantioselectivity. Due to the higher p$K_{aH}$ of α-sulfonyl anions than ketone enolates, for example, allylic alkylation reactions of α-sulfonyl anions might be presumed to proceed *via* an inner-sphere mechanism. Surprisingly, stereochemical labelling studies conclusively corroborated an outer-sphere alkylation mechanism, where the α-sulfonyl anion reacts outside the coordination sphere of palladium, such as in **89**.




**88**

R=aryl, alkyl
46-99% ee

**89**

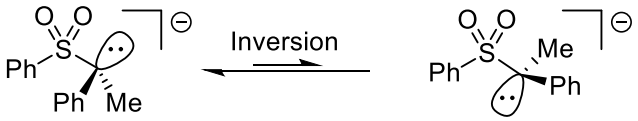
cee = conservation of ee
(Based on ee of SM)

**90**

82-99% yield
43-99% ee
91-99% cee

**Scheme 26**

The observed conservation of enantioselectivity was unexpected at elevated temperatures. It has been determined by X-ray crystallography that the most stable conformation of the sulfonyl carbanion has the lobe of the lone pair antiperiplanar with respect to the sulfur-bound phenyl group (Figure 7),[46] and whilst it has been shown that α-sulfonyl anions are more stable than other carbanions, there have been previous reports of rapid racemisation of anion **91** even at -80 °C.[47]

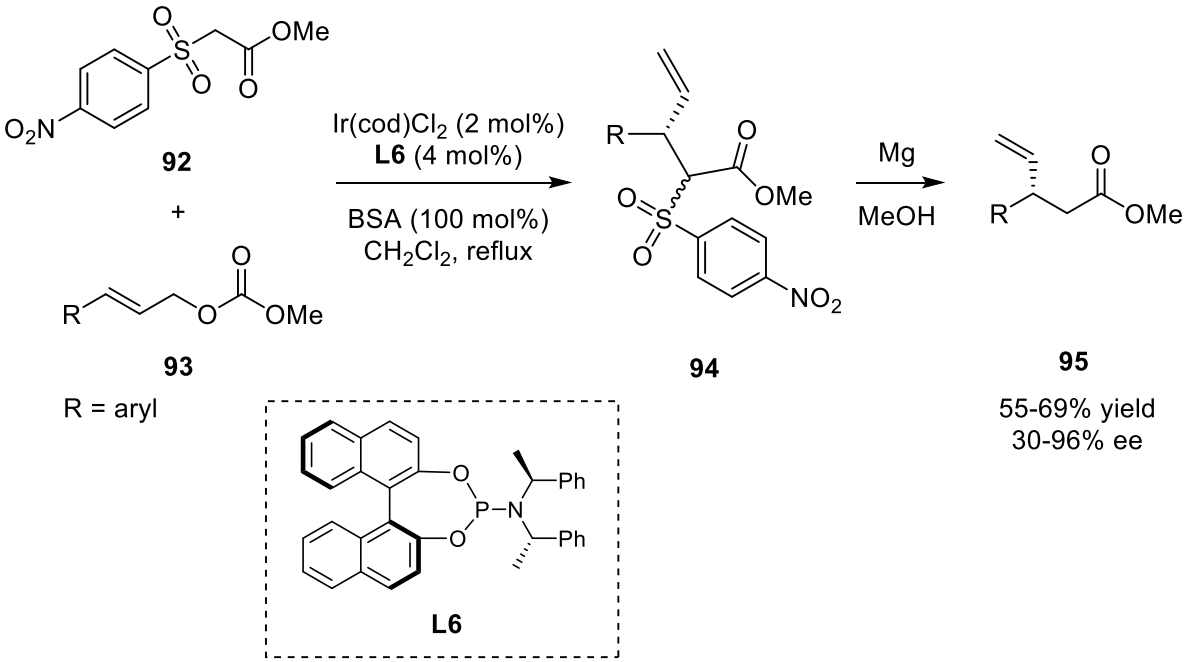



**91**

**Figure 7**

To rationalise the lack of racemisation, DFT calculations were used to provide evidence that the highly electrophilic nature of the π-allylpalladium(II) complex, in conjunction with the reactivity of the α-sulfonyl anion, was causing the bond formation to occur faster than racemisation.[45]

In 2012, the iridium-catalysed asymmetric allylic alkylation of sulfonylacetates **92** to afford **94** as a mixture of diastereoisomers, was reported, using phosphoramidite ligands, such as **L6** (Scheme 27).[48] The reaction of **92** with a wide range of aryl allylic substrates proved successful, due to the presence of the ester group alpha- to the sulfonyl moiety which stabilises the anion. Moderate to high ees of **95** were obtained, with controlled stereochemical induction taking place at the prochiral electrophile.



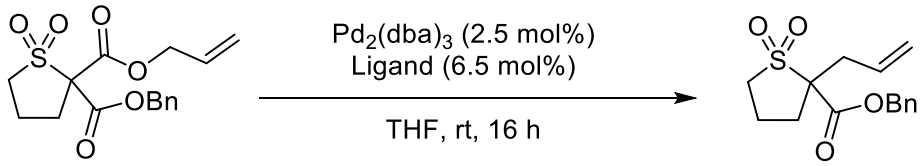

**Scheme 27**

Thus far, the construction of α-sulfonyl chiral centres in high enantiomeric excess using metal-catalysed allylic alkylation has proved successful, although the previous methods have either required the use of enantioenriched starting materials, or the chiral centre has been generated at the prochiral electrophile.

## 1.8 Previous Work in the Research Group

In contrast to the previous work described in the preceding section, we are interested in the construction of a chiral tetrasubstituted centre at the prochiral nucleophile, the α-sulfonyl moiety, from racemic starting materials. Previous work, both within the research group and externally, has shown that decarboxylative allylic alkylation of sulfones presents additional challenges that arise from the instability of α-sulfonyl anions. Therefore, appending the sulfone with an electron-withdrawing carbonyl substituent should allow for more facile decarboxylation, due to the increased stability of the anion generated.

Previous work in the research group has involved the optimisation of the reaction conditions for the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction of sulfones **96**, focusing primarily on five-membered cyclic sulfones bearing ester and ketone substituents (Table 2). The conditions used were found to have a considerable effect on the observed enantioselectivity.




**96** **97**

| Entry | Ligand | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|
| 1 | (*S,S*)-**L1** | 78 | 11 |
| 2 | (*S*)-**L2** | 83 | 0 |
| 3 | (*S,S*)-**L3** | 54 | 67 |
| 4 | (*S,S*)-**L5** | 61 | 31 |

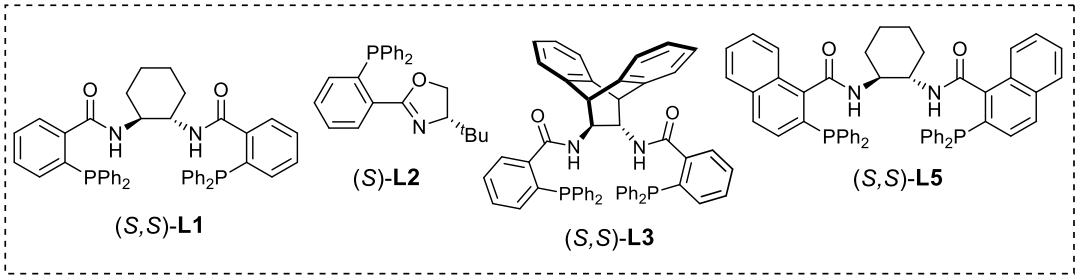
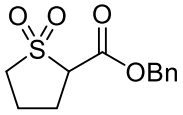



**Table 2:** [a]Isolated yield, [b]Determined by chiral HPLC

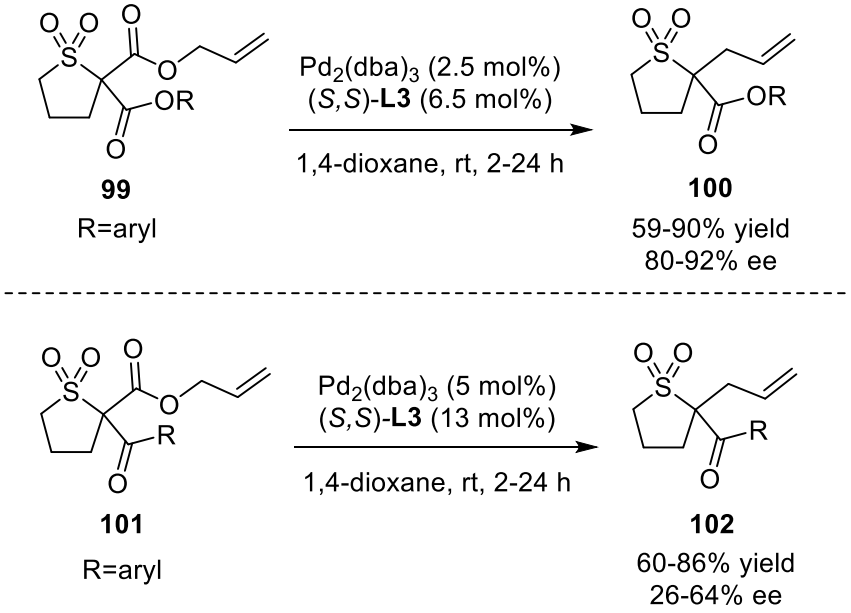
The optimisation began by performing a screening of chiral phosphine ligands: (*S,S*)-DACH phenyl Trost (*S,S*)-**L1**; (*S*)-*t*-Bu-PHOX (*S*)-**L2**; (*S,S*)-ANDEN phenyl Trost (*S,S*)-**L3**; and (*S,S*)-DACH naphthyl Trost (*S,S*)-**L5**, used in conjunction with $Pd_2(dba)_3$ as the palladium(0) source. Whilst the highest yielding reaction utilised (*S*)-**L2** as the ligand, this reaction was racemic, as determined by chiral HPLC. Ligands (*S,S*)-**L1** and (*S,S*)-**L5** gave good yields of **97**, but enantioselectivity was low. (*S,S*)-**L3** afforded the lowest yield, but also offered the highest enantioselectivity. It was decided that (*S,S*)-**L3** would be used to continue optimisation as the lower yield was due to the formation of by-product **98** that had undergone decarboxylation but had failed to alkylate (Figure 8). Upon further optimisation, the formation of by-product **98** was suppressed and 1,4-dioxane was found to be the optimal solvent to give **97** in 91% yield and 86% ee.




**98**

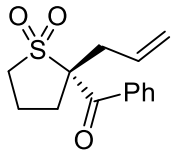
**Figure 8**

Most recently, attention was turned to assessing the substrate scope of the reaction. A range of sulfones appended with electron-withdrawing ester, **99**, and ketone functionalities, **101**, were investigated (Scheme 28).




**Scheme 28**

The sulfones appended with an ester substituent **99** underwent the enantioselective decarboxylative allylic alkylation in moderate to high yields (59-90%) and high ee values (80-92%). The sulfones appended with ketone substituents **101** gave similar yields (60-86%), however, enantioselectivity was significantly lower (26-64%). Additionally, the ester substrates required shorter reaction times and lower catalyst loading compared to the ketones. It was hypothesised that the marked difference in enantioselectivity between the ester and ketone substituents could potentially be caused by a switch in reaction mechanism between inner- or outer-sphere.




**103**

**Figure 9**

Finally, a crystal structure of **103** was obtained, indicating the absolute configuration to be the *R* enantiomer.

## 1.9 Conclusions

The synthesis of saturated three-dimensional molecules remains challenging, particularly those bearing a chiral quaternary centre. This is a key obstacle to overcome in order to enrich fragment libraries with novel three-dimensional compounds. AAA and DAAA are reliable methods that enable the assembly of molecules with increased complexity through the construction of highly congested chiral quaternary centres with high enantioselectivity.

There are benefits to utilising decarboxylative AAA rather than direct AAA. The decarboxylative process is more sustainable as it does not require stoichiometric addition of the nucleophile, making it more attractive to industry. Decarboxylative AAA can also be performed under neutral reaction conditions, meaning it has utility over a wider range of substrates than the direct process which often requires a strong base. Crucially, decarboxylative AAA can also form products that are inaccessible *via* direct AAA.

The reaction mechanism that the palladium-catalysed allylic alkylation reaction proceeds by, either inner- or outer-sphere, can often be predicted as the mechanism is highly dependent on the p$K_{aH}$ of the nucleophile employed. However, there are exceptions, which suggest that the mechanism may also be dependent on other factors, including substrate structure and the chiral ligand used.

Two main models have been developed to rationalise the observed enantioselectivity of AAA reactions. The first being the 'Wall-and-Flap' model, based on steric and stereoelectronic effects, which is simplistic but is broadly applicable to most AAA reactions. A modified model was developed involving three interactions with opposing selectivities that compete with one another based on the substrates and their counterions. Whilst the latter is more descriptive and therefore potentially more applicable for direct AAA processes, the 'Wall-and-Flap' model can be applied to decarboxylative AAA where the electrophile and nucleophile are generated *in situ* in the absence of counterions. A mechanism for inner-sphere processes based on DFT calculations has also been proposed, where other models rationalise outer sphere processes.

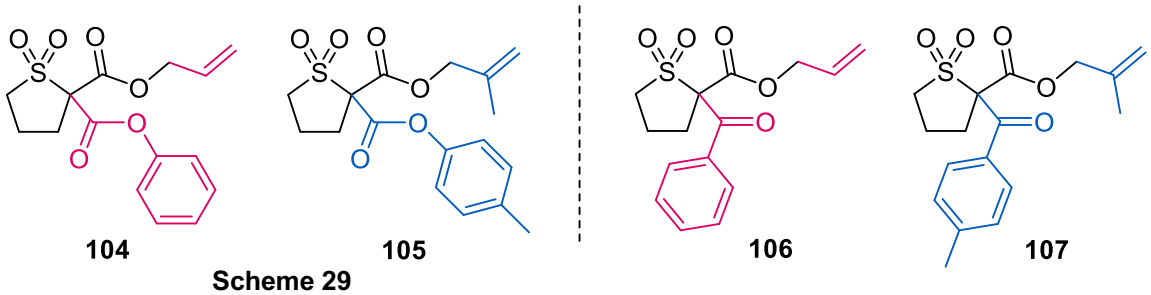
Sulfones are often incorporated into drug molecules, and AAA and DAAA reactions have the potential to be used for the construction of enantioenriched sulfone products. Research into allylic alkylation of sulfones is limited, however, and previous reactions have required the use of enantiopure starting materials, or stereoinduction at the allylic centre. Work in our group, however, has shown that Pd-DAAA can successfully provide chiral quaternary α-sulfone products from racemic starting materials.

## Chapter 2: Results and Discussion

### 2.1 Aims and Objectives

The aims for this project were to gain a deeper understanding of the mechanism of the Pd-DAAA of cyclic sulfones bearing ester and ketone stabilising groups, which would allow for more targeted optimisation of the process, particularly given the large difference in enantioselectivity observed between substrates with ester and ketone substituents. The aims of this research were three-fold: a mechanistic study; reaction optimisation; and extension of substrate scope of 5- and 6-membered cyclic sulfones.

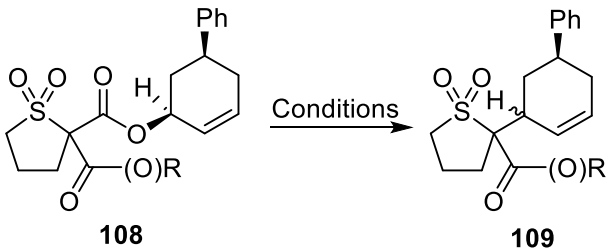
The objective of the mechanistic investigation was to establish whether an inner- or outer-sphere alkylation mechanism is in operation for both ester- and ketone-substituted sulfones and included crossover experiments and stereochemical labelling. Two ester-substituted precursors, **104** and **105**, and two ketone-substituted precursors, **106** and **107**, were to be synthesised (Scheme 29). Each pair of substrates was to be subjected to Pd-DAAA conditions to check whether crossover of enolates takes place, or whether palladium remains tightly bound.



**104** **105** **106** **107**

**Scheme 29**

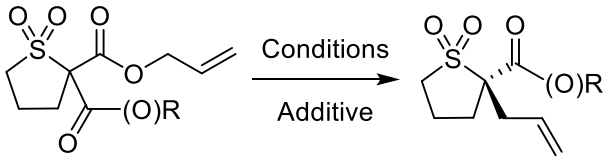
A substrate bearing a stereochemical label **108** was to be prepared (Scheme 30). Relative stereochemistry determination of the Pd-DAAA product should indicate whether an inner- or outer-sphere alkylation reaction operates based on whether retention or inversion in product **109** is observed.




**108** **109**

**Scheme 30:** Pd-DAAA of a substrate bearing the stereochemical label

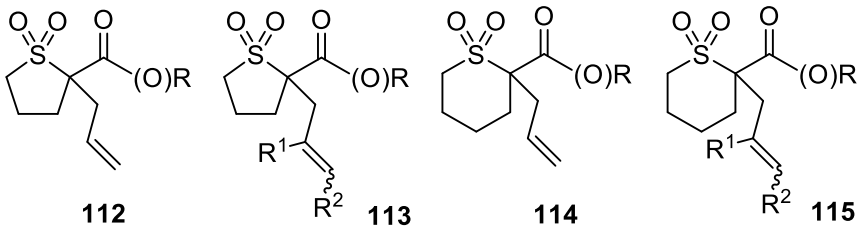
Once a deeper understanding of the mechanism has been established, the addition of a range of additives was to be tested in order to optimise reaction yield and enantioselectivity (Scheme 31).




**110** *(S)*-**111**

**Scheme 31**

Following the mechanistic study and reaction optimisation, extension of the substrate scope was to be investigated under the optimised reaction conditions (Figure 10). This was to include both 5-membered and 6-membered cyclic sulfones, with a range of ester and ketone aryl and alkyl substituents, as well as allyl substitution.



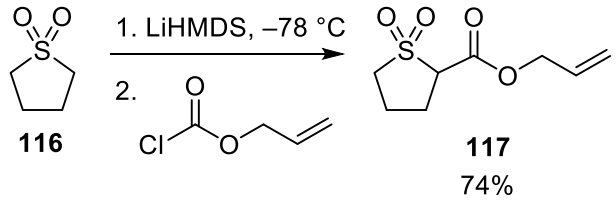

**112** **113** **114** **115**

**Figure 10**

Once a range of enantioenriched cyclic sulfone products have been produced, they could then be transformed into novel spirocyclic three-dimensional building blocks.

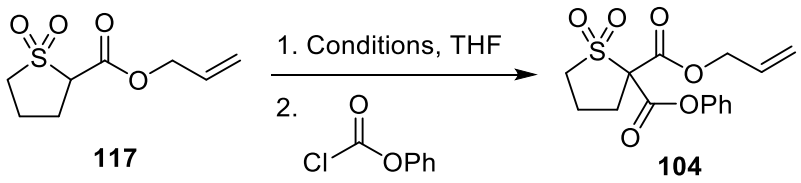
## 2.2 Optimisation of Reaction Conditions for the Synthesis of Precursors

To begin, sulfone **117**, bearing an allyl ester, was prepared in up to 74% yield from sulfolane (**116**) using LiHMDS (2 equiv) as the base at –78 °C, followed by addition of the allyl chloroformate electrophile (1.1 equiv) (Scheme 32).




**Scheme 32**

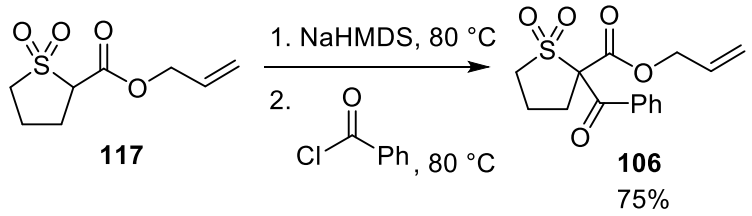
Reaction conditions were then optimised for the incorporation of the phenyl ester substituent, where both the base and reaction temperature were varied (Table 3). Sulfone **117** was deprotonated using a base (1.1 equiv), and phenyl chloroformate (1.1 equiv) was then added. Using NaHMDS at room temperature gave the highest yield of **104**, of 79% (0.25 mmol, Table 3, entry 1). No reaction occurred when using NaHMDS at 80 °C (entry 2), nor when using LiHMDS or sodium hydride at room temperature (entries 3 and 4). Using caesium carbonate or DBU as the base (entries 5 and 6), with both reactions performed at reflux due to their lower basicity, led to low formation of **104**. Therefore, the reaction using NaHMDS as the base was scaled up to 4.90 mmol and afforded **104** in 59% yield (entry 7).




| Entry | Conditions | 117:104[a] | Yield (%)[b] |
|---|---|---|---|
| 1 | NaHMDS, rt | 1:2.5 | 79 |
| 2 | NaHMDS, 80 °C | No reaction | - |
| 3 | LiHMDS, rt | No reaction | - |
| 4 | NaH, rt | No reaction | - |
| 5 | $Cs_2CO_3$, 80 °C | 9.5:1 | n.d. |
| 6 | DBU, 80 °C | 3.6:1 | n.d. |
| 7 | NaHMDS, rt | 1:2.3 | 59 |

**Table 3:** [a]Determined by $^1$H NMR spectroscopy of the crude mixture, [b]Isolated yield;
n.d. = not determined

A phenyl ketone substituent was also incorporated into sulfone **117** using previously optimised conditions (Scheme 33). Specifically, sulfone **117** was deprotonated with NaHMDS (1.1 equiv), and benzoyl chloride (1.1 equiv) was added at 80 °C, to give product **106** in 75% yield.




**117** **106** 75%

**Scheme 33**

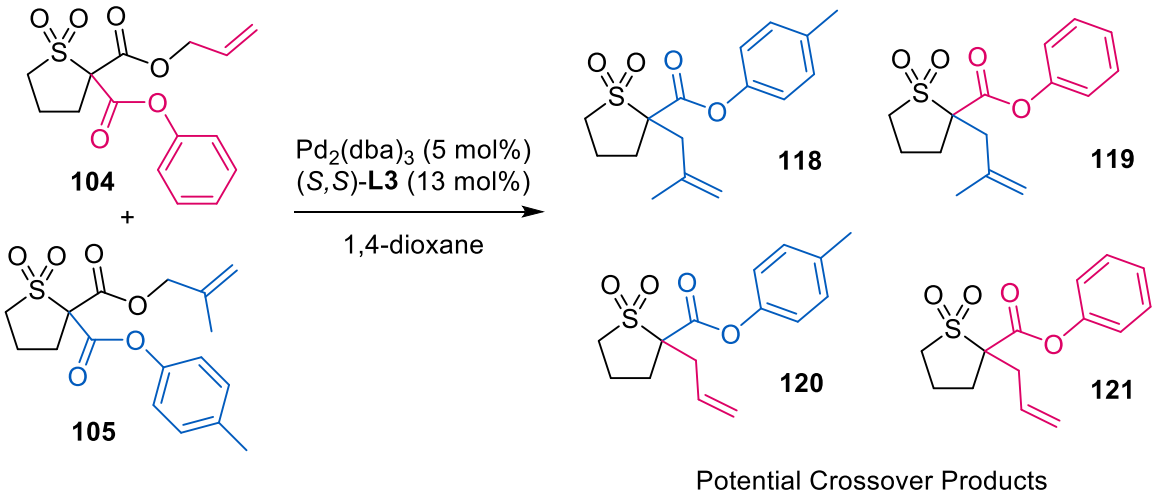
With practical quantities of substrates **104** and **106** in hand, a mechanistic study was to be performed.

## 2.3 Mechanistic Studies

The primary aim of this research was to undertake a mechanistic study in order to gain a deeper understanding of the Pd-DAAA of cyclic sulfones. In this context, we set out to test whether the enolate, following decarboxylation, remains tightly bound to the π-allylpalladium(II) cation, and to perform stereochemical labelling to conclusively establish an whether inner- or outer-sphere alkylation mechanism operates.

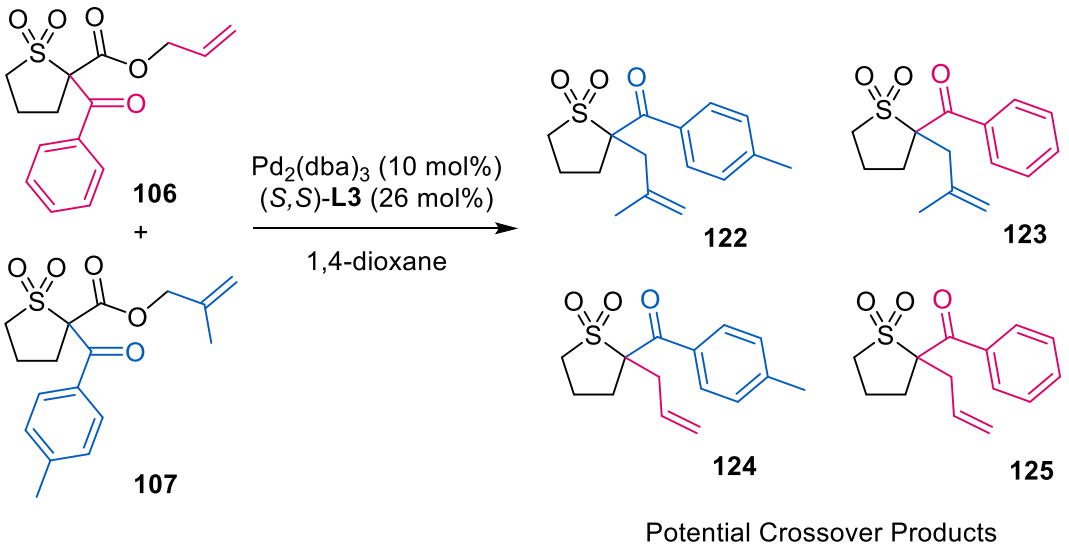
### 2.3.1 2-Methylallyl Ester Crossover Experiments

Our study began with crossover experiments. The first substrates to be tested were the 2-methylallyl ester and *para*-tolyl substituted sulfone **105**, for crossover with the allyl ester and phenyl substituted sulfone **104** (Scheme 34). The proposed crossover reaction for the ester could in principle give four crossover products **118**-**121**. If the reaction proceeds *via* an outer-sphere alkylation mechanism, where the enolate and π-allylpalladium(II) complex are not closely associated with one another, then this would allow for either enolate to react with either allyllic electrophile, leading to a mixture of products **118**-**121**. If no crossover is observed, then this could be attributed to either an inner-sphere mechanism or an outer-sphere alkylation mechanism where the rate of alkylation surpasses the rate of diffusion. In this scenario, only the formation of products **118** and **121** should be observed.



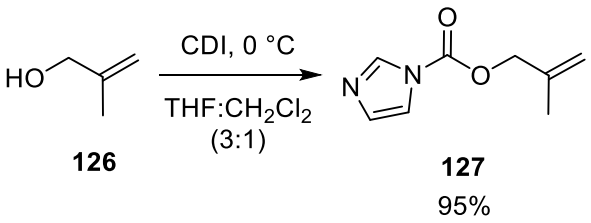

**Scheme 34**

By analogy, ketone substituted **106** and **107** were to be used in a crossover study (Scheme 35), with potential to afford four crossover products **122**-**125**.



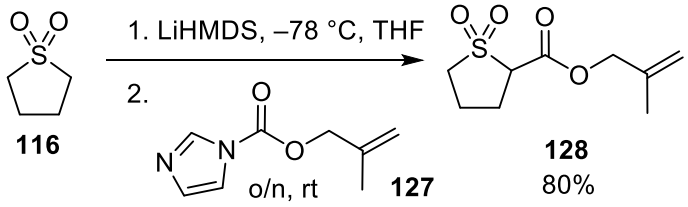

**Scheme 35**

First, the precursors to the potential crossover products that had not been previously prepared, were synthesised. 1,1'-Carbonyldiimidazole (1.5 equiv) was used at 0 °C in a THF:$CH_2Cl_2$ (3:1) solvent mixture to convert 2-methyl-2-propen-1-ol (**126**) into carbamate **127** in 95% yield (Scheme 36).




**Scheme 36**

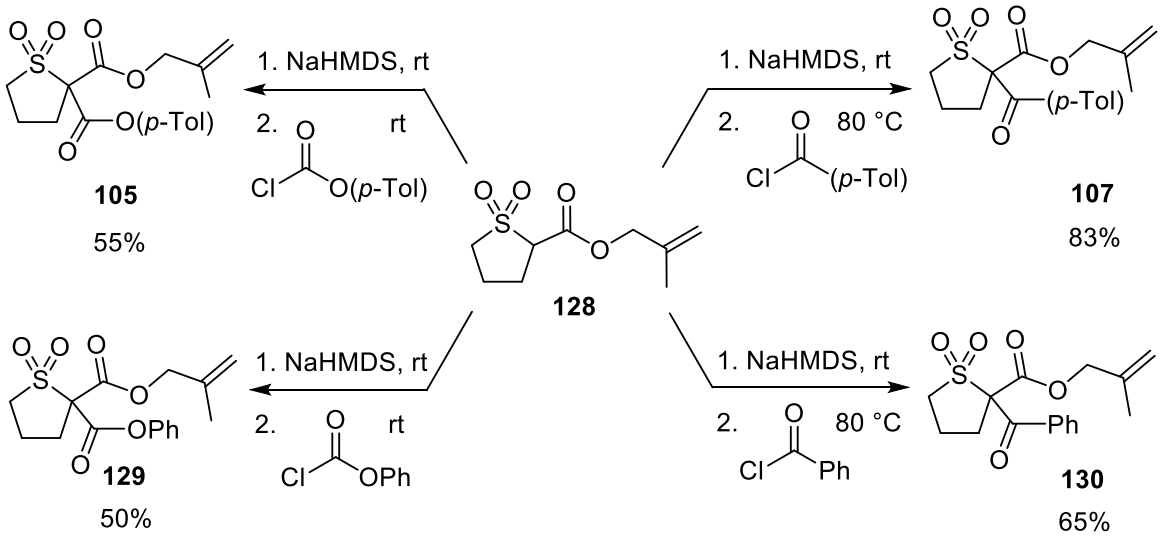
Carbamate **127** was then added to sulfolane (**116**) in 80% yield using LiHMDS (2 equiv) as the base, followed by addition of electrophile **127** (Scheme 37).




**Scheme 37**

*para*-Tolyl chloroformate, *para*-toluoyl chloride, phenyl chloroformate and benzoyl chloride were all added to the sulfone appended with the substituted allyl ester **128**, using previously

optimised conditions for addition of esters and ketones, to give **105**, **107**, **129** and **130** respectively, in moderate to good yields (Scheme 38).



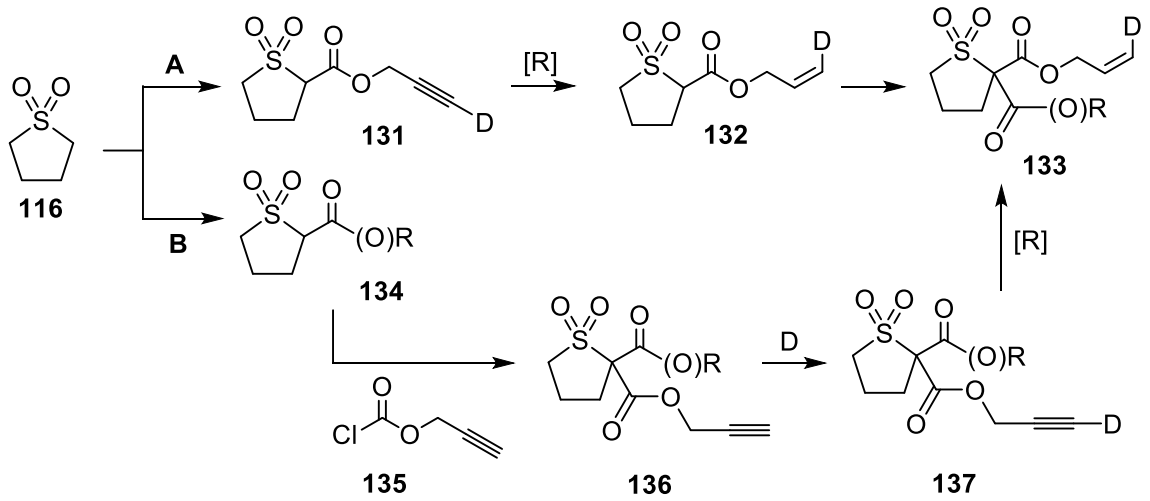

**Scheme 38**

Each of the precursors **105**, **107**, **129** and **130** were then individually subjected to both the racemic and enantioselective Pd-DAAA conditions to produce each of the eight potential crossover products, four for the ester-containing substrates, and four for the ketone-containing substrates, the results of which will be discussed as part of the substrate scope investigation (*vide infra*, Section 2.5.1, page 65). It was found that both ester and ketone substrates containing the methyl-substituted allylic ester reacted far too slowly compared with those containing the non-substituted allyl ester to be useful in a crossover experiment. Therefore, the synthesis of substrates that were closer in structure to the original non-substituted allyl ester substrates **104** and **106** was explored in the hope that their reactivity would be more comparable.

### 2.3.2 $^{2}$H-labelled Allyl Ester Crossover Experiments

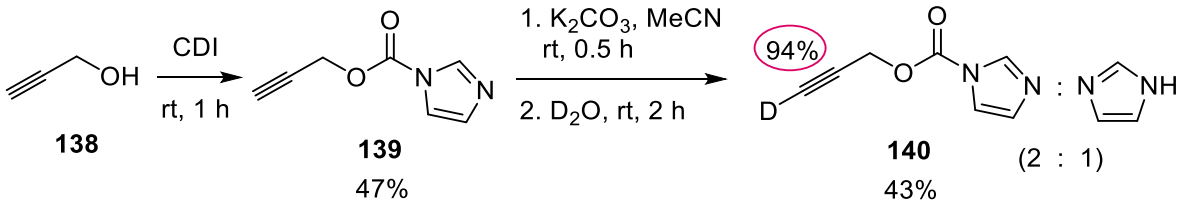
Due to the substantially lower reactivity of substituted allylic ester substrates than their non-substituted counterparts, $^{2}$H-labelling of the allyl moiety was explored in order to achieve similar rates of reaction, which is essential for a meaningful enolate crossover investigation.

In this context, two strategies were explored. The first approach was based on the synthesis of a deuterated propargylic ester **131** which could then be reduced to deuterated alkene **132** under Lindlar conditions (Scheme 39, **A**). The second approach was to append a propargylic ester substituent to an ester- or ketone-substituted sulfone **134** using propargyl chloroformate (**135**) to afford **136**, which could subsequently be deuterated and then reduced under Lindlar conditions (Scheme 39, **B**).



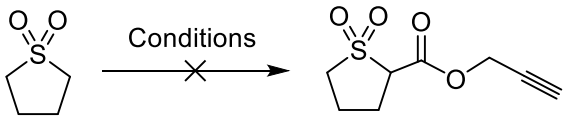

**Scheme 39**

Beginning with route **A**, propargyl alcohol (**138**) was converted to carbamate **139** with CDI, in moderate yield (Scheme 40). The terminal alkyne position of **139** could then be $^{2}$H-labelled using potassium carbonate and deuterium oxide, leading to 94% deuterium incorporation in **140**. In this process, base-catalysed carbamate cleavage also occurred.




**Scheme 40**

Installation of the propargylic ester-side chain onto sulfolane (**116**) was then attempted, using the non-deuterated carbamate **139** in a test reaction. When using LiHMDS (2 equiv) as the base, carbamate **139** decomposed, and only starting sulfolane (**116**) was recovered (Table 4, entry 1). The same observation was made when propargyl chloroformate was used as the electrophile in place of carbamate **139** (entry 2). When sodium hydride (2 equiv) was used as the base and the reaction was heated to 80 °C (entry 3), the chloroformate did not decompose, but no reaction occurred, suggesting that sodium hydride did not remove the α-sulfonyl proton. Given that at least 2 equivalents of a base is essential for a successful reaction, the presence of an acidic terminal alkyne in the electrophile structure was likely to be responsible for high levels of decomposition and the lack of the desired reactivity.




**116** **146**

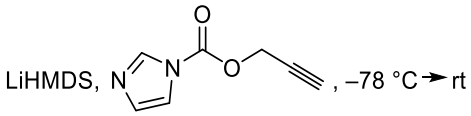
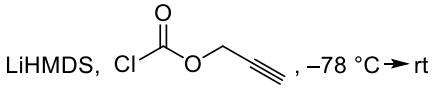
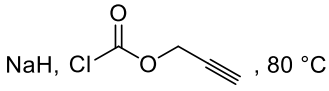
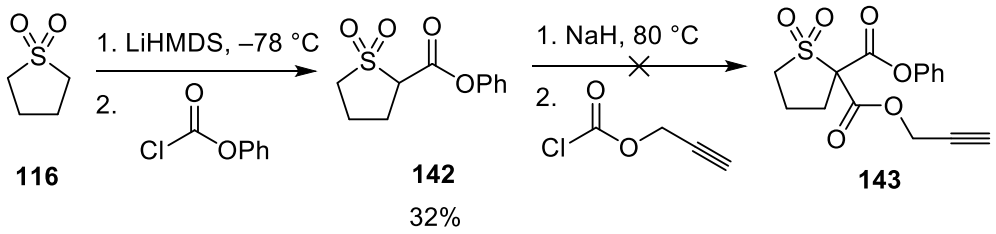
| Entry | Conditions | Observations[a] |
|---|---|---|
| 1 |  | Only starting material observed |
| 2 |  | Only starting material observed |
| 3 |  | Starting material and chloroformate observed |

**Table 4:** [a]Determined by $^{1}$H NMR spectroscopy of the crude mixture

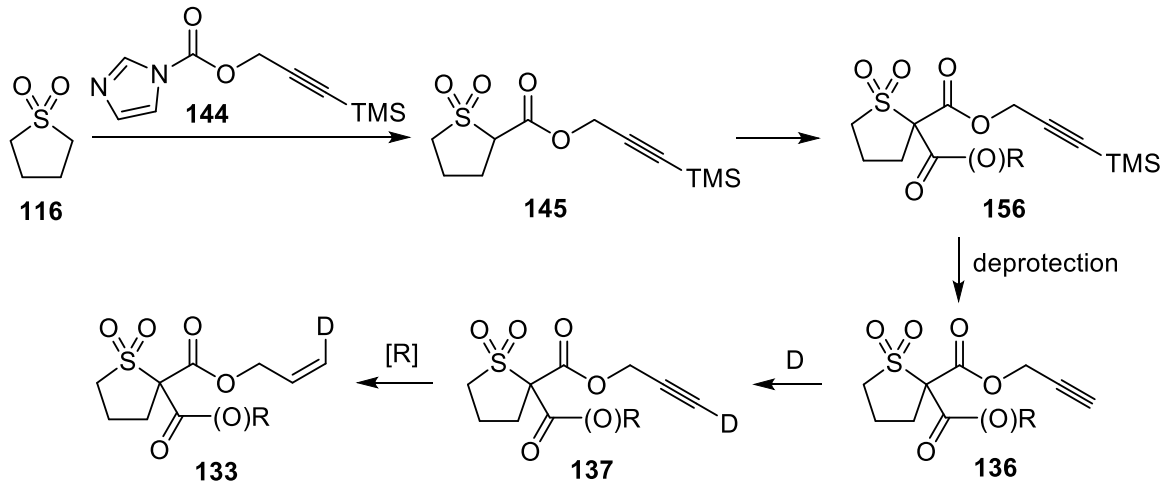
In this context, strategy **B** was explored, where installation of the propargyl ester as a second substituent onto sulfone **142** was attempted (Scheme 41). In this process, only one equivalent of the base is necessary for a successful reaction. In light of the higher acidity of **142** than sulfolane (**116**), sodium hydride should be basic enough to generate an ester enolate intermediate for reaction with propargyl chloroformate. Thus, using sodium hydride (1.1 equiv), addition of propargyl chloroformate was attempted. Unfortunately, no reaction occurred with exclusive recovery of sulfone **142**. It was concluded that the presence of an acetylenic proton was interfering with the reaction.




**116** **142** 32% **143**

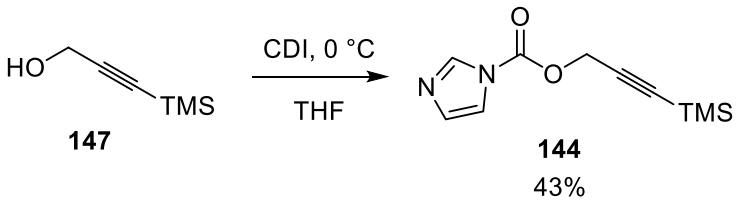
**Scheme 41**

In an attempt to avoid issues with deprotonation of the terminal alkyne proton, a route based on a protected alkyne was explored. The approach was based on the synthesis of TMS-protected propargylic ester **145**, followed by installation of a second ester or ketone substituent to give sulfone **146** (Scheme 42). Subsequently, TMS-deprotection of alkyne **146** would be attempted, affording **136**, which could then be deuterated. Finally, alkyne **137** could be reduced under Lindlar conditions.



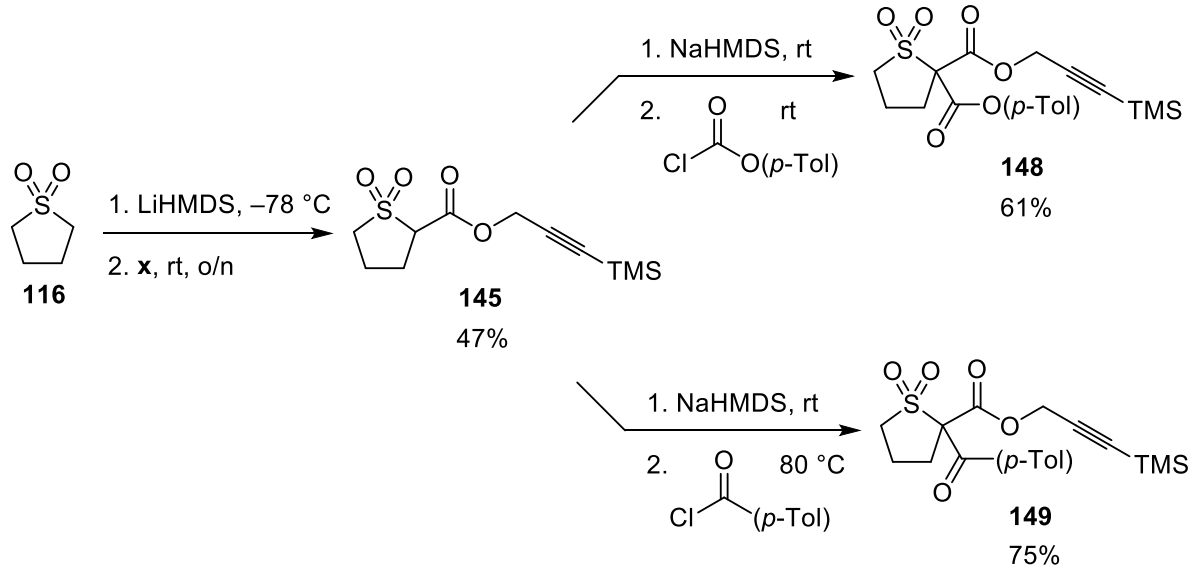

**Scheme 42**

In this context, TMS-protected propargyl alcohol **147** was converted to carbamate **144** using CDI (1.5 equiv) in THF in 43% yield (Scheme 43).



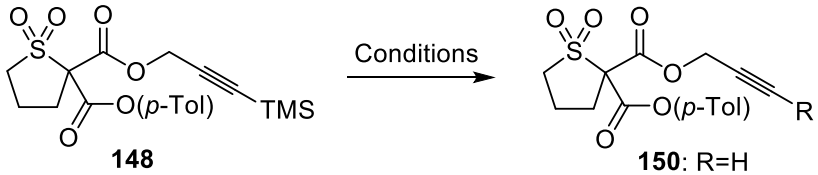

**Scheme 43**

Sulfolane (**116**) was then deprotonated with LiHMDS, and carbamate **144** was added to give sulfone **145** in 47% yield (Scheme 44). We were pleased to discover that *para*-tolyl chloroformate and *para*-toluoyl chloride could each be successfully added to sulfone **145** to give disubstituted sulfones **148** and **149** in 61% and 75% yields, respectively.




**Scheme 44**

Subsequently, deprotection of the alkyne was attempted for *para*-tolyl ester substituted sulfone **148** (Table 5). Four methods for TMS deprotection were explored. First, potassium carbonate (1 equiv) was added to **148** in deuterated methanol (Table 5, entry 1). Under these conditions, both ester substituents were cleaved, with no formation of desired product **150**. When **148** was treated with TBAF (1.1 equiv) in THF, the desired product **150** was not formed, with tolyl ester cleavage being a major side reaction (entry 2). A reaction of **148** with TBAF (1.1 equiv) under acidic conditions in THF and acetic acid (1.1 equiv) was performed, to minimise the amount of ester cleavage (entry 3). These conditions led to successful formation of the deprotected product **150** in 83% yield. However, when this reaction was repeated with TBAF (1.1 equiv) in a mixture of THF and deuterium oxide (3:1), the desired deuterated product **151** was isolated in 83% yield, with 96% deuterium incorporation at the terminal alkyne position (entry 4). In this way, a one-pot deprotection and deuteration could be successfully achieved.




**148**

**150**: R=H
**151**: R=D

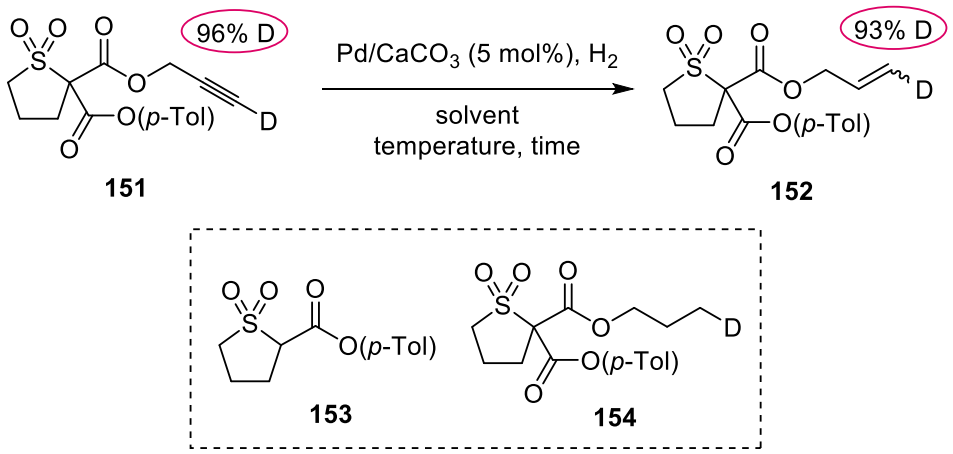
| Entry | Conditions | Observations | Yield (%)[a] |
|---|---|---|---|
| 1 | $K_2CO_3$ (1 equiv) / $d_4$-MeOH | Cleavage of both ester substituents | - |
| 2 | TBAF (1.1 equiv) / THF | Tolyl ester cleavage, no desired product formation | - |
| 3 | TBAF (1.1 equiv), AcOH (1.1 equiv) / THF | **150** formation | 83 |
| 4 | TBAF (1.1 equiv) / THF:$D_2O$ | **151** formation (96% D)[b] | 83 |

**Table 5:** [a]Isolated yield, [b]Determined by $^1$H NMR spectroscopy

Finally, reduction of alkyne **151** to alkene **152** was then explored using Lindlar's catalyst (Table 6). **151** was subjected to Pd/$CaCO_3$ (5 mol%) in quinoline (1 drop) and EtOAc under a hydrogen atmosphere for 1.5 hours at room temperature. These conditions led to a mixture of cleaved product **153**, resulting from hydrogenolysis of the propargyl ester and decarboxylation, and an over-reduced alkane ester product **154** (Table 6, entry 1). This reaction was repeated using 2 equivalents of quinoline with a reduced reaction time of 30 minutes (entry 2), which led to a mixture of alkynyl ester cleaved product **153**, over-reduced alkane ester product **154**, and

an 18% yield of the desired reduced product **152**. When the reaction solvent was changed from EtOAc to MeOH, a mixture of **153** and **154** was observed with no formation of product **152** (entry 3). When pyridine was used as the reaction solvent, and no quinoline was added, alkynyl ester cleaved product **153** was obtained exclusively in quantitative yield (entry 4). Finally, using the original reagents and solvents, the reaction temperature was lowered to 0 °C and the reaction was allowed to proceed for 20 minutes (entry 5). Under these reaction conditions, the desired product **152** was obtained in 82% yield.

Whilst the Lindlar reduction of alkynes occurs *via* a concerted mechanism, and therefore observation of deuterium at the *trans* position relative to the vicinal proton would be expected, deuterium scrambling was observed. Deuterium incorporation of 76% and 17% at the *cis* and *trans* positions, respectively, was observed, giving a combined deuterium incorporation of 93% at the terminal alkene position in **152**.

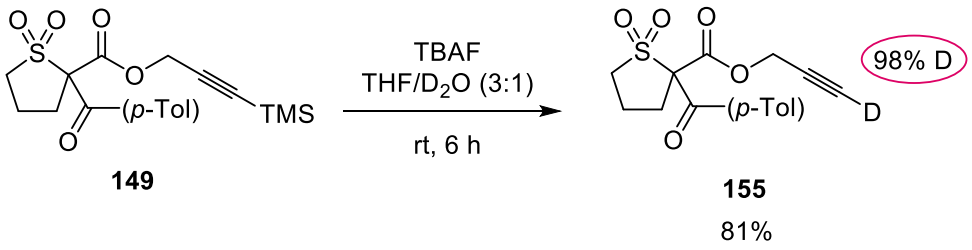



| Entry | Conditions | 153 : 154 : 152[a] | Yield (%) |
|---|---|---|---|
| 1 | Quinoline (1 drop), EtOAc, rt, 1.5 h | 1.2 : 1.0 : 0 | - |
| 2 | Quinoline (2 equiv), EtOAc, rt, 30 minutes | 1.6 : 1.0 : 1.1 | 18[b] |
| 3 | Quinoline (2 equiv), MeOH, rt, 30 minutes | 1.6 : 1.0 : 0 | - |
| 4 | Pyridine, rt, 30 minutes | **153** only | quant[c] |
| 5 | Quinoline (2 equiv), EtOAc, 0 °C, 20 minutes | desired **152** only | 82[b] |

**Table 6:** [a]Determined by $^{1}$H NMR spectroscopy of the crude mixture, [b]Isolated yield of **152**, [c]Isolated yield of **153**

Using the TMS-deprotection conditions optimised for the ester substrate **151**, the ketone substrate **149** was also $^{2}$H-labelled (Scheme 45). Specifically, **149** was treated with TBAF (1.1

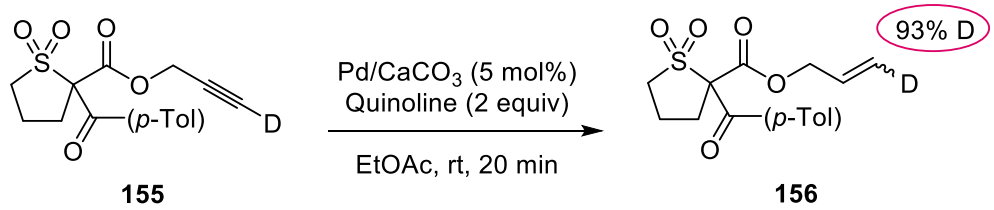
equiv) in a mixture of THF and deuterium oxide (3:1), and the desired product **155** was isolated in 81% yield, with 98% deuterium incorporation at the terminal alkyne position.




**149** **155**
81%

**Scheme 45**

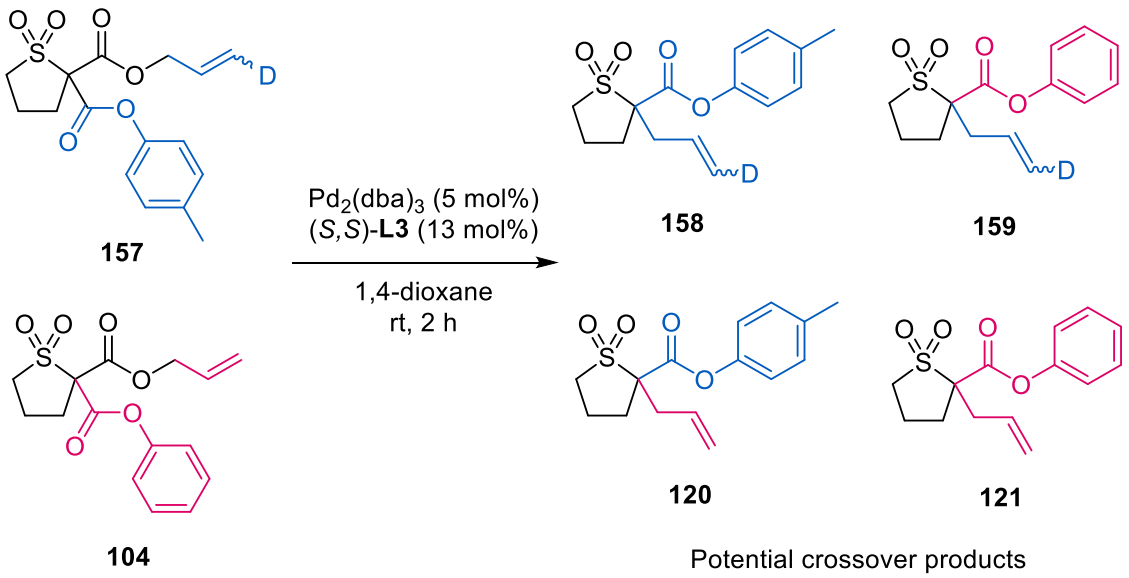
$^{2}$H-Labelled substrate **155** was then subjected to the optimised alkyne reduction conditions. **155** was stirred with Pd/$CaCO_3$ (5 mol%) in quinoline (2 equiv) and EtOAc, in a hydrogen atmosphere, at 0 °C for 20 minutes. However, under these conditions, no reaction occurred, with starting material **155** being recovered exclusively. The reaction was, therefore, repeated at room temperature (Scheme 46), and reduced product **156** was successfully isolated in 71% yield, with 93% $^{2}$H incorporation at the terminal alkene position, as determined by $^{1}$H NMR spectroscopy. It was not possible to determine the degree of deuteration at the *cis* and *trans* positions due to peak overlap in the $^{1}$H NMR spectrum of **156**.




**155** **156**
71%

**Scheme 46**

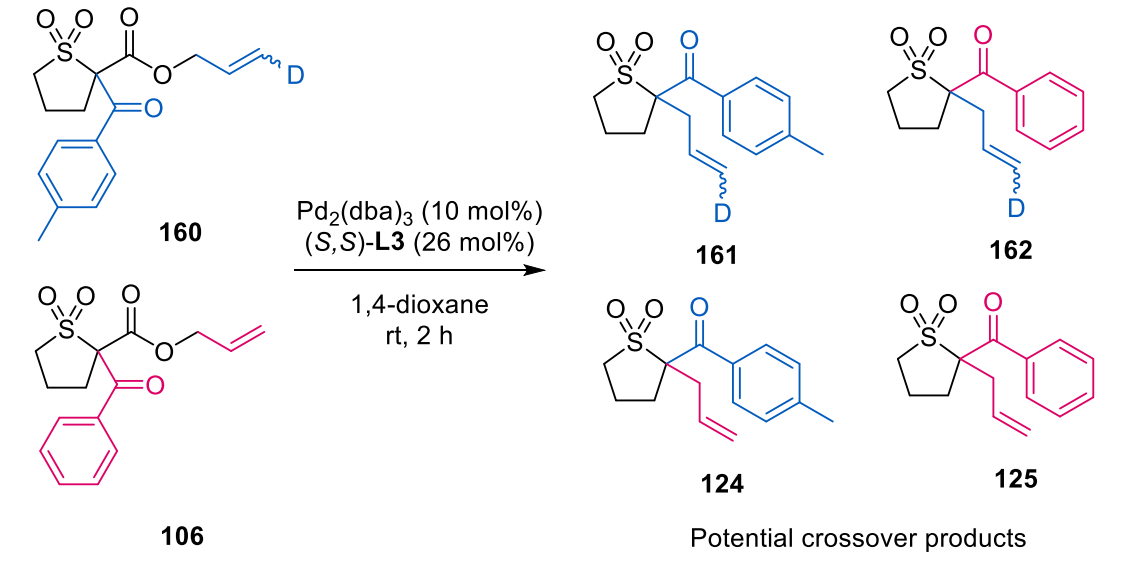
With both $^{2}$H-labelled ester and ketone substrates **152** and **155** in hand, attention turned to the crossover experiments. Crossover of the *para*-tolyl substrates **157** and **160** with the analogous phenyl substrates **104** and **106** was desirable in order to keep the reactivity of each pair as similar as possible. One equivalent of both $^{2}$H-labelled ester substrate **157** and unlabelled phenyl ester substrate **104** were subjected to the Pd-DAAA conditions (Scheme 47). Although full conversion of starting materials **104** and **157** had taken place after 2 hours, the products of the reaction were found to be barely distinguishable from one another by $^{1}$H NMR spectroscopy due to peak overlaps, and were inseparable by column chromatography. Therefore, observation of potential crossover products by $^{1}$H NMR spectroscopy was not possible. Instead, the product mixture was analysed by mass spectrometry.




**Scheme 47**

Mass spectrometric analysis of the resulting mixture showed significant amounts of all four crossover products, with a 2.4:1 ratio of **158** to **120**, and a 2.2:1 ratio of **121** to **159**. Interestingly, the ratio of tolyl products (**120** and **158**) observed to phenyl products (**121** and **159**) was 2.5:1, presumably due to the tolyl ester products having higher ionisation efficiencies than those of the phenyl ester products. The observation of all four crossover products in significant amounts provides strong evidence towards the likelihood that an outer-sphere alkylation mechanism operates.

Similarly, one equivalent of both $^{2}$H-labelled ketone substrate **160** and unlabelled phenyl ketone substrate **106** were subjected to the Pd-DAAA conditions (Scheme 48).



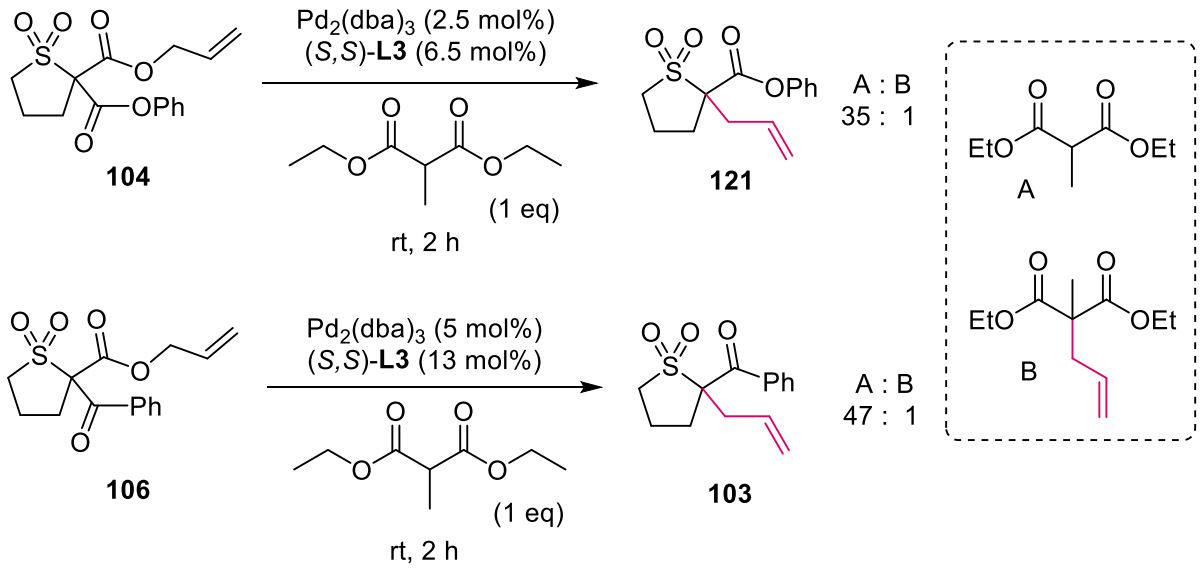

**Scheme 48**

Mass spectrometric analysis of the resulting mixture showed significant amounts of all four crossover products, with a 1.2:1 ratio of **161** to **124**, and a 1:1 ratio of **125** to **162**. As was seen for the ester substrate crossover, the ratio of tolyl products (**124** and **161**) observed to phenyl products (**125** and **162**) was 2.7:1. Once again, the presence of all four crossover products indicates that an outer-sphere alkylation mechanism is highly likely. These results suggest that ester substrates and ketone substrates are likely to react *via* the same mechanism. Therefore, a difference in the mechanism is not the likely cause for the lower enantioselectivity observed for ketone substrates as compared to the ester substrates.

The observation of crossover products, and the conclusion that an outer-sphere alkylation mechanism is likely in operation, is in accord with previous work on allylic alkylation reactions of α-sulfonyl anions where an outer-sphere alkylation mechanism was conclusively corroborated (*vide supra*, Section 1.7, page 31).[45]

### 2.3.3 Malonate Crossover

An additional crossover experiment was also performed in order to gain more evidence for an outer-sphere alkylation mechanism. Standard conditions for the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction were used for phenyl ester substituted sulfone **104** and phenyl ketone substituted sulfone **106**, in the presence of one equivalent of diethyl methyl malonate (Scheme 49).




**Scheme 49**

In theory, the intermediate enolate derived from **104** or **106** could deprotonate the malonate if the reaction proceeds *via* an outer-sphere mechanism where the enolate and π-allylpalladium(II) complex are not closely associated with one another as was indicated by

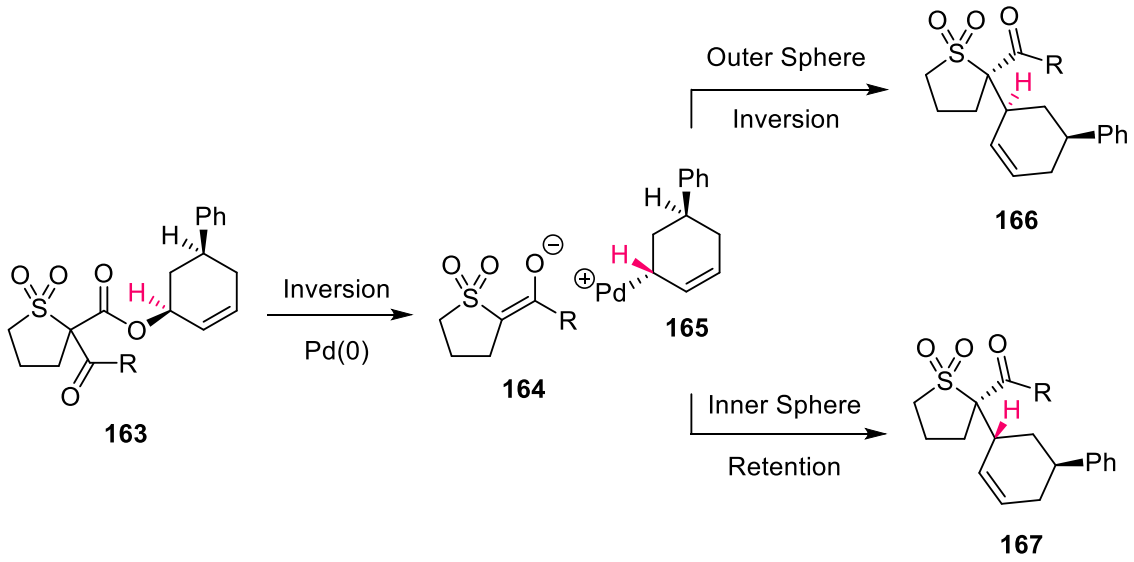
substantial enolate crossover (*vide supra*, Section 2.3.2, page 51). Once the deprotonation of the malonate occurs, it could then be alkylated with the allylic fragment. Although observation of crossover products of the malonate was anticipated in light of the previous crossover studies, for the reactions of both ester substrate **104** and ketone substrate **106**, the major malonate product remained non-alkylated. For phenyl ester substituted sulfone **104** the ratio of non-alkylated malonate A to alkylated malonate B was 35:1, and for phenyl ketone substituted sulfone **106** the ratio of A to B was 47:1.

A lack of crossover would typically be indicative of either an inner-sphere mechanism, or an outer-sphere mechanism where the rate of alkylation surpasses the rate of diffusion. However, it is feasible that in this case, the malonate is simply not acidic enough to be deprotonated by the ester or ketone enolate. This experiment could be repeated with a more acidic 1,3-dicarbonyl that will still form a stabilised anion, such as a 1,3-diketone.

To establish whether the alkylation reaction proceeds *via* the inner- or outer-sphere mechanism more conclusively, additional mechanistic tools were explored next.

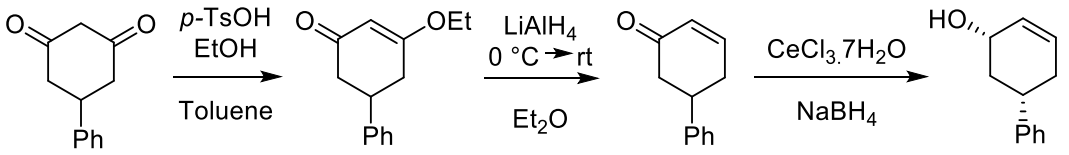
## 2.4 Relative Stereochemistry Determination

We sought to explore the use of a stereochemical probe as another tool to provide further mechanistic evidence, and to unambiguously determine whether the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction occurs by an inner- or outer-sphere mechanism. As such, our aim was to gain access to stereodefined allylic electrophile **163** and to test the stereochemical outcome of the Pd-DAAA reaction thereof (Scheme 50). Mechanistically, oxidative addition of allylic electrophile **163** to the palladium catalyst proceeds with inversion to afford π-allylpalladium(II) complex **165** and an enolate **164** after decarboxylation. Then, in the case of an outer-sphere alkylation mechanism, alkylation should take place by displacement of palladium with inversion, leading to a net retention of stereochemistry in **166**. In the case of an inner-sphere alkylation mechanism, reductive elimination would lead to retention of stereochemistry, thus, resulting in a net inversion of stereochemistry in **167**.



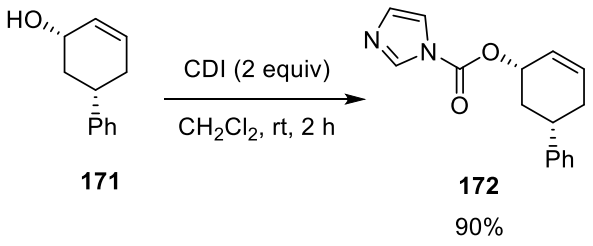

**Scheme 50:** Expected stereochemical outcomes for an outer-sphere vs. an inner-sphere mechanism

First, *cis*-5-phenyl-2-cyclohexen-1-ol (**171**) was produced from 5-phenyl-1,3-cyclohexanedione (**168**) over 3 steps by literature methods (Scheme 51).[20] 5-phenyl-1,3-cyclohexanedione (**168**) was converted to ethoxy-substituted enone **169**, using *p*-toluenesulfonic acid and ethanol, in 86% yield. **169** then underwent conjugate reduction using lithium aluminium hydride to afford enone **170** in 46% yield. Finally, a Luche reduction of **170** afforded *cis*-5-phenyl-2-cyclohexen-1-ol (**171**), as a single diastereomer, in 86% yield.



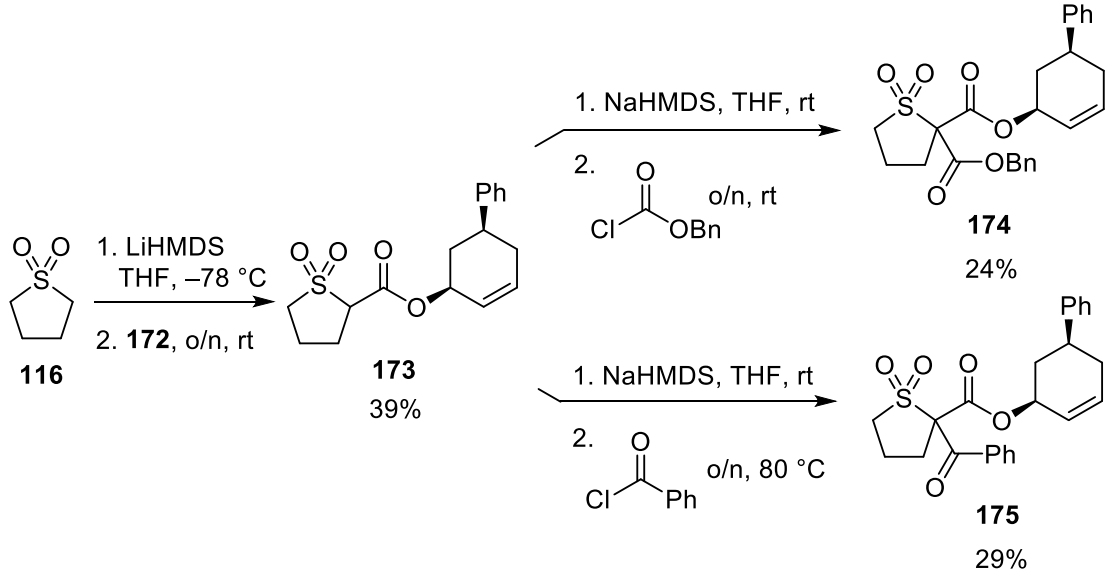

**Scheme 51**

Allylic alcohol **171** was then treated with CDI for 2 hours at room temperature to afford carbamate **172** in excellent yield (Scheme 52).



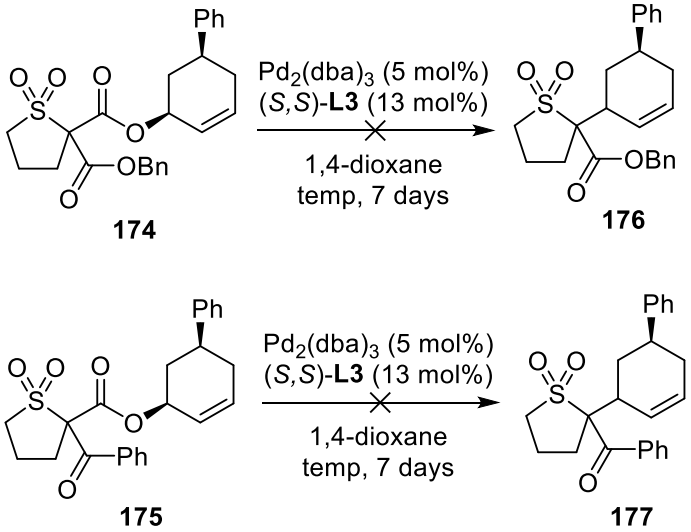

**Scheme 52**

Subsequently, sulfolane (**116**) was reacted with carbamate **172** to afford sulfone **173** in 39% yield (Scheme 53). Next, the addition of the second substituent was performed. Sulfone **173** was deprotonated with NaHMDS and reacted with benzyl chloroformate or benzoyl chloride. The reaction of sulfone **173** with benzyl chloroformate was stirred at room temperature overnight to afford ester substrate **174** in 24% yield, and the reaction of **173** with benzoyl chloride was heated to 80 °C overnight to give ketone substrate **175** in 29% yield.




**Scheme 53**

Precursors **174** and **175** were then subjected to the palladium-catalysed decarboxylative allylic alkylation conditions (Scheme 54). Unfortunately, no reaction occurred at either room temperature, 40 °C or even 120 °C, with starting materials **174** and **175** being recovered exclusively. As was exhibited by the slow reaction times and poor yields for the Pd-DAAA reactions of the methyl-substituted allylic ester substrates **105**, **107**, **129** and **130** (*vide supra*, Section 2.3.1, page 44), this reaction does not appear to be particularly tolerant to substitution on the allylic moiety, and these compounds may unfortunately be too bulky to react.




**Scheme 54**

## 2.4 Additive Screen for Optimisation of the Pd-DAAA Reaction

Whilst the malonate crossover experiment and the relative stereochemistry determination experiments could not be used to confirm the results of the initial crossover results (*vide supra*, Section 2.3.2), there was strong evidence that indicated an outer-sphere alkylation mechanism was in operation. An additive screen was, therefore, carried out, wherein various salts and acids were added to the Pd-DAAA reactions of both ester and ketone substrates to test whether they have any effect on enantioselectivity.

The counterions could affect the enantioselectivity of an outer-sphere alkylation mechanism by the model proposed by Lloyd-Jones and coworkers,[42] in which the coordinating strength of the counterions affects the strength of electrostatic interactions of the enolate to the chiral ligand (Figure 11). It was proposed that three interactions were responsible for dictating the observed selectivity of the reaction, two of which are dependent on the coordinating strength of the counterions: nucleophilic attack, directed by hydrogen bonding of the enolate with the concave amide proton, promoting pro-*S* selectivity for an (*R,R*)-ligand; and nucleophilic attack, directed by the metal counterion bound to the enolate, coordinating to the concave amide carbonyl, promoting pro-*R* selectivity.

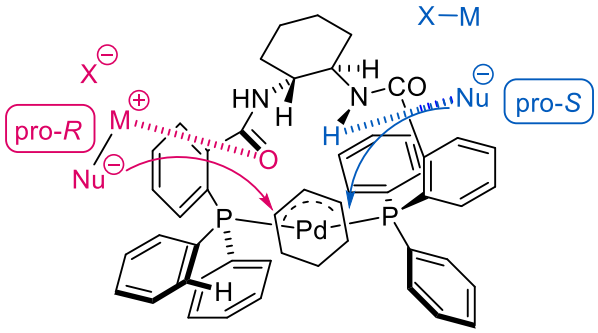
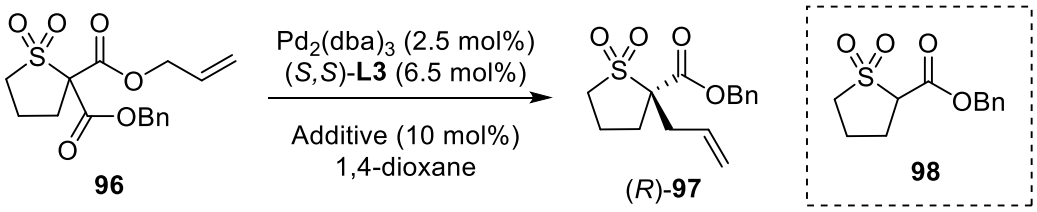



**Figure 11.** The counterion-dependent factors governing enantioselectivity when using an (*R,R*)-Trost ligand[42]

It was hypothesised that smaller cations are able to strongly coordinate to the enolate, preventing efficient hydrogen bonding to the amide proton, and are able to coordinate strongly to the amide carbonyl leading to decreased enantioselectivity, and *vice versa* for larger cations.




| Entry | Additive | Yield (%)[a] | ee (*R*)-97 (%)[b] |
|---|---|---|---|
| 1 | None | 90 | 86 |
| 2 | LiCl | - | - |
| 3 | KCl | 78 | 58 |
| 4 | RbCl | 62 | 64 |
| 5 | CsCl | 63 | 66 |
| 6 | TBACl | 74 | 54 |
| 7 | $LiBF_4$ | - | - |
| 8 | LiOAc | 88 | 86 |
| 9 | LiF | 15 | 84 |
| 10 | TBAF | 76 | 32 |
| 11 | TBAOAc | 94 | 52 |
| 12 | $AgBF_4$ | - | - |
| 13 | AgOTf | - | - |
| 14 | $Zn(OTf)_2$ | - | - |
| 15 | $ZnCl_2$ | 40 | 52 |
| 16 | CSA | - | - |
| 17 | TFA | - | - |
| 18 | $PhCO_2H$ | 23 | 80 |
| 19 | AcOH | Non-alkylated product **98** (87%) | - |

**Table 7:** [a]Isolated yield, [b]Determined by chiral HPLC

In light of these observations, salts with varying cation sizes were tested (Table 7). Without an additive, the Pd-DAAA reaction for the benzyl ester substituted sulfone **96** proceeded in 90% yield, giving the alkylated product (*R*)-**97** with 86% ee (Table 7, entry 1). When comparing chloride salt additives (entries 2-6), a lithium cation led to no reaction occurring, larger group 1 cations; namely potassium, rubidium and caesium, caused a decrease in enantioselectivity from 86% to between 58-66% ee, and the large non-coordinating tetrabutylammonium cation gave the lowest ee of 54%. These results contrast those found by Lloyd-Jones and coworkers on a different system. In our hands, the large, non-coordinating tetrabutylammonium cation led to the greatest erosion of enantioselectivity. In addition, the increase in cation size of potassium, rubidium, and caesium, did not afford large differences in the observed enantioselectivity.

With the exception of lithium acetate (entry 8), which had no effect on either yield or enantioselectivity, all lithium salts added (entries 2, 7 and 9) performed poorly, appearing to affect the reactivity of the system with either no reaction, or very poor yields of (*R*)-**97** being obtained. With other tetrabutylammonium salts (entries 10 and 11), similarly poor enantioselectivities were observed, as was the case for TBACl (entry 6).

Silver(I) cations (entries 12 and 13) did not allow for oxidative addition to occur, with exclusive recovery of starting material. It is possible that the silver cation binds the alkene moiety in preference to palladium, preventing oxidative addition to palladium. Similarly, zinc(II) cations (entries 14 and 15) led to either no oxidative addition or incomplete conversion.

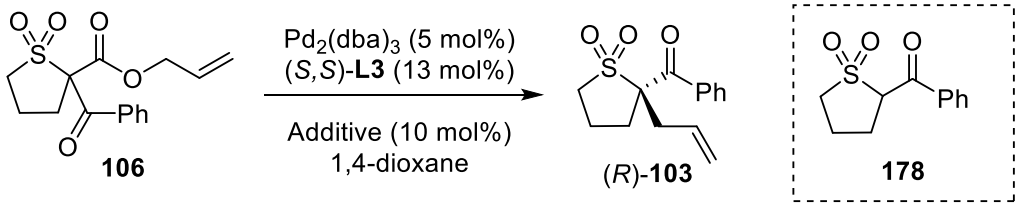
The addition of strong Brønsted acids, CSA ($pK_a = 1.2$[49]) and TFA ($pK_a = 0.2$[50]) (entries 16 and 17), resulted in no reaction occurring. With benzoic acid (entry 18), a weaker acid in comparison ($pK_a = 4.2$[51]), a poor yield of (*R*)-**97** was obtained and slightly decreased enantioselectivity was observed (80% ee). It appears that stronger acids do not allow for oxidative addition to occur, or, in the case of benzoic acid, only allows for a small amount of oxidative addition. Finally, addition of acetic acid ($pK_a = 4.75$[50]) (entry 19), which is only slightly weaker than benzoic acid, protonated the intermediate enolate fully, affording the non-alkylated product **98** exclusively. To conclude, no increase in enantioselectivity was observed as compared to previously optimised additive-free conditions for the Pd-DAAA of ester substituted sulfones.

The same optimisation was performed for the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction for the phenyl ketone substituted sulfone **106**, which, without an additive, proceeded in 96% yield, giving the alkyated product (*R*)-**103** with 72% ee (Table 8, entry 1). For chloride salt additives (entries 2-6), both a small lithium cation and a large tetrabutylammonium cation led to poor enantioselectivity. In contrast, other group 1 cations (potassium, rubidium and caesium) had no effect on the enantioselectivity of the reaction. Again, there is a disparity between these results and those found by Lloyd-Jones and coworkers. Addition of other lithium salts (entries 7-9) had no effect on the enantioselectivity, with the exception of lithium tetrafluoroborate (entry 7) where a low ee of (*R*)-**103** was obtained. Additionally, when other tetrabutylammonium salts were tested (entries 10 and 11), poor enantioselectivities were observed, that were similar to TBACl (entry 6).

As was the case in the phenyl ester substituted sulfone additive screen, silver(I) cations (entries 12 and 13) did not allow for oxidative addition to occur, with only starting material **106** being recovered, whereas zinc(II) cations (entries 14 and 15) led to lower yields and low enantioselectivities.

In contrast to the additive screen of the phenyl ester substrate, addition of Brønsted acid, CSA (entry 16), led to (*R*)-**103** formation in comparable yield, however, low enantioselectivity was observed. TFA (entry 17), the strongest acid tested, allowed for small amounts of product (*R*)-**103** formation, but again with poor ee. Benzoic acid (entry 18) appeared to have no effect on either reactivity or enantioselectivity. Finally, as was seen in the additive screen of the phenyl ester substrate, addition of acetic acid (entry 19) protonated the intermediate enolate fully, giving the non-alkylated product **178** exclusively.

Ultimately, as was observed for the additive screen for the phenyl ester substrate, the previously optimised additive-free conditions gave the best results for the Pd-DAAA of the ketone substituted sulfone.




| Entry | Additive | Yield (%)[a] | ee (*R*)-103 (%)[b] |
|---|---|---|---|
| 1 | None | 96 | 72 |
| 2 | LiCl | 84 | 34 |
| 3 | KCl | 96 | 72 |
| 4 | RbCl | 83 | 74 |
| 5 | CsCl | 88 | 72 |
| 6 | TBACl | 94 | 24 |
| 7 | $LiBF_4$ | 89 | 46 |
| 8 | LiOAc | 81 | 72 |
| 9 | LiF | 84 | 74 |
| 10 | TBAF | 94 | 26 |
| 11 | TBAOAc | 91 | 28 |
| 12 | $AgBF_4$ | - | - |
| 13 | AgOTf | - | - |
| 14 | $Zn(OTf)_2$ | 38 | 54 |
| 15 | $ZnCl_2$ | 73 | 40 |
| 16 | CSA | 88 | 52 |
| 17 | TFA | 23 | 44 |
| 18 | $PhCO_2H$ | 93 | 72 |
| 19 | AcOH | Non-alkylated product **178** (89%) | - |

**Table 8:** [a]Isolated yield, [b]Determined by chiral HPLC

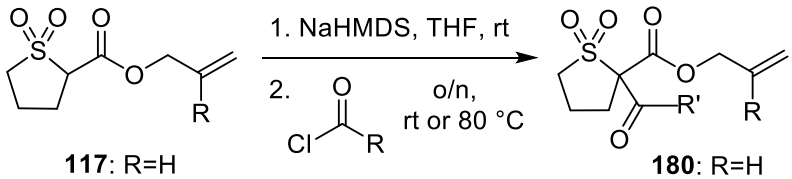
The inclusion of some additives led to a decrease in enantioselectivity, whereas with others, there was no change. It is, therefore, possible that an outer-sphere alkylation mechanism operates and the success of the reaction in terms of yield and enantioselectivity can be altered with the inclusion of additives. The counter-cation effect does not follow the trend observed by Lloyd-Jones and coworkers. In addition, the counter-anion is clearly having an effect on enantioselectivity, although there is no apparent trend.

Ultimately, the efficiency and enantioselectivity of the Pd-DAAA reactions of substrates **96** and **106** could not be improved through the use of additives. Therefore, the subsequent substrate scope investigation was performed using the original optimised conditions without an additive.

## 2.5 Substrate Scope Investigation

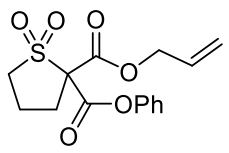
### 2.5.1 5-Membered Cyclic Sulfones

In addition to the substituted allylic ester substrates **105**, **107**, **129** and **130** synthesised as part of the mechanistic investigation (*vide supra*, Section 2.3.1, page 44), a number of other 5-membered cyclic sulfones were produced (Table 9). These substrates were selected based on their differing steric and electronic properties. The precursors for Pd-DAAA were all synthesised under the optimised reaction conditions in moderate to good yields.

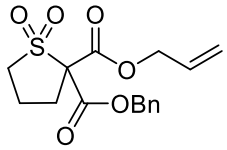



**117**: R=H
**179**: R=Me

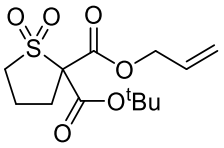
**180**: R=H
**181**: R=Me



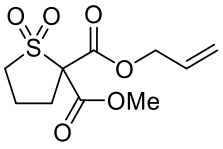

**104**
79%



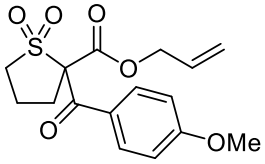

**96**
70%



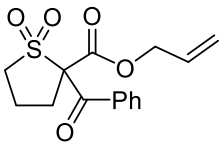

**182**
34%



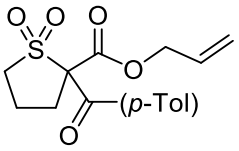

**183**
55%



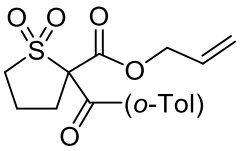

**184**
33%



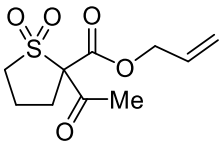

**106**
75%



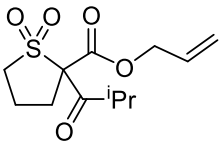

**185**
50%



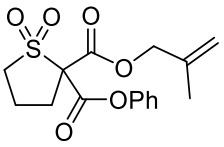

**186**
42%



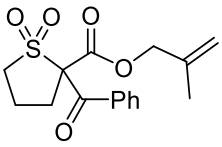

**187**
50%



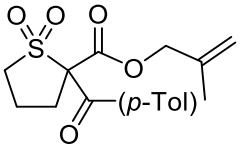

**188**
60%



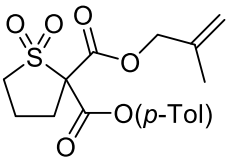

**129**
50%




**130**
65%




**107**
83%




**105**
55%

**Table 9:** Isolated yields for 5-membered precursors for Pd-DAAA reactions

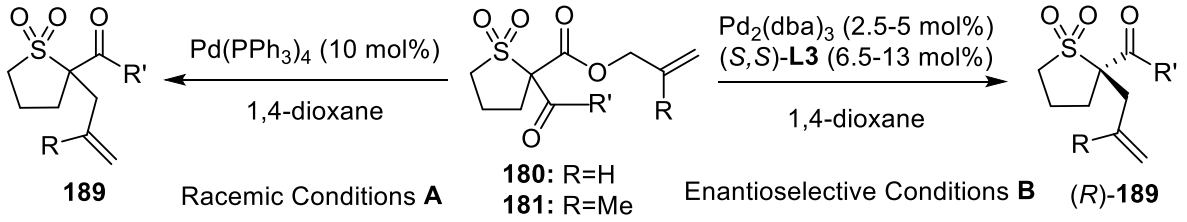
Ester-containing substrates **96**, **104**, **182** and **183** were synthesised by deprotonation of **117** using NaHMDS (1.1 equiv) in THF at room temperature, followed by addition of the appropriate chloroformate (1.1 equiv) at room temperature with stirring overnight, with the exception of **182**, where Boc anhydride (1.1 equiv) was used as the electrophile. Ketone-containing substrates **106** and **184**-**188** were synthesised by deprotonation of **117** using NaHMDS (1.1 equiv) in THF at room temperature, followed by addition of the appropriate acid chloride (1.1 equiv) and heating to 80 °C overnight.

The precursors were then subjected to both racemic and enantioselective palladium-catalysed decarboxylative allylic alkylation conditions (Table 10). The alkylated products were produced using $Pd(PPh_3)_4$ (10 mol%) in 1,4-dioxane in >90% yield in most cases. Ester-containing substrates **96**, **104**, **182** and **183** underwent Pd-DAAA using $Pd_2(dba)_3$ (2.5 mol%) and (*S,S*)-ANDEN phenyl Trost ligand (6.5 mol%), whereas ketone-containing substrates **106** and **184**-**188**, which had been found to be less reactive, required the use of $Pd_2(dba)_3$ (5 mol%) and (*S,S*)-ANDEN phenyl Trost ligand (13 mol%). Reactions under both racemic and enantioselective conditions were typically complete after 2 hours at room temperature; however, substrates containing the methyl-substituted allyl ester, **105**, **107**, **129** and **130**, were complete after 4 hours at room temperature under racemic conditions. Pd-DAAA reactions of these substrates did not reach completion after 7 days at either room temperature or 40 °C under enantioselective conditions, which is reflected in the poorer yields in comparison to their non-substituted counterparts.

Although we have not been able to obtain suitable crystals for the determination of the absolute stereochemical configuration of the major enantiomer of the Pd-DAAA reaction products, it was assumed that the sense of stereoinduction for all Pd-DAAA reaction products synthesised in this research project was the same as that for substrate **103**, where the absolute configuration was found to be the *R* enantiomer (*vide supra*, Section 1.8, figure 9).

For the ester-containing substrates, substrates with phenyl substituent **121** and benzyl substituent **97** gave good ees of 94% and 86%, respectively. The bulky *tert*-butyl substituent in **190** gave a poor ee of 38%, and the small methyl substituent in **191** gave a higher 70% ee, which could suggest that steric bulk can cause erosion of enantioselectivity. However, since the aromatic substituents offered higher ee than both alkyl substituents, it is likely that electronic effects also play a key role in determining enantioselectivity. For the ketone substrates, aromatic substituents, **103** and **124**, afforded moderate ees of 72% and 62%, respectively. The enantioselectivity decreased considerably to 10% ee with an electron-donating *para*-methoxyphenyl substituent on sulfone **192**. When a bulkier aromatic *ortho*-tolyl substituent **193** was appended to the sulfone, likely to be twisted out of plane, the

enantioselectivity also decreased significantly to 10% ee. However, the opposite was found for alkyl substituents, with the small methyl substituent **194** giving a poor ee of 20%, whereas a bulkier isopropyl substituent afforded **195** with 88% ee.



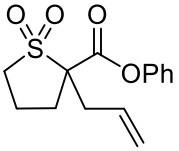
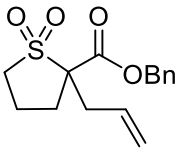
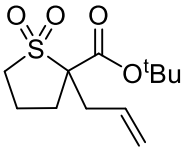
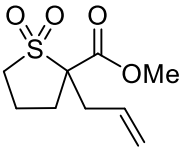
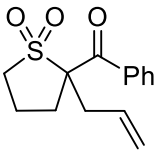
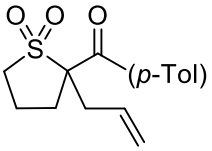
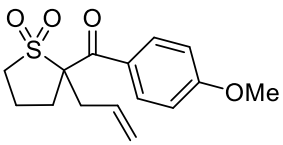
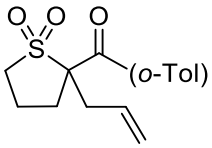
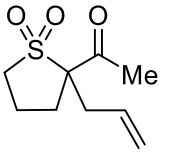
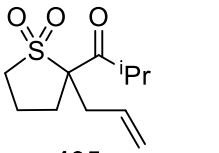
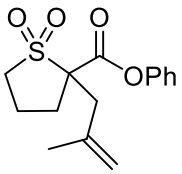
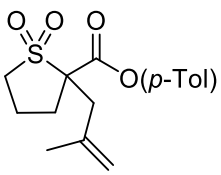
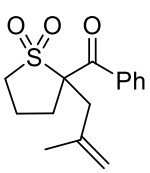
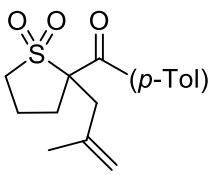

| | | | | |
|---|---|---|---|---|
| |  |  |  |  |
| | **121** | **97** | **190** | **191** |
| **A**[a] | 93% | 91% | 98% | 94% |
| **B**[a,b] | 90%, 94% ee | 90%, 86% ee | 94%, 38% ee | 92%, 70% ee |
| |  |  |  | |
| | **103** | **124** | **192** | |
| **A**[a] | 92% | 90% | 87% | |
| **B**[a,b] | 98%, 72% ee | 89%, 62% ee | 92%, 10% ee | |
| |  |  |  | |
| | **193** | **194** | **195** | |
| **A**[a] | 95% | 92% | 96% | |
| **B**[a,b] | 95%, 10% ee | 90%, 20% ee | 97%, 88% ee | |
| |  |  |  |  |
| | **119** | **118** | **123** | **122** |
| **A**[a] | 92% | 91% | 89% | 88% |
| **B**[a,b] | 62%, 82% ee | 60%, 86% ee | 65%, 14% ee | 59%, 10% ee |

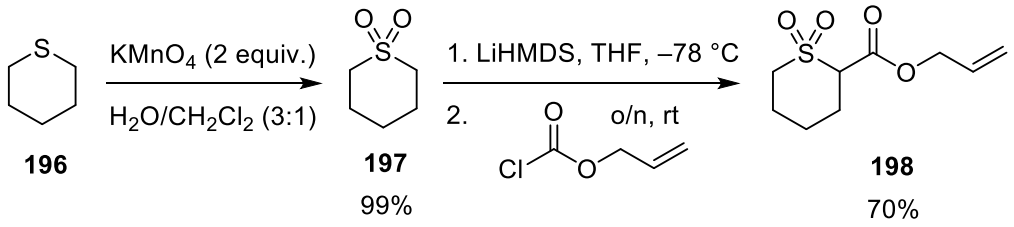
**Table 10:** [a]Isolated yield, [b]ee determined by chiral HPLC

The enantioselectivity of the *para*-tolyl ester substrate containing the substituted allyl group **118** was unaffected compared the non-substituted *para*-tolyl ester substrate, which was previously synthesised in the research group.[52] The enantioselectivity of the phenyl ester substrate **119** decreased from 94% (in **121**) to 82% when the allyl ester is substituted. Substitution of the allyl group had a greater effect on enantioselectivity for the ketone substrates than the ester substrates. For the *para*-toluoyl ketone substrate **122**, the enantioselectivity decreased from 62% ee for the non-substituted allyl ester substrate **124**, to 10% ee. Similarly, for the substituted phenyl ketone substrate **123** the enantioselectivity decreased from 72% ee in non-substituted substrate **103**, to 14% ee.

The difference in reactivity and the significant decrease in enantioselectivity, particularly for the ketone substrates, when the allyl ester was substituted with a methyl group was surprising, as the methyl substituent will be planar, and should, in theory, not have a significant impact on the facial selectivity.

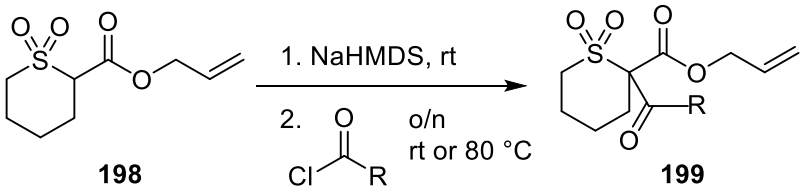
### 2.5.2 6-Membered Cyclic Sulfones

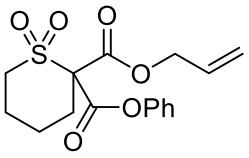
To extend the substrate scope, 6-membered cyclic sulfones were also investigated, in order to compare the enantioselectivity to the 5-membered cyclic sulfones. To begin, tetrahydrothiopyran (**196**) was oxidised to sulfone **197** in 99% yield using potassium permanganate (2 equiv) in a 3:1 mixture of water to $CH_2Cl_2$ (Scheme 55). Subsequently, sulfone **197** was deprotonated using LiHMDS (2 equiv) in THF at –78 °C, which was followed by addition of allyl chloroformate (1.1 equiv) at –78 °C, and the mixture was allowed to reach room temperature overnight, to afford sulfone **198** appended with an allylic ester side chain in 70% yield.



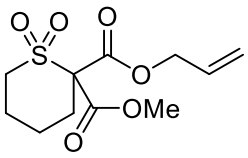

**Scheme 55**

Sulfone **198** was deprotonated with NaHMDS (1.1 equiv) at room temperature, and then, to append an ester substituent, the appropriate chloroformate (1.1 equiv) was added and the reaction stirred at room temperature overnight to give ester-containing substrates **200** and **201** in moderate yields (Table 11). To append a ketone substituent, the appropriate acid chloride was added, and the reaction was heated to 80 °C overnight to afford ketone-containing substrates **202** and **203** in moderate yields.

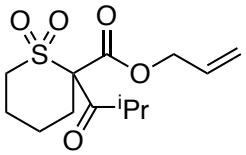


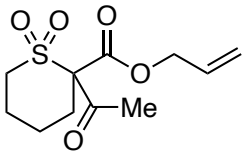

**200**
43%[a]




**201**
41%[b]




**202**
48%[a]

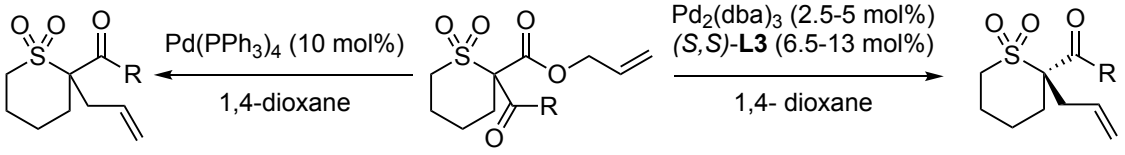



**203**
37%[a]

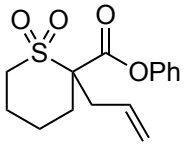
**Table 11:** [a]Isolated yield, [b]Determined by $^1$H NMR spectroscopy of the mixture

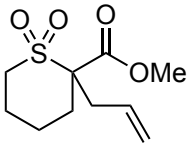
Precursors **200**-**203** were then subjected to both racemic and enantioselective palladium-catalysed decarboxylative allylic alkylation conditions (Table 12). The alkylated products **205**, **207** and **208** were produced in 91-95% yields using $Pd(PPh_3)_4$ (10 mol%) in 1,4-dioxane. Unfortunately, ester-containing substrate **201** did not decarboxylate to give **206**, with starting material **201** being recovered exclusively.

Based on the lower reactivity of ketone substrates compared to ester substrates found for the 5-membered cyclic sulfones, the same catalyst loadings were used for the 6-membered sulfones. Ester-containing substrates underwent Pd-DAAA using $Pd_2(dba)_3$ (2.5 mol%) and (*S,S*)-ANDEN phenyl Trost ligand (6.5 mol%), whereas ketone-containing substrates required $Pd_2(dba)_3$ (5 mol%) and (*S,S*)-ANDEN phenyl Trost ligand (13 mol%).

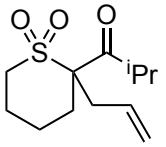


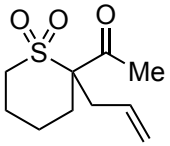

**204** Racemic Conditions **A** **199** Enantioselective Conditions **B** *(R)*-**204**




| | **205** | **206** |
|---|---|---|
| **A**[a] | 92% | - |
| **B**[a, b] | 96%, 64% ee | - |




| | **207** | **208** |
|---|---|---|
| **A**[a] | 95% | 91% |
| **B**[a, b] | 94%, 88% ee | 93%, 32% ee |

**Table 12:** [a]Isolated yield, [b]ee determined by chiral HPLC

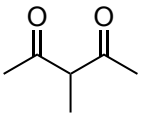
For ester-appended substrates, only the phenyl ester substituted sulfone **200** underwent the Pd-DAAA process, affording alkylated sulfone **205** in good yield, with a moderate ee of 64%. Substrate **201** did not decarboxylate under either racemic or enantioselective conditions, even with double catalyst-loading.

For the ketone substrates, when the steric bulk of the substituent was greater, as in isopropyl ketone substituted sulfone **207**, a good ee of 88% was observed. The enantioselectivity was decreased considerably to 32% ee when a small methyl ketone substituent **208** was appended to the sulfone. These results suggest steric bulk could be an important factor in determining the enantioselectivity for this system.

## 2.6 Future Work

### 2.6.1 Mechanistic Work

To gain additional mechanistic evidence for this process, future work will build on this research to include repeat experiments for the malonate crossover (*vide supra*, Section 2.3.3) using more acidic 1,3-dicarbonyls, such as 1,3-diketone **209** (Figure 12), which may lead to observation of crossover. Indeed, the intermediate enolate can be protonated with a strong acid, as was evidenced by the non-alkylated product formation when acetic acid was used as an additive in the reaction (*vide supra*, Section 2.4).

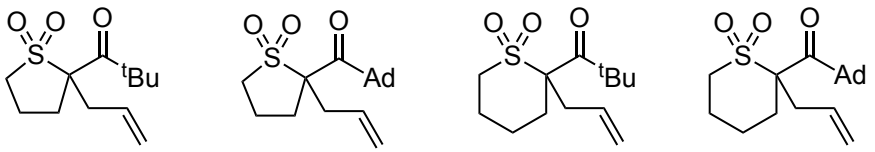


**209**

**Figure 12:** Structure of 3-methyl-2,4-pentanedione

### 2.6.2 Substrate Scope Extension

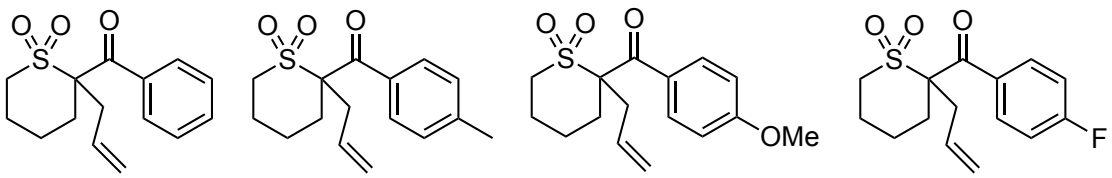
Future work will include further extension of the substrate scope. Of particular interest will be bulky alkyl ketone substituents on both the 5- and 6-membered sulfones due to the high enantioselectivity observed with substrates bearing an isopropyl ketone substituent, **195** and **207**, relative to smaller substituents. Substrates to test will include *tert*-butyl and adamantyl ketone substituents (**210**-**213**) appended to a cyclic sulfone (Figure 13).




**210** **211** **212** **213**

**Figure 13**

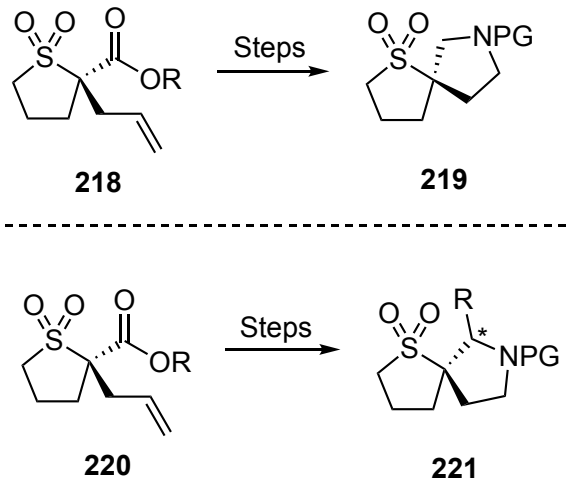
A thorough investigation of 6-membered aryl ketone substrates is also warranted, and substrates to test will include sulfones bearing phenyl (**214**), *para*-tolyl (**215**), *para*-methoxy (**216**) and *para*-fluoro (**217**) substituents (Figure 14).




**214** **215** **216** **217**

**Figure 14**

Once highly enantioenriched products have been produced, the cyclic sulfone substrates will be transformed into spirocyclic amine compounds using the electron withdrawing ester or ketone handle and the allylic chain in a ring-closing process (Scheme 56). Since the enantioselectivity will already be imparted on the substrates, these routes will enable access to enantioenriched spirocycles. Functionalisation of esters will give rise to unsubstituted spirocyclic complexes **219**, whereas substrates bearing a ketone substituent are of particular interest as the spirocyclic complex **221** produced will comprise two contiguous stereocentres, maximising the interrogation of three-dimensional chemical space.




**Scheme 56:** General scheme to transform **218** and **220** into spirocyclic amine complexes **219** and **221**

## 2.7 Conclusions

The aims of this project were to perform a mechanistic study of the Pd-DAAA of cyclic sulfones bearing ester and ketone substituents, optimise the reaction conditions; and extend the substrate scope of this process.

The mechanistic study was performed to establish whether an inner- or outer-sphere alkylation mechanism operates for both ester and ketone substituted sulfones. In particular, we sought to determine whether the Pd-DAAA of sulfones bearing an ester substituent occurs *via* a different mechanism to that of sulfones bearing a ketone substituent in light of the marked difference in enantioselectivity between the two processes. The mechanistic investigation encompassed both crossover experiments and relative stereochemistry determination.

Enolate crossover studies indicated that sulfone substrates containing 2-methyl substituted allylic esters were considerably less reactive than their non-substituted counterparts, and so were deemed unsuitable for a crossover experiment. Instead, $^{2}$H-labelling of the allylic ester with 93% deuterium incorporation was achieved, and enolate crossover experiments were successfully performed. These experiments provided evidence that an outer-sphere alkylation mechanism was in operation for both ester and ketone substrates due to the observation of significant crossover, which concurred with previous work on allylic alkylation reactions of unstabilised α-sulfonyl anions.

Furthermore, relative stereochemistry determination experiments were attempted to conclusively confirm the mechanism of the Pd-DAAA of cyclic sulfones. Although stereochemical probes of both ester and ketone substrates were successfully made, Pd-DAAA reactions for these two substrates were unsuccessful, with no reaction occurring over a period of 7 days with temperatures of up to 120 °C, presumably due to the sterically hindered nature of the allylic electrophile.

An additive screen was performed in order to optimise the Pd-DAAA reaction of cyclic sulfones in terms of enantioselectivity. Various salt and acid additives were used in the reaction, with no increase in enantioselectivity compared to the additive-free conditions.

Since the reaction could not be further optimised using additives, previously optimised conditions were used to broaden the substrate scope of this reaction. The substrate scope for 5-membered sulfones bearing ester and ketone substituents has been substantially broadened. Generally, high ees can be obtained, however, the reaction is sensitive to both steric and electronic factors.

A range of 6-membered cyclic sulfones were also synthesised for comparison with the 5-membered cyclic sulfones. Only one alkylated ester substituted sulfone was produced, bearing a phenyl ester substituent, and affording a moderate ee of 64%. For the ketone substrates, enantioselectivity appeared to correlate to steric bulk, with a bulky *tert*-butyl ester substituted sulfone giving a good ee of 88%.

To conclude, whilst the result could not be confirmed by means of stereochemical labelling, the crossover reaction provided strong evidence for the operation of an outer-sphere alkylation mechanism for this process. Additionally, a number of novel 5- and 6-membered alkylated products have been successfully synthesised, and future work has been proposed for the transformation of enantioenriched alkylated products into spirocyclic building blocks for drug discovery.

# Chapter 3: Experimental

## 3.1 General Procedures

Oven-dried glassware was used for all reactions under an argon atmosphere. Dry solvents were obtained from commercial sources or obtained from an Innovative Technologies PureSolv solvent drying system. All reagents and solvents were used as supplied. Petrol refers to the fraction of petroleum that boils between 40 °C and 60 °C. Aqueous solutions were saturated unless otherwise stated. Removal of solvents *in vacuo* refers to the use of a rotary evaporator at 40 °C, with further drying on a high vacuum line.

VWR Chemicals silica gel (40–63 μm particle size) was used for flash column chromatography. Thin layer chromatography (TLC) was carried out using Merck KgaA silica gel 60 F254 aluminium-backed plates. Ultraviolet irradiation (254 nm) and staining with potassium permanganate solutions as appropriate were used to visualise TLC plates.

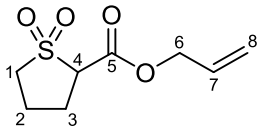
$^{1}$H NMR spectra were obtained using either a Bruker AVANCE III 400 spectrometer or a Bruker FOURIER 300 spectrometer, in $CDCl_3$. $^{13}$C NMR spectra were recorded on the same spectrometers at 100 MHz or 75 MHz, respectively. For $^{1}$H NMR spectra recorded in $CDCl_3$, the residual protic solvent $CHCl_3$ ($\delta_H$ = 7.26 ppm) was used as the internal reference. For $^{13}$C NMR spectra, the central resonance of CDCl3 ($\delta_C$ = 77.0 ppm) was used as the internal reference. NMR data are reported as follows: chemical shift, $\delta_H$ (in parts per million, ppm), (number of protons, multiplicity, coupling constant, *J* in Hertz, and assignment). Couplings are expressed as one, or a combination of: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sextet; septet and m, multiplet. When coincidental couplings constants were observed in the NMR spectra, the apparent multiplicity of the proton resonance in these cases was reported. Various NMR experiments (DEPT-135, COSY, HSQC, HMBC) were used in order to assign the $^{1}$H and $^{13}$C NMR spectra. The atoms of the products reported below are numbered for clarity in NMR assignments, however, the numbering does not correspond to IUPAC nomenclature.

High resolution mass spectra (HRMS) were recorded using a Shimadzu LCMS-IT-TOF instrument using ESI or APCI conditions. Infra-red spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were measured on a Sanyo Gallenkamp capillary melting point apparatus. Enantiomeric excesses were determined by chiral HPLC on a Shimadzu NEXERA X2 UHPLC instrument equipped with a UV detector, using either a CHIRALCEL OD-H or CHIRALPAK AD-H column. Optical rotations were measured in $CHCl_3$ using an AA-65 Automatic Polarimeter.

## 3.2 Synthetic Procedures

### 3.2.1 Synthesis of Precursors for Reaction Optimisation

**Allyl tetrahydrothiophene-2-carboxylate 1,1-dioxide 117**



Sulfolane (3.00 g, 25 mmol) was dissolved in THF (200 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 50 mL, 50 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. Allyl chloroformate (2.97 mL, 28 mmol) was added dropwise at –78 °C. The solution was allowed to reach room temperature and was stirred overnight. The solution was quenched with aq. HCl (1 N, 50 mL), and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 2:1] gave **117** (2.43 g, 74%) as a yellow oil. $\boldsymbol{R_f}$ = 0.21 [petrol:EtOAc 2:1].

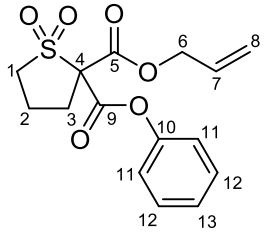
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.97 (1H, ddt, *J* = 17.2, 10.5, 5.9 Hz, **H7**), 5.42 (1H, dq, *J* = 17.2, 1.4 Hz, **H8a**), 5.32 (1H, dq, *J* = 10.4, 1.2 Hz, **H8b**), 4.76 (2H, m, **H6**), 3.97 (1H, t, *J* = 7.6 Hz, **H4**), 3.18-3.04 (2H, m, **H1**), 2.59-2.49 (1H, m, **H3a**), 2.43-2.30 (2H, m, **H3b** and **H2a**), 2.21-2.09 (1H, m, **H2b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 165.3 (**C5**), 131.2 (**C7**), 119.3 (**C8**), 67.1 (**C6**), 64.7 (**C4**), 51.6 (**C1**), 26.0 (**C3**), 20.4 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_8H_{12}O_4S$ $[M–H]^-$ 203.0384, found 203.0381.

**IR:** $\nu_{max}$ (neat): 2969 (C–H), 1737 (C=O) $cm^{-1}$.

**2-Allyl 2-phenyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 104**



**117** (50 mg, 0.25 mmol) was dissolved in THF (2 mL). NaHMDS (1 M in THF, 0.28 mL, 0.28 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Phenyl chloroformate (35 µL, 0.28 mmol) was added dropwise, and the solution was stirred overnight. The solution was quenched with aq. HCl (1 N, 2 mL). The mixture was extracted with EtOAc (3 x 2 mL), washed with brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **104** (63.4 mg, 79%) as a colourless solid. $R_f$ = 0.19 [petrol:EtOAc 4:1]. **m.p.:** 58–60 °C.

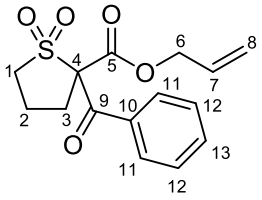
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.43-7.36 (2H, m, **H12**), 7.30-7.25 (1H, m, **H13**), 7.20-7.14 (2H, m, **H11**), 5.96 (1H, dddd, *J* = 16.2, 10.4, 6.7, 5.9 Hz, **H7**), 5.45 (1H, dq, *J* = 17.2, 1.5 Hz, **H8a**), 5.32 (1H, dq, *J* = 10.4, 1.2 Hz, **H8b**), 4.84 (2H, m, **H6**), 3.50-3.34 (2H, m, **H1**), 2.92 (1H, quint, *J* = 7.8 Hz, **H3a**), 2.79 (1H, quint, *J* = 7.5 Hz, **H3b**), 2.33 (2H, quint, *J* = 8.4 Hz, **H2**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 164.2 (**C5**), 162.9 (**C9**), 150.2 (**C10**), 130.5 (**C7**), 128.9 (**C12**), 126.9 (**C13**), 121.3 (**C11**), 120.0 (**C8**), 75.2 (**C4**), 68.0 (**C6**), 50.6 (**C1**), 30.3 (**C3**), 17.4 (**C2**).

**HRMS (*m/z*):** (ESI) calcd for $C_{15}H_{16}O_6S$ $[M+Na]^+$ 347.0560, found 347.0553.

**IR:** $\nu_{max}$ (neat): 3017 (C–H), 2967 (C–H), 1765 (C=O), 1735 (C=O) $cm^{-1}$.

### Allyl 2-benzoyltetrahydrothiophene-2-carboxylate 1,1-dioxide 106




**117** (1.00 g, 4.90 mmol) was dissolved in THF (50 mL) and NaHMDS (1 M in THF, 5.39 mL, 5.39 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzoyl chloride (0.63 mL, 5.39 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 40 mL). The mixture was extracted with EtOAc (3 x 40 mL), washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **106** (1.13 g, 75%) as a colourless solid. $R_f$ = 0.18 [petrol:EtOAc 4:1]. **m.p.:** 81–83 °C.

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.96-7.92 (2H, m, **H11**), 7.58 (1H, tt, *J* = 6.5, 1.3 Hz, **H13**), 7.49-7.43 (2H, m, **H12**), 5.63 (1H, dddd, *J* = 15.9, 10.3, 7.4, 5.5 Hz, **H7**), 5.19-5.11 (2H, m, **H8**),

4.62 (2H, dt, *J* = 5.9, 1.4 Hz, **H6**), 3.49-3.22 (2H, m, **H1**), 3.14 (1H, quint, *J* = 6.9 Hz, **H3a**), 2.72 (1H, quint, *J* = 6.6 Hz, **H3b**), 2.40-2.17 (2H, m, **H2**).

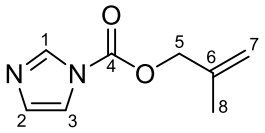
**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 188.5 (**C9**), 166.3 (**C5**), 135.4 (**C10**), 133.8 (**C13**), 130.2 (**C7**), 129.0 (**C11**), 128.7 (**C12**), 120.0 (**C8**), 77.8 (**C4**), 67.3 (**C6**), 51.9 (**C1**), 31.9 (**C3**), 17.6 (**C2**).

**HRMS (*m/z*):** (ESI) calcd for $C_{15}H_{16}O_5S$ $[M+Na]^+$ 331.0611, found 331.0597.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 2954 (C–H), 1735 (C=O), 1685 (C=O) $cm^{-1}$.

### 3.2.2 Synthesis of 2-Methyl Allyl Ester Crossover Experiment Precursors

**2-Methylallyl imidazole-1-carboxylate 127[20]**




1,1'-Carbonyldiimidazole (1.46 g, 9.00 mmol) was dissolved in THF (65 mL) and the solution was cooled to 0 °C. A solution of 2-methyl-2-propen-1-ol (0.50 mL, 5.94 mmol) in $CH_2Cl_2$ (22 mL) was added dropwise at 0 °C. The solution was stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **127** (937 mg, 95%) as a colourless solid. $R_f$ = 0.32 [petrol:EtOAc 4:1].

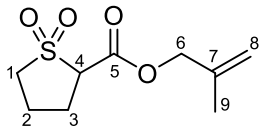
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 8.17 (1H, br s, **H1**), 7.45 (1H, br s, **H2**), 7.09 (1H, br s, **H3**), 5.09 (1H, s, **H7a**), 5.06 (1H, s, **H7b**), 4.82 (2H, s, **H5**), 1.82 (3H, s, **H8**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 148.8 (**C4**), 138.5 (**C1**), 137.2 (**C6**), 130.7 (**C3**), 117.2 (**C2**), 115.0 (**C7**), 71.4 (**C5**), 19.4 (**C8**).

**HRMS (*m/z*):** (ESI) calcd for $C_8H_{10}N_2O_2$ $[M+H]^+$ 167.00815, found 167.0810.

Analytical data matches literature values.[20]

**(2-Methylallyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 128**



Sulfolane (334 mg, 2.78 mmol) was dissolved in THF (25 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 5.57 mL, 5.57 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. A solution of **127** (500 mg, 3.00 mmol) in THF (5 mL) was added dropwise at –78 °C. The solution was allowed to reach room temperature and was stirred overnight. The solution was quenched with aq. HCl (1 N, 8 mL), and the mixture was extracted with EtOAc (3 x 8 mL). The combined organic phase was washed with brine (8 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 2:1] gave **128** (485 mg, 80%) as a colourless oil. $\boldsymbol{R_f}$ = 0.32 [petrol:EtOAc 2:1].

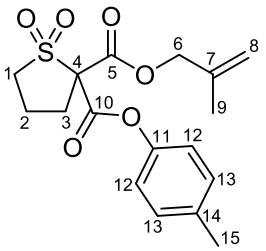
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.05 (1H, t, *J* = 1.2 Hz, **H8a**), 4.97 (1H, quint, *J* = 0.8 Hz, **H8b**), 4.71 (1H, d, *J* = 12.8 Hz, **H6a**), 4.64 (1H, d, *J* = 12.8 Hz, **H6b**), 3.95 (1H, t, *J* = 7.5 Hz, **H4**), 3.18-3.07 (2H, m, **H1**), 2.62-2.52 (1H, m, **H3a**), 2.45-2.32 (2H, m, **H2a** and **H3b**), 2.23-2.12 (1H, m, **H2b**), 1.80 (3H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 165.4 (**C5**), 139.1 (**C7**), 114.4 (**C8**), 70.0 (**C6**), 64.9 (**C4**), 51.4 (**C1**), 25.9 (**C3**), 20.3 (**C2**), 19.6 (**C9**).

**HRMS (*m/z*):** (APCI) calcd for $C_9H_{14}O_4S$ $[M+H]^+$ 219.0686, found 219.0676.

**IR:** $\nu_{max}$ (neat): 3084 (C–H), 2952 (C–H), 1735 (C=O) $cm^{-1}$.

**2-(2-Methylallyl) 2-(*p*-tolyl) dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 105**



**128** (240 mg, 1.10 mmol) was dissolved in THF (10 mL) at room temperature. NaHMDS (1 M in THF, 1.35 mL, 1.35 mmol) was added dropwise. The solution was stirred at room

temperature for 30 minutes. *p*-Tolyl chloroformate (200 µL, 1.35 mmol) was added dropwise, and the solution was stirred overnight. The solution was quenched with aq. HCl (1 N, 10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **105** (213 mg, 55%) as a yellow solid. $R_f$ = 0.30 [petrol:EtOAc 4:1]. **m.p.:** 70–71 °C.

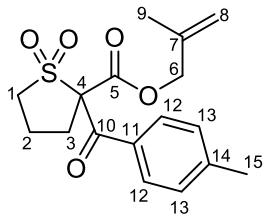
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.5 Hz, **H13**), 7.05 (2H, dt, *J* = 9.0, 2.4 Hz, **H12**), 5.10 (1H, t, *J* = 1.1 Hz, **H8a**), 5.00 (1H, quint, *J* = 0.8 Hz, **H8b**), 4.80 (1H, d, *J* = 12.9 Hz, **H6a**), 4.75 (1H, d, *J* = 12.8 Hz, **H6b**), 3.48-3.36 (2H, m, **H1**), 2.91 (1H, quint, *J* = 7.5 Hz, **H3a**), 2.79 (1H, quint, *J* = 7.4 Hz, **H3b**), 2.38-2.28 (5H, m, **H2** and **H15**), 1.79 (3H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.4 (**C5**), 163.2 (**C10**), 148.1 (**C11**), 138.6 (**C7**), 136.5 (**C14**), 130.1 (**C13**), 120.9 (**C12**), 114.8 (**C8**), 75.1 (**C4**), 70.6 (**C6**), 50.6 (**C1**), 30.3 (**C3**), 20.9 (**C15**), 19.4 (**C9**), 17.3 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{17}H_{20}O_6S$ $[M+H]^+$ 353.1053, found 353.1052.

**IR:** $\nu_{max}$ (neat): 3017 (C–H), 2970 (C–H), 2920 (C–H), 1765 (C=O), 1730 (C=O) $cm^{-1}$.

### (2-Methylallyl) 2-(*p*-toluoyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 107




**128** (240 mg, 1.10 mmol) was dissolved in THF (10 mL) and NaHMDS (1 M in THF, 1.35 mL, 1.35 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. *p*-Toluoyl chloride (180 µL, 1.35 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **107** (306 mg, 83%) as a yellow oil. $R_f$ = 0.30 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.6 Hz, **H13**), 7.25 (2H, d, *J* = 8.6 Hz, **H12**), 4.86 (1H, s, **H8a**), 4.86 (1H, s, **H8b**), 4.53 (2H, s, **H6**), 3.49-3.34 (2H, m, **H1**), 3.13 (1H, quint, *J* =

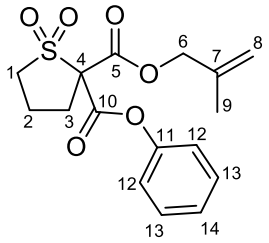
7.6 Hz, **H3a**), 2.69 (1H, quint, *J* = 7.2 Hz, **H3b**), 2.39 (3H, s, **H15**), 2.35-2.19 (2H, m, **H2**), 1.46 (3H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 187.5 (**C10**), 166.3 (**C5**), 144.9 (**C14**), 138.2 (**C7**), 132.9 (**C11**), 129.6 (**C12**), 129.2 (**C13**), 115.1 (**C8**), 77.8 (**C4**), 70.4 (**C6**), 51.9 (**C1**), 32.0 (**C3**), 21.7 (**C15**), 19.3 (**C9**), 17.6 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{17}H_{20}O_5S$ $[M+H]^+$ 337.1104, found 337.1096.

**IR:** $\nu_{max}$ (neat): 3062 (C–H), 2952 (C–H), 1733 (C=O), 1682 (C=O) $cm^{-1}$.

### 2-(2-Methylallyl) 2-phenyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 129



**128** (100 mg, 0.46 mmol) was dissolved in THF (6 mL). NaHMDS (1 M in THF, 0.51 mL, 0.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Phenyl chloroformate (64 µL, 0.51 mmol) was added dropwise, and the solution was stirred overnight. The solution was quenched with aq. HCl (1 N, 6 mL). The mixture was extracted with EtOAc (3 x 6 mL), washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **129** (77 mg, 50%) as a colourless oil. $R_f$ = 0.21 [petrol:EtOAc 4:1].

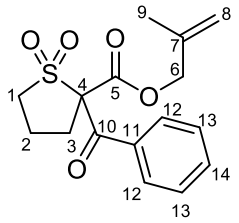
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.41-7.37 (2H, m, **H12**), 7.29-7.25 (1H, m, **H14**), 7.19-7.16 (2H, m, **H13**), 5.10 (1H, s, **H8a**), 5.00 (1H, s, **H8b**), 4.79 (1H, d, *J* = 12.6 Hz, **H6a**), 4.74 (1H, d, *J* = 12.8 Hz, **H6b**), 3.45-3.32 (2H, m, **H1**), 2.91 (1H, quint, *J* = 8.4 Hz, **H3a**), 2.78 (1H, quint, *J* = 7.6 Hz, **H3b**), 2.31 (2H, quint, *J* = 8.0 Hz, **H2**), 1.80 (3H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.3 (**C5**), 162.3 (**C10**), 150.3 (**C11**), 138.5 (**C7**), 129.6 (**C12**), 126.7 (**C14**), 121.2 (**C13**), 114.7 (**C8**), 75.2 (**C4**), 70.6 (**C6**), 50.6 (**C1**), 30.3 (**C3**), 19.5 (**C9**), 17.5 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_6S$ $[M+H]^+$ 339.0897, found 339.0895.

**IR:** $\nu_{max}$ (neat): 3073 (C–H), 2956 (C–H), 1735 (C=O) $cm^{-1}$.

**(2-Methylallyl) 2-benzoyltetrahydrothiophene-2-carboxylate 1,1-dioxide 130**



**128** (100 mg, 0.46 mmol) was dissolved in THF (6 mL) and NaHMDS (1 M in THF, 0.51 mL, 0.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzoyl chloride (59 µL, 0.51 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 6 mL). The mixture was extracted with EtOAc (3 x 6 mL), washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **130** (100 mg, 65%) as a colourless oil. $\boldsymbol{R_f}$ = 0.22 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.3 Hz, **H12**), 7.54 (1H, t, *J* = 7.2 Hz, **H14**), 7.42 (2H, t, *J* = 7.7 Hz, **H13**), 4.78 (2H, s, **H8**), 4.49 (2H, t, *J* = 14.0 Hz, **H6**), 3.47-3.33 (2H, m, **H1**), 3.10 (1H, quint, *J* = 6.8 Hz, **H3a**), 2.69 (1H, quint, *J* = 6.8 Hz, **H3b**), 2.34-2.15 (2H, m, **H2**), 1.40 (3H, s, **H9**).

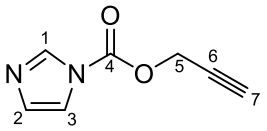
**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 188.2 (**C10**), 166.2 (**C5**), 138.2 (**C7**), 135.4 (**C11**), 133.9 (**C14**), 129.0 (**C12**), 128.8 (**C13**), 115.1 (**C8**), 77.7 (**C4**), 70.3 (**C6**), 51.8 (**C1**), 32.0 (**C3**), 19.2 (**C9**), 17.7 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_5S$ $[M+H]^+$ 323.0948, found 323.0955.

**IR:** $\nu_{max}$ (neat): 3062 (C–H), 2950 (C–H), 1733 (C=O), 1685 (C=O) $cm^{-1}$.

### 3.2.3 Synthesis of $^{2}$H Labelled Allyl Ester Crossover Experiment Precursors

#### Prop-2-ynyl imidazole-1-carboxylate 139[53]




1,1'-Carbonyldiimidazole (2.51 g, 15.5 mmol) was dissolved in $CH_2Cl_2$ (20 mL). Propargyl alcohol (0.5 mL, 8.59 mmol) was added dropwise. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [Petrol:EtOAc 2:1] gave **139** (607 mg, 47%) as an off-white solid. $R_f$ = 0.26 [petrol:EtOAc 2:1].

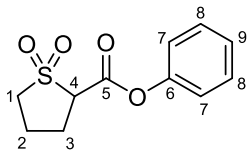
**$^{1}$H NMR:** (400 MHz, $CDCl_3$) δ 8.16 (1H, s, **H1**), 7.44 (1H, s, **H2**), 7.08 (1H, s, **H3**), 4.99 (2H, d, *J* = 2.4 Hz, **H5**), 2.62 (1H, t, *J* = 2.5 Hz, **H7**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 148.0 (**C4**), 137.1 (**C1**), 130.9 (**C2**), 117.2 (**C3**), 76.9 (**C6**), 75.8 (**C7**), 55.5 (**C5**).

**IR:** $\nu_{max}$ (neat): 3010 (C–H), 2911 (C–H), 2827 (C–H), 2130 (C≡C), 1752 (C=O) $cm^{-1}$.

Analytical data matches literature values.[53]

#### Phenyl tetrahydrothiophene-2-carboxylate 1,1-dioxide 142




Sulfolane (120 mg, 1.00 mmol) was dissolved in THF (10 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 2 mL, 2.00 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. Phenyl chloroformate (140 µL, 1.10 mmol) was added dropwise at –78 °C. The solution was allowed to reach room temperature and was stirred overnight. The solution was quenched with aq. HCl (1 N, 10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **142** (77 mg, 32%) as a yellow oil. $R_f$ = 0.25 [petrol:EtOAc 4:1].

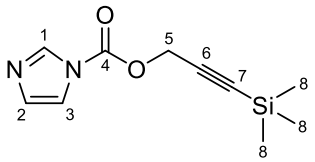
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.39 (2H, t, *J* = 5.6 Hz, **H7**), 7.26 (1H, tt, *J* = 5.3, 1.0 Hz, **H9**), 7.19-7.16 (2H, m, **H8**), 4.17 (1H, t, *J* = 5.6 Hz, **H4**), 3.24-3.12 (2H, m, **H1**), 2.69-2.60 (1H, m, **H3a**), 2.52-2.34 (2H, m, **H2a** and **H3b**), 2.26-2.15 (1H, m, **H2b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 164.8 (**C5**), 150.5 (**C6**), 129.5 (**C7**), 126.4 (**C9**), 121.5 (**C8**), 64.7 (**C4**), 52.0 (**C1**), 26.0 (**C3**), 20.5 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{12}O_4S$ $[M+H]^+$ 241.0529, found 241.0531.

**IR:** $\nu_{max}$ (neat): 3021 (C–H), 2960 (C–H), 2887 (C–H), 1754 (C=O) $cm^{-1}$.

### 3-Trimethylsilylprop-2-ynyl imidazole-1-carboxylate 144




A solution of 1,1'-carbonyldiimidazole (8.51 g, 52.5 mmol) in THF (200 mL) was cooled to 0 °C. (3-Trimethylsilyl)propargyl alcohol (5.18 mL, 35 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [Petrol:EtOAc 9:1–4:1] gave **144** (3.35 g, 43%) as a colourless oil. $\boldsymbol{R_f}$ = 0.32 [petrol:EtOAc 2:1].

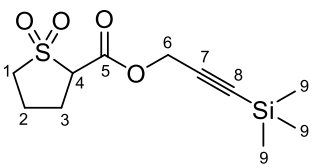
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 8.21 (1H, br s, **H1**), 7.48 (1H, t, *J* = 1.4 Hz, **H2**), 7.11 (1H, dd, *J* = 1.65, 0.80 Hz, **H3**), 5.01 (2H, s, **H5**), 0.22 (9H, s, **H8**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 148.1 (**C4**), 137.3 (**C1**), 130.7 (**C2**), 117.2 (**C3**), 96.7 (**C6**), 94.7 (**C7**), 56.2 (**C5**), –0.42 (**C8**).

**HRMS (*m/z*):** (APCI) calcd for $C_{10}H_{14}N_2O_2Si$ $[M+H]^+$ 223.0897, found 223.0890.

**IR:** $\nu_{max}$ (neat): 2961 (C–H), 2902 (C–H), 2186 (C≡C), 1763 (C=O) $cm^{-1}$.

### 3-Trimethylsilylprop-2-ynyl 1,1-dioxothiolane-2-carboxylate 145



Sulfolane (600 mg, 5 mmol) was dissolved in THF (40 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 10.5 mL, 10.5 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. The solution was allowed to reach room temperature, and a solution of **144** (1.22 g, 5.5 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with aq. HCl (1 N, 30 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **145** (645 mg, 47%) as a colourless solid. $R_f$ = 0.29 [petrol:EtOAc 2:1]. **m.p.:** 105–106 °C.

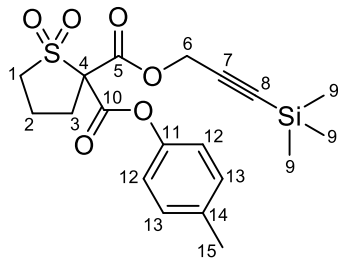
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 4.92 (1H, d, *J* = 15.5 Hz, **H6a**), 4.70 (1H, d, *J* = 15.8 Hz, **H6b**), 3.96 (1H, t, *J* = 7.0 Hz, **H4**), 3.18-3.06 (2H, m, **H1**), 2.60-2.51 (1H, m, **H3a**), 2.45-2.32 (2H, m, **H2a** and **H3b**), 2.22-2.11 (1H, m, **H2b**), 0.17 (9H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 165.2 (**C5**), 97.7 (**C7**), 93.2 (**C8**), 64.6 (**C4**), 54.6 (**C6**), 51.6 (**C1**), 26.2 (**C3**), 20.5 (**C2**), –0.37 (**C9**).

**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{18}O_4SiS$ $[M+H]^+$ 275.0768, found 275.0767.

**IR:** $\nu_{max}$ (neat): 2965 (C–H), 2902 (C–H), 2190 (C≡C), 1739 (C=O) $cm^{-1}$.

### 2-(3-Trimethylsilylprop-2-ynyl) 2-tolyl dihydrothiophene-2,2(3H)-dicarboxylate 1,1-dioxide 148




**145** (588 mg, 2.15 mmol) was dissolved in THF (25 mL). NaHMDS (1 M in THF, 2.37 mL, 2.37 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. *p*-Tolyl chloroformate (0.34 mL, 2.37 mmol) was added dropwise, and the solution was stirred at room temperature for 5 hours. The reaction was quenched with aq. HCl (1 N, 20 mL). The mixture was extracted with EtOAc (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–6:1] gave **148** (538 mg, 61%) as a colourless oil. $R_f$ = 0.61 [petrol:EtOAc 2:1].

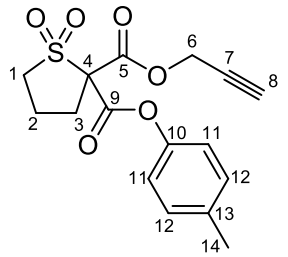
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.5 Hz, **H13**), 7.08 (2H, d, *J* = 9.0 Hz, **H12**), 4.91 (2H, d, *J* = 2.1 Hz, **H6**), 3.50-3.32 (2H, m, **H1**), 2.94 (1H, quint, *J* = 7.5 Hz, **H3a**), 2.75 (1H, quint, *J* = 6.9 Hz, **H3b**), 2.37-2.27 (5H, m, **H2** and **H15**), 0.16 (9H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.0 (**C5**), 162.8 (**C10**), 148.1 (**C11**), 136.4 (**C14**), 130.0 (**C13**), 121.0 (**C12**), 97.1 (**C7**), 93.9 (**C8**), 74.8 (**C4**), 55.3 (**C6**), 50.6 (**C1**), 30.3 (**C3**), 20.9 (**C15**), 17.3 (**C2**), –0.43 (**C9**).

**HRMS (*m/z*):** (APCI) calcd for $C_{19}H_{24}O_6SiS$ $[M+H]^+$ 409.1136, found 409.1126.

**IR:** $\nu_{max}$ (neat): 3034 (C–H), 2960 (C–H), 2193 (C≡C), 1746 (C=O) $cm^{-1}$.

### 2-(Prop-2-ynyl) 2-tolyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 150




**148** (20.4 mg, 0.05 mmol) was dissolved in THF (2 mL). Acetic acid (3.2 µL, 0.055 mmol) and tetrabutylammonium fluoride (1 M in THF, 55 µL, 0.055 mmol) were added, and the reaction mixture was stirred at room temperature for 2 hours. The solution was quenched with aq. $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **150** (14 mg, 83%) as a pale brown solid. $R_f$ = 0.32 [petrol:EtOAc 2:1]. **m.p.:** 96–97 °C.

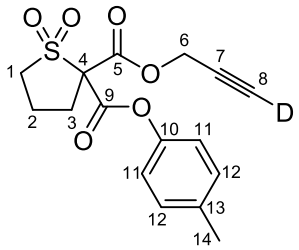
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.4 Hz, **H12**), 7.07 (2H, d, *J* = 8.5 Hz, **H11**), 4.92 (2H, qd, *J* = 15.4, 2.4 Hz, **H6**), 3.47-3.35 (2H, m, **H1**), 2.93 (1H, quint, *J* = 7.4 Hz, **H3a**), 2.79 (1H, quint, *J* = 7.7 Hz, **H3b**), 2.55 (1H, t, *J* = 2.5 Hz, **H8**), 2.37-2.30 (5H, m, **H2** and **H14**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 163.9 (**C5**), 162.8 (**C9**), 148.1 (**C10**), 136.5 (**C13**), 130.1 (**C12**), 120.8 (**C11**), 76.4 (**C8**), 76.0 (**C7**), 74.9 (**C4**), 54.5 (**C6**), 50.6 (**C1**), 30.2 (**C3**), 20.9 (**C14**), 17.4 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{16}O_6S$ $[M+H]^+$ 337.0740, found 337.0734.

**IR:** $\nu_{max}$ (neat): 3012 (C–H), 2965 (C–H), 2918 (C–H), 2850 (C–H), 2126 (C≡C), 1769 (C=O), 1743 (C=O) $cm^{-1}$.

**2-(3-$^2$H-Prop-2-ynyl) 2-tolyl dihydrothiophene-2,2(3H)-dicarboxylate 1,1-dioxide 151**



**148** (414 mg, 1.01 mmol) was dissolved in THF (15 mL). Deuterium oxide (5 mL) was added, followed by tetrabutylammonium fluoride (1 M in THF, 1.12 mL, 1.12 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The solution was diluted with water. The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 6:1–4:1] gave **151** (304 mg, 89%, 96% D) as a pale yellow solid. $\boldsymbol{R_f}$ = 0.32 [petrol:EtOAc 2:1]. **m.p.:** 97–98 °C.

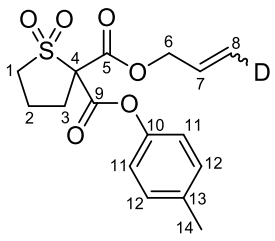
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.4 Hz, **H12**), 7.07 (2H, d, *J* = 8.5 Hz, **H11**), 4.92 (2H, qd, *J* = 15.4, 2.4 Hz, **H6**), 3.47-3.35 (2H, m, **H1**), 2.93 (1H, quint, *J* = 7.4 Hz, **H3a**), 2.79 (1H, quint, *J* = 7.7 Hz, **H3b**), 2.55 (0.04H, t, *J* = 2.4 Hz, **H8**), 2.37-2.30 (5H, m, **H2** and **H14**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 163.9 (**C5**), 162.8 (**C9**), 148.1 (**C10**), 136.5 (**C13**), 130.1 (**C12**), 120.8 (**C11**), 74.9 (**C4**), 54.5 (**C6**), 50.6 (**C1**), 30.2 (**C3**), 20.9 (**C14**), 17.4 (**C2**), **C7** and **C8** signals not observed.

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{15}DO_6S$ $[M+H]^+$ 338.0803, found 338.0794.

**IR:** $\nu_{max}$ (neat): 3017 (C–H), 2965 (C–H), 2918 (C–H), 2850 (C–H), 2579 (C–D), 1984 (C≡C), 1767 (C=O), 1743 (C=O) $cm^{-1}$.

**2-(3-$^2$H-Allyl) 2-tolyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 152**



A suspension of **151** (194 mg, 0.58 mmol), $Pd/CaCO_3$ (19.4 mg) and quinoline (136 µL, 1.15 mmol) in EtOAc (11.5 mL) was degassed with argon. The mixture was cooled to 0 °C, and

then stirred at 0 °C under a hydrogen atmosphere for 20 minutes. The suspension was filtered though a pad of celite, washed with aq. HCl (1 N, 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1] gave **152** (160 mg, 82%, 93%D) as a colourless solid. $R_f$ = 0.32 [petrol:EtOAc 2:1]. **m.p.:** 60–61 °C.

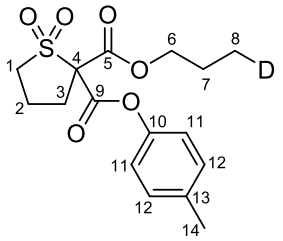
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.2 Hz, **H12**), 7.05 (2H, d, *J* = 9.2 Hz, **H11**), 6.00-5.91 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz, **H7**), 5.47 (0.24H, dq, *J* = 17.2, 1.3 Hz, **H8a**), 5.34 (0.83H, dq, *J* = 10.5, 1.1 Hz, **H8b**), 4.86 (2H, dq, *J* = 5.7, 1.3 Hz, **H6**), 3.49-3.35 (2H, m **H1**), 2.94 (1H, quint, *J* = 7.8 Hz, **H3a**), 2.82 (1H, quint, *J* = 7.8 Hz, **H3b**), 2.39-2.31 (5H, m, **H2** and **H14**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.2 (**C5**), 163.2 (**C9**), 148.1 (**C10**), 136.5 (**C13**), 130.5 (**C7**), 130.1 (**C12**), 120.8 (**C11**), 119.5 (t, *J* = 93.6 Hz, **C8**), 75.0 (**C4**), 67.7 (**C6**), 50.5 (**C1**), 30.2 (**C3**), 21.0 (**C14**), 17.3 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{17}DO_6S$ $[M+H]^+$ 340.0960, found 340.0947.

**IR:** $\nu_{max}$ (neat): 3034 (C–H), 2954 (C–H), 1735 (C=O) $cm^{-1}$.

### 2-(3-$^2$H-Propyl) 2-tolyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 154




A suspension of **151** (16.9 mg, 0.05 mmol), $Pd/CaCO_3$ (2 mg) and quinoline (12 µL, 0.1 mmol) in EtOAc (1 mL) was degassed with argon, and then stirred at room temperature under a hydrogen atmosphere for 30 minutes. The suspension was filtered though a pad of celite, washed with aq. HCl (1 N, 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–3:1] gave **154** (1 mg, 6%, >99% D) as a colourless solid. $R_f$ = 0.36 [petrol:EtOAc 2:1]. **m.p.:** 66–67 °C.

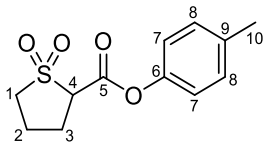
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.7 Hz, **H12**), 7.05 (2H, d, *J* = 8.5 Hz, **H11**), 4.31 (2H, ddt, *J* = 19.3, 10.7, 6.6 Hz, **H6**), 3.48-3.37 (2H, m, **H1**), 2.90 (1H, quint, *J* = 7.6 Hz, **H3a**), 2.77 (1H, quint, *J* = 7.3 Hz, **H3b**), 2.36-2.29 (5H, m, **H2** and **H14**), 1.76 (2H, quint, *J* = 7.0 Hz, **H7**), 1.04-0.98 (2H, m, **H8**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.5 (**C5**), 163.4 (**C9**), 148.0 (**C10**), 136.6 (**C13**), 130.1 (**C12**), 120.9 (**C11**), 75.1 (**C4**), 69.1 (**C6**), 50.5 (**C1**), 30.2 (**C3**), 21.8 (**C7**), 20.9 (**C14**), 17.3 (**C2**), 10.0 (t, *J* = 76.8 Hz, **C8**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{19}DO_6S$ $[M+H]^+$ 342.1116, found 342.1104.

**IR:** $\nu_{max}$ (neat): 3017 (C–H), 2969 (C–H), 1767 (C=O), 1733 (C=O) $cm^{-1}$.

### *p*-Tolyl 1,1-dioxothiolane-2-carboxylate 153



A suspension of **151** (16.9 mg, 0.05 mmol) and $Pd/CaCO_3$ (2 mg) in pyridine (1 mL) was degassed with argon, and then stirred at room temperature under a hydrogen atmosphere for 30 minutes. The suspension was filtered though a pad of celite, diluted with EtOAc (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **153** (13 mg, quant.) as a pale yellow solid. $R_f$ = 0.20 [petrol:EtOAc 2:1]. **m.p.:** 137–138 °C.

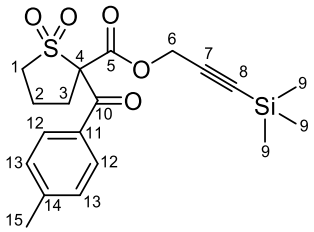
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.3 Hz, **H8**), 7.05 (2H, d, *J* = 8.5 Hz, **H7**), 4.16 (1H, t, *J* = 7.5 Hz, **H4**), 3.24-3.12 (2H, m **H1**), 2.70-2.60 (1H, m, **H3a**), 2.52-2.34 (5H, m, **H2a**, **H3b** and **H10**), 2.27-2.16 (1H, m, **H2b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.8 (**C5**), 148.3 (**C6**), 136.2 (**C9**), 130.1 (**C8**), 121.0 (**C7**), 64.7 (**C4**), 51.8 (**C1**), 26.0 (**C3**), 20.9 (**C10**), 20.5 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{14}O_4S$ $[M+H]^+$ 255.0686, found 255.0676.

**IR:** $\nu_{max}$ (neat): 3032 (C–H), 2952 (C–H), 2924 (C–H), 2853 (C–H), 1754 (C=O) $cm^{-1}$.

### 3-Trimethylsilylprop-2-ynyl 2-(4-methylbenzoyl)-1,1-dioxo-thiolane-2-carboxylate 149



**145** (533 mg, 1.95 mmol) was dissolved in THF (20 mL) and NaHMDS (1 M in THF, 2.14 mL, 2.14 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. *p*-Toluoyl chloride (283 µL, 2.14 mmol) was added dropwise, and the mixture was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 20 mL). The mixture was extracted with EtOAc (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **149** (577 mg, 75%) as a colourless oil. $R_f$ = 0.52 [petrol:EtOAc 2:1].

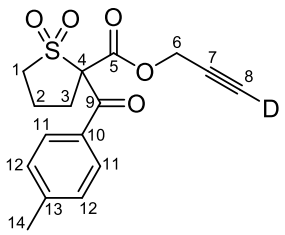
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.3 Hz, **H12**), 7.26 (2H, d, *J* = 8.1 Hz, **H13**), 4.74 (2H, q, *J* = 15.6 Hz, **H6**), 3.47 (1H, ddd, *J* = 12.9, 9.0, 6.4 Hz, **H1a**), 3.35 (1H, ddd, *J* = 13.4, 8.7, 6.1 Hz, **H1b**), 3.20 (1H, dt, *J* = 14.4, 7.1 Hz, **H3a**), 2.65 (1H, quint, *J* = 6.6 Hz, **H3b**), 2.40 (3H, s, **H15**), 2.33-2.22 (2H, m, **H2**), 0.12 (9H, s, **H9**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 186.5 (**C10**), 165.9 (**C5**), 145.1 (**C14**), 132.6 (**C11**), 129.5 and 129.4 (**C12** and **C13**), 97.0 (**C7**), 93.5 (**C8**), 77.4 (**C4**), 54.7 (**C6**), 51.9 (**C1**), 32.0 (**C3**), 21.8 (**C15**), 17.6 (**C2**), –0.42 (**C9**).

**HRMS (*m/z*):** (APCI) calcd for $C_{19}H_{24}O_5SiS$ $[M+H]^+$ 393.1186, found 393.1170.

**IR:** $\nu_{max}$ (neat): 2957 (C–H), 2917 (C–H), 2849 (C–H), 2186 (C≡C), 1740 (C=O), 1683 (C=O) $cm^{-1}$.

**(3-$^2$H-Prop-2-ynyl) 2-(4-methylbenzoyl)-1,1-dioxo-thiolane-2-carboxylate 155**




**149** (517 mg, 1.32 mmol) was dissolved in THF (15 mL). Deuterium oxide (5 mL) was added, followed by tetrabutylammonium fluoride (1 M in THF, 1.98 mL, 1.98 mmol), and the reaction mixture was stirred at room temperature for 6 hours. The solution was diluted with water (15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 6:1] gave **155** (343 mg, 81%, 98% D) as a colourless solid. $R_f$ = 0.24 [petrol:EtOAc 2:1]. **m.p.:** 143–144 °C.

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.2 Hz, **H12**), 7.26 (2H, d, *J* = 8.3 Hz, **H11**), 4.78 (1H, d, *J* = 15.2 Hz, **H6a**), 4.68 (1H, d, *J* = 15.4 Hz, **H6b**), 3.52-3.36 (2H, m, **H1**), 3.18 (1H, dt,

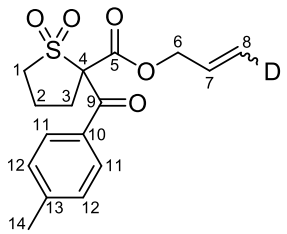
*J* = 14.7, 7.4 Hz, **H3a**), 2.69 (1H, quint, *J* = 6.8 Hz, **H3b**), 2.56 (0.02H, s, **H8**), 2.40 (3H, s, **H14**), 2.36-2.22 (2H, m, **H2**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 186.8 (**C9**), 165.9 (**C5**), 145.3 (**C13**), 132.7 (**C10**), 129.5 and 129.4 (**C11** and **C12**), 77.4 (**C4**), 53.9 (**C6**), 51.9 (**C1**), 32.0 (**C3**), 21.8 (**C14**), 17.7 (**C2**), **C7** and **C8** signals not observed.

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{15}DO_5S$ $[M+H]^+$ 322.0854, found 322.0838.

**IR:** $\nu_{max}$ (neat): 3013 (C–H), 2958 (C–H), 2920 (C–H), 2578 (C–D), 1981 (C≡C), 1744 (C=O), 1677 (C=O) $cm^{-1}$.

### (3-$^2$H-Allyl) 2-(4-methylbenzoyl)-1,1-dioxo-thiolane-2-carboxylate 156




A suspension of **155** (212 mg, 0.66 mmol), $Pd/CaCO_3$ (21.2 mg) and quinoline (156 µL, 1.32 mmol) in EtOAc (13 mL) was degassed with argon, and then stirred under a hydrogen atmosphere at room temperature for 15 minutes. The suspension was filtered though a pad of celite, washed with aq. HCl (1 N, 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–6:1] gave **156** (152 mg, 71%, 93% D) as a colourless solid. $R_f$ = 0.34 [petrol:EtOAc 2:1]. **m.p.:** 68–69 °C.

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.4 Hz, **H12**), 7.24 (2H, d, *J* = 8.0 Hz, **H11**), 5.65 (1H, dddd, *J* = 16.7, 10.7, 6.2, 6.0 Hz, **H7**), 5.19-5.11 (1.07H, m, **H8**), 4.61 (2H, dd, *J* = 7.8, 1.2 Hz, **H6**), 3.47-3.31 (2H, m, **H1**), 3.11 (1H, quint, *J* = 6.9 Hz, **H3a**), 2.68 (1H, quint, *J* = 7.3 Hz, **H3b**), 2.38 (3H, s, **H14**), 2.33-2.16 (2H, m, **H2**).

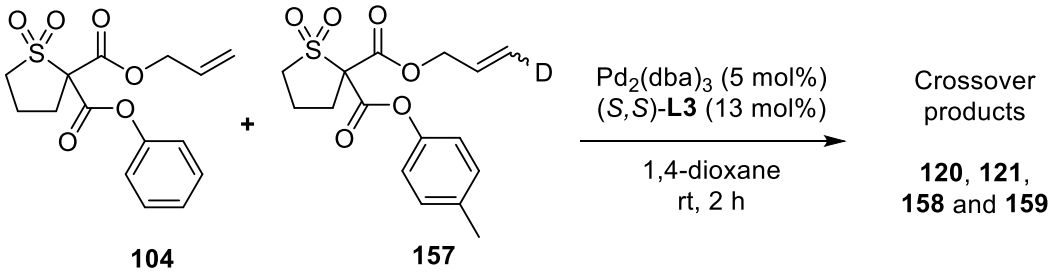
**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 187.7 (**C9**), 166.5 (**C5**), 145.1 (**C13**), 133.1 (**C10**), 130.2 (**C7**), 129.4 (**C11**), 129.2 (**C12**), 119.9 (t, *J* = 92.4 Hz, **C8**), 77.7 (**C4**), 67.3 (**C6**), 51.8 (**C1**), 31.9 (**C3**), 21.7 (**C14**), 17.6 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{17}DO_5S$ $[M+H]^+$ 324.1010, found 324.0997.

**IR:** $\nu_{max}$ (neat): 3050 (C–H), 3017 (C–H), 2999 (C–H), 2953 (C–H), 1733 (C=O), 1675 (C=O) $cm^{-1}$.

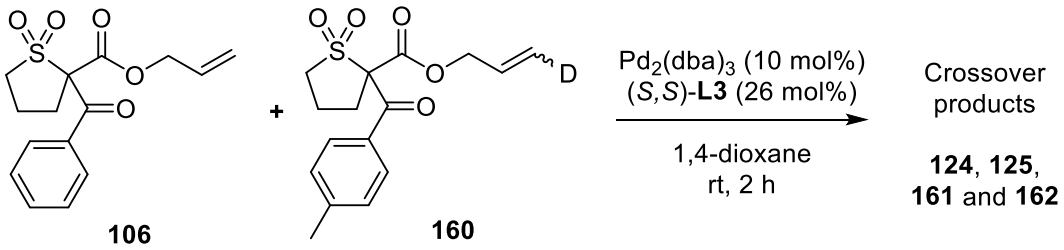
### 3.2.4 Enolate Crossover High Resolution Mass Spectrometry Data

Crossover Experiment for Ester Substrates



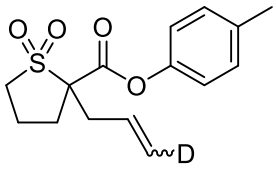

**104** **157**

Crossover Experiment for Ketone Substrates

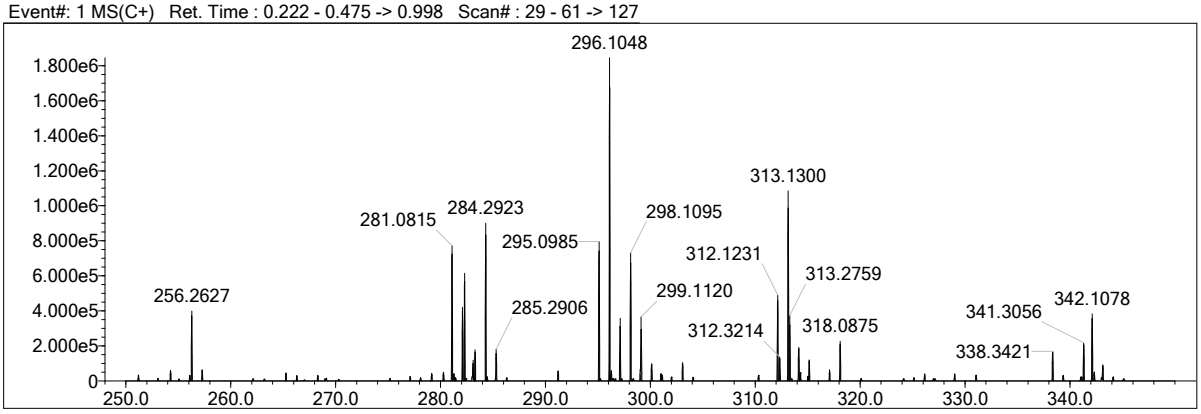



**106** **160**

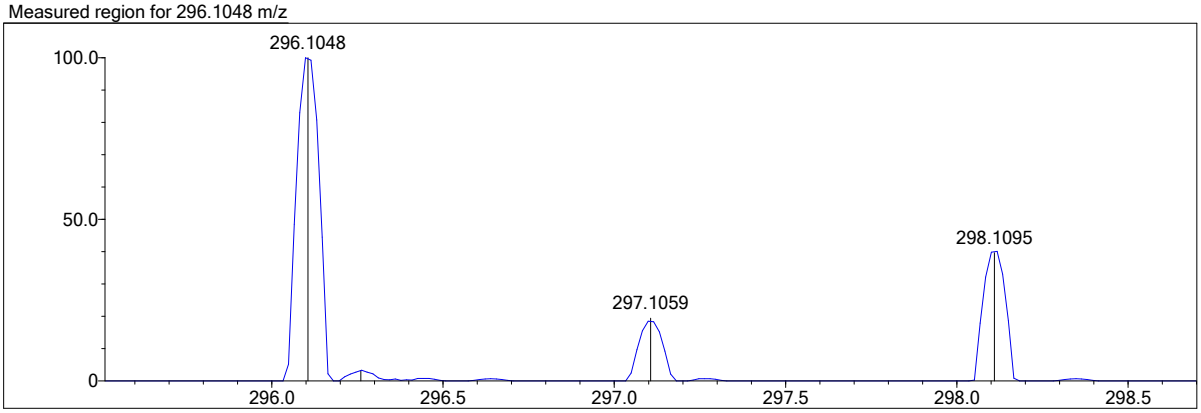
## *p*-Tolyl 2-(3-$^{2}$H-allyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 158



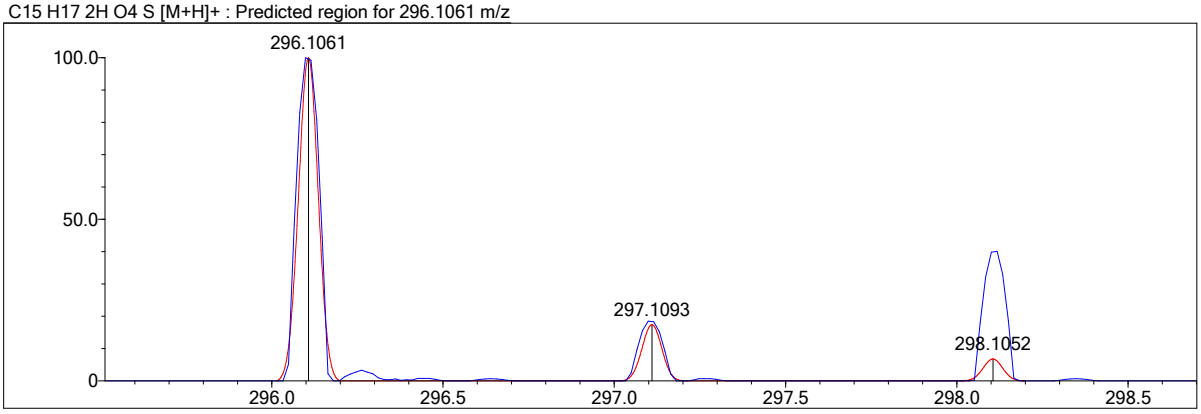

Event#: 1 MS(C+) Ret. Time : 0.222 - 0.475 -> 0.998 Scan# : 29 - 61 -> 127




Measured region for 296.1048 m/z

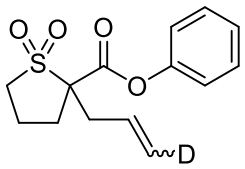



C15 H17 2H O4 S [M+H]+ : Predicted region for 296.1061 m/z

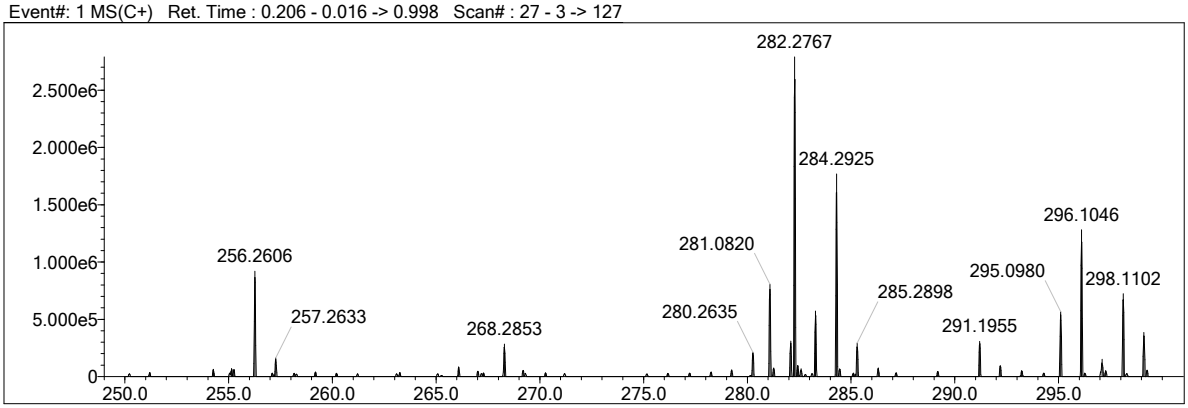



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 45.76 | C15 H17 2H O4 S | [M+H]+ | 296.1048 | 296.1061 | -1.3 | -4.39 | 50.00 | 7.0 |

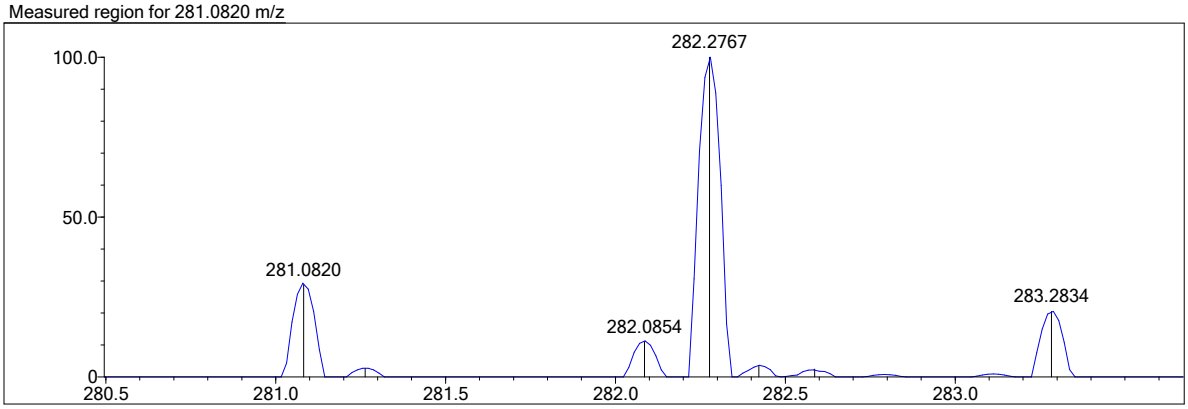
## Phenyl 2-(3-$^{2}$H-allyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 159



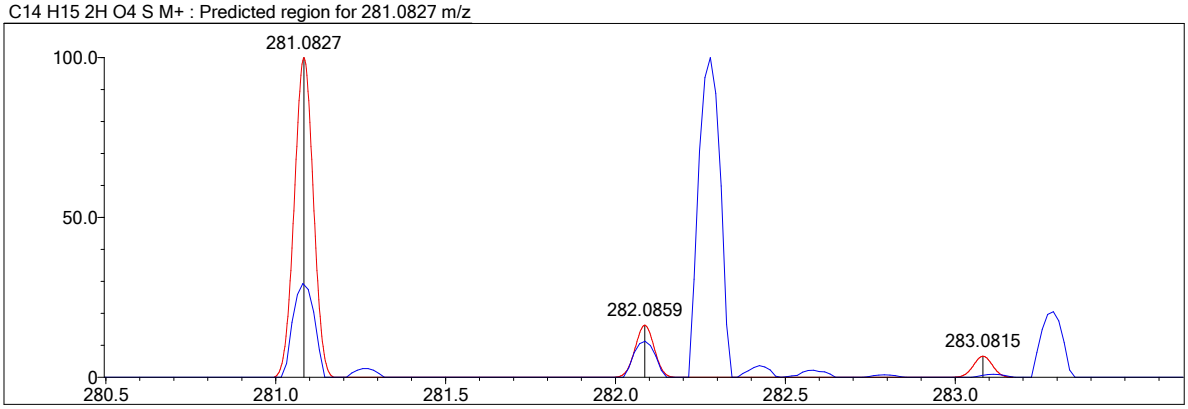

Event#: 1 MS(C+) Ret. Time : 0.206 - 0.016 -> 0.998 Scan# : 27 - 3 -> 127




Measured region for 281.0820 m/z

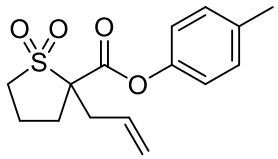



C14 H15 2H O4 S M+ : Predicted region for 281.0827 m/z

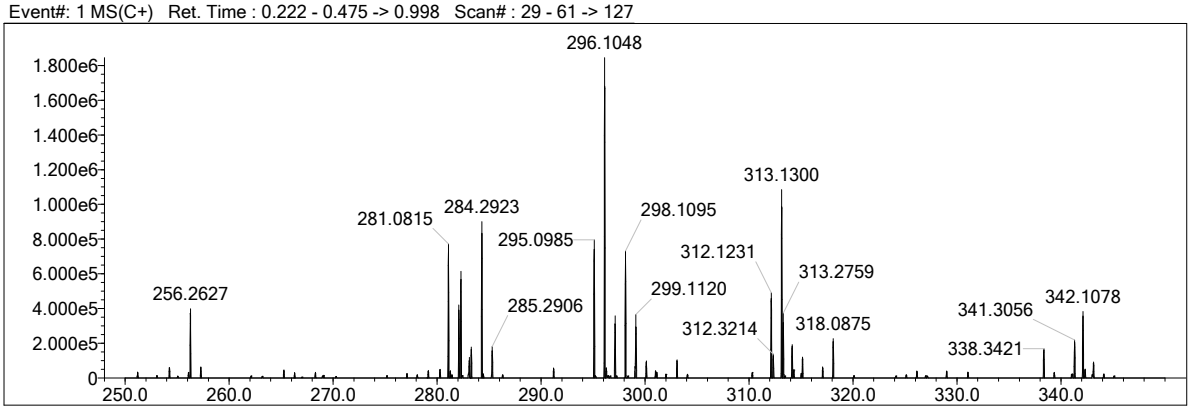



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 14.05 | C14 H15 2H O4 S | M+ | 281.0820 | 281.0827 | -0.7 | -2.49 | 14.59 | 7.0 |

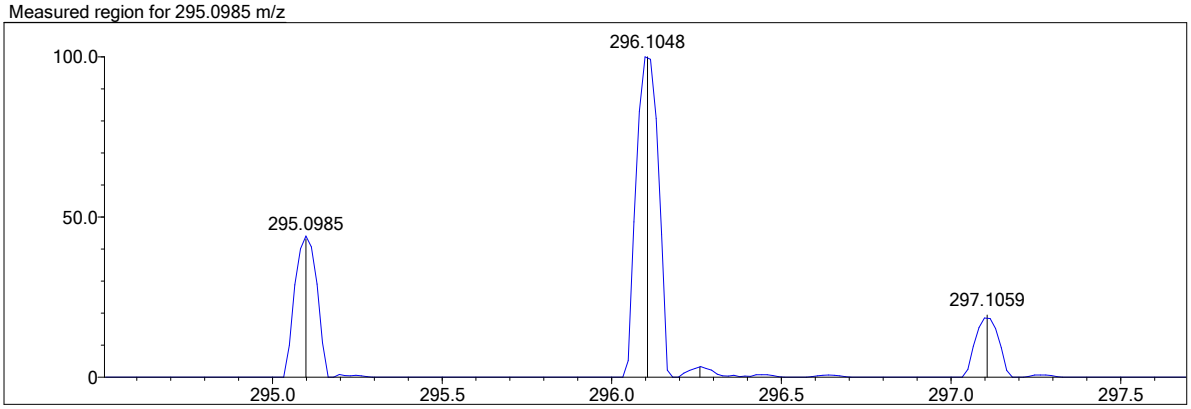
## *p*-Tolyl 2-(allyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 120



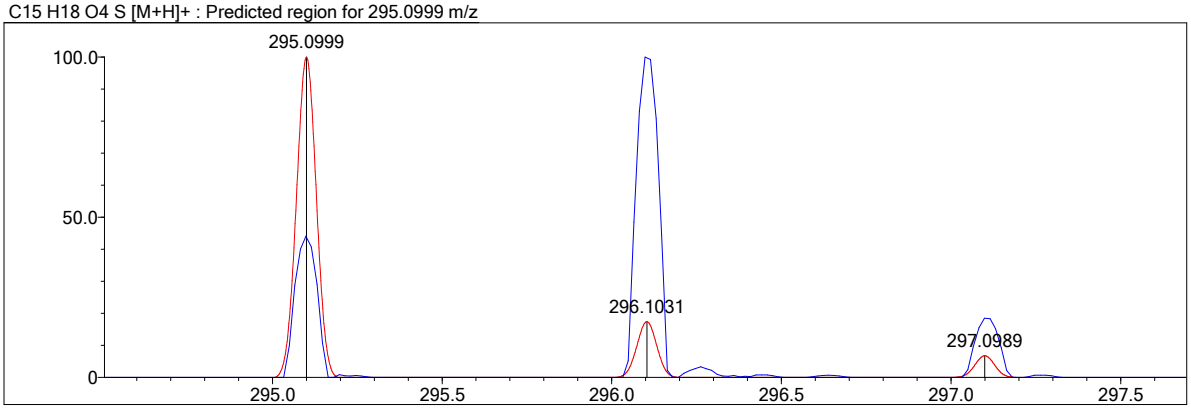
Event#: 1 MS(C+)  Ret. Time : 0.222 - 0.475 -> 0.998  Scan# : 29 - 61 -> 127




Measured region for 295.0985 m/z

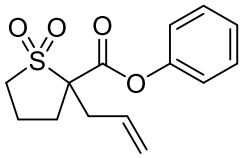



C15 H18 O4 S [M+H]+ : Predicted region for 295.0999 m/z

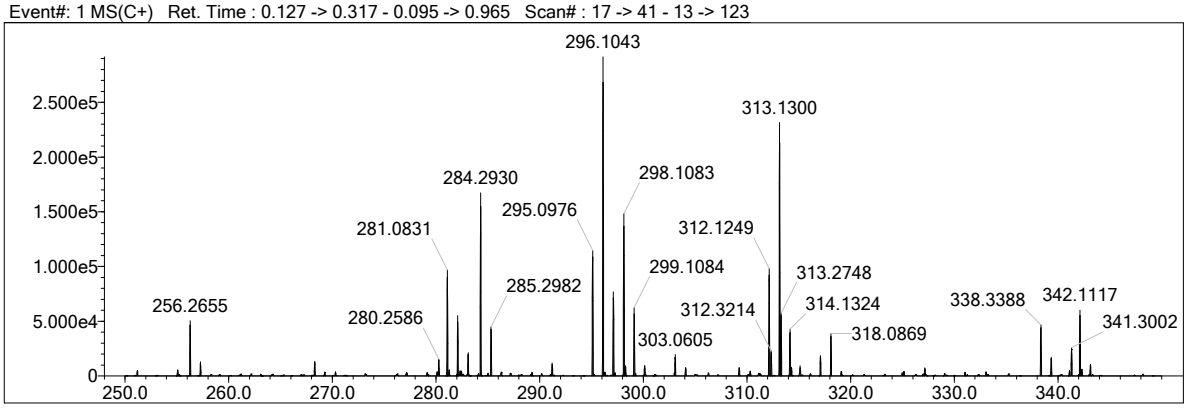



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 43.23 | C15 H18 O4 S | [M+H]+ | 295.0985 | 295.0999 | -1.4 | -4.74 | 47.69 | 7.0 |

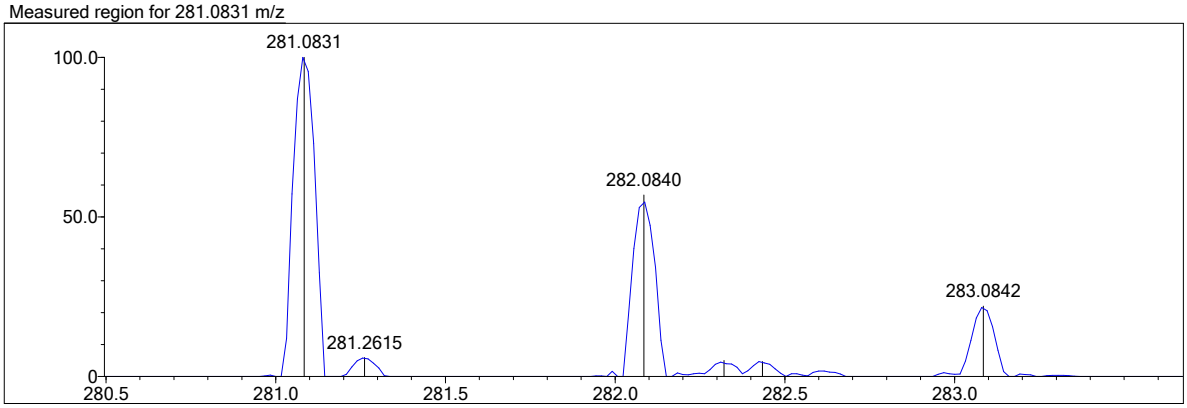
## Phenyl 2-(allyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 121



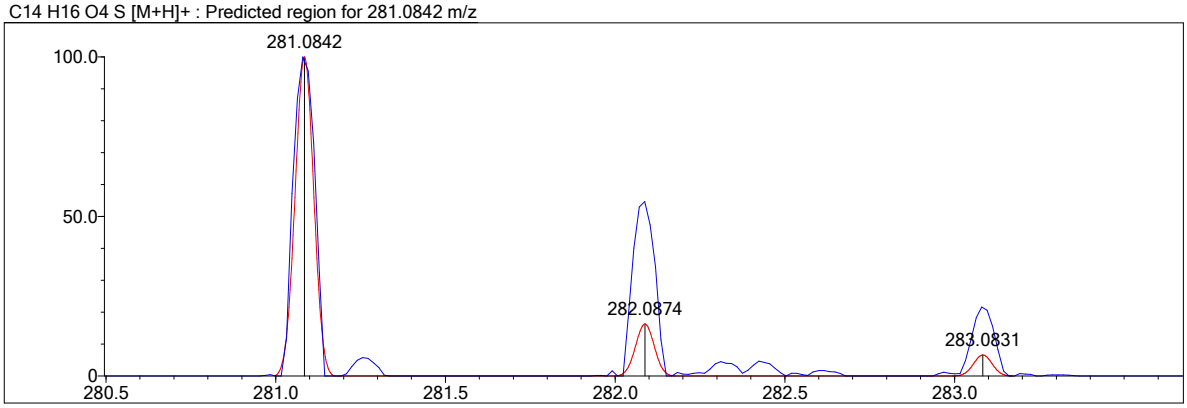
Event#: 1 MS(C+) Ret. Time : 0.127 -> 0.317 - 0.095 -> 0.965 Scan# : 17 -> 41 - 13 -> 123




Measured region for 281.0831 m/z

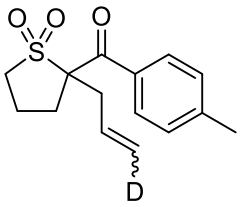



C14 H16 O4 S [M+H]+ : Predicted region for 281.0842 m/z

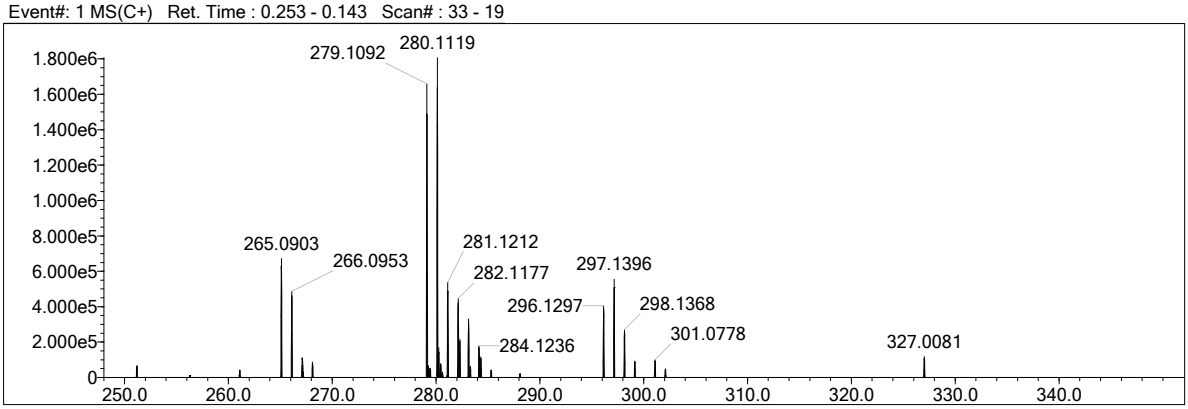



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 46.36 | C14 H16 O4 S | [M+H]+ | 281.0831 | 281.0842 | -1.1 | -3.91 | 50.00 | 7.0 |

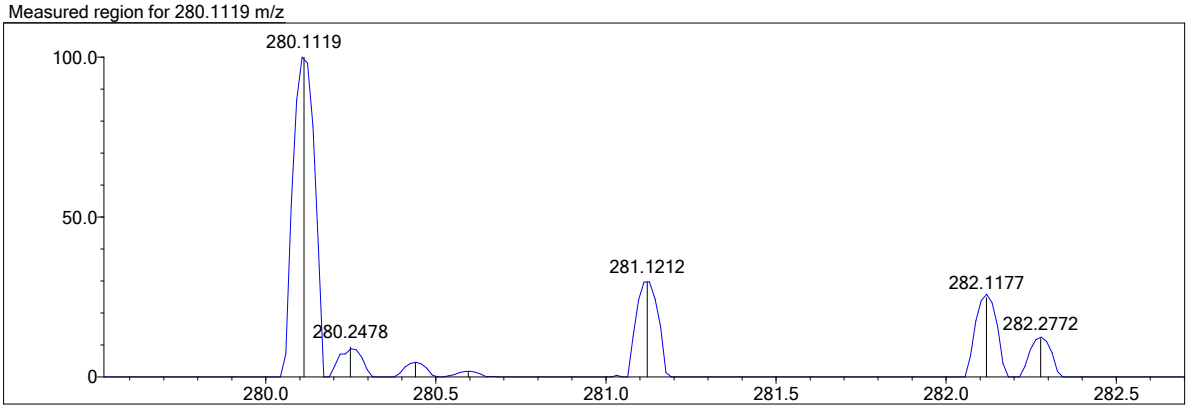
## (2-(3-$^{2}$H-Allyl)-1,1-dioxidotetrahydrothiophen-2-yl)(*p*-tolyl)methanone 161



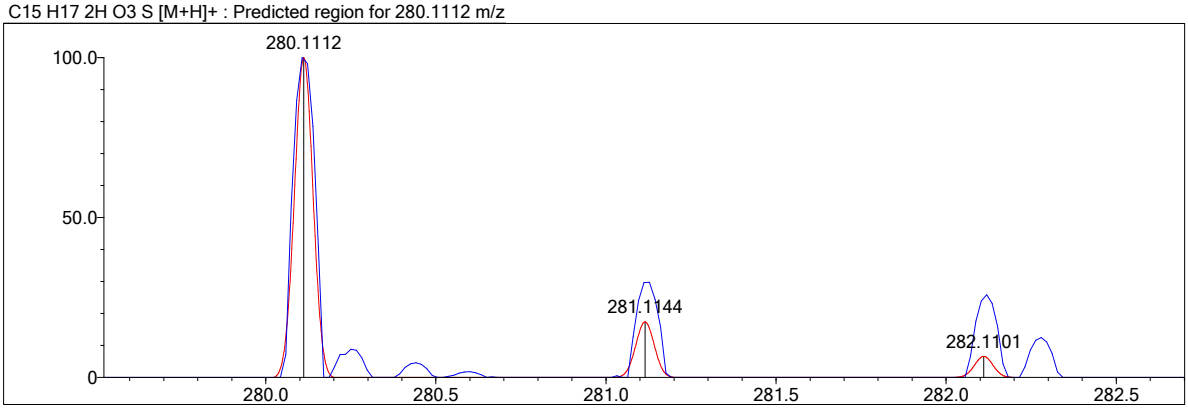

Event#: 1 MS(C+) Ret. Time : 0.253 - 0.143 Scan# : 33 - 19




Measured region for 280.1119 m/z

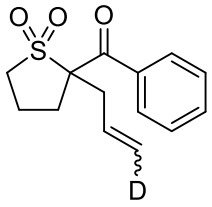



C15 H17 2H O3 S [M+H]+ : Predicted region for 280.1112 m/z

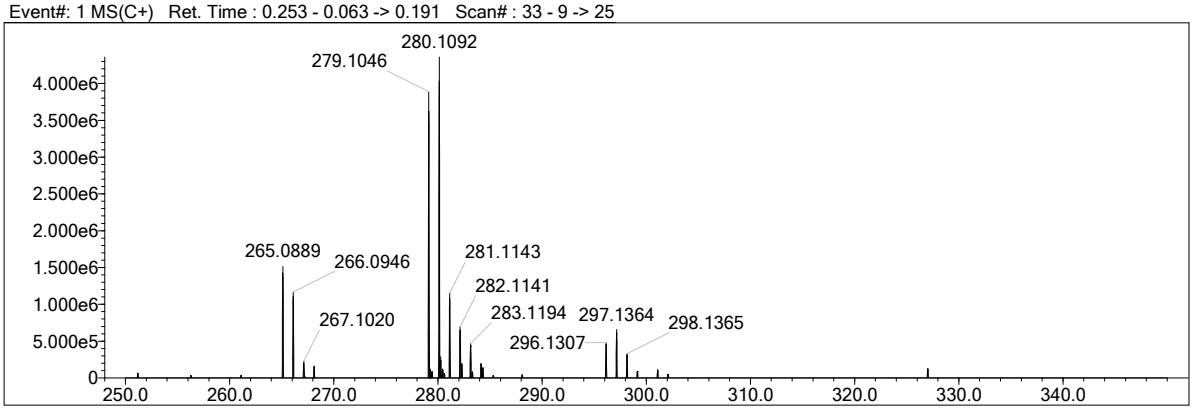



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 36.59 | C15 H17 2H O3 S | [M+H]+ | 280.1119 | 280.1112 | 0.7 | 2.50 | 38.01 | 7.0 |

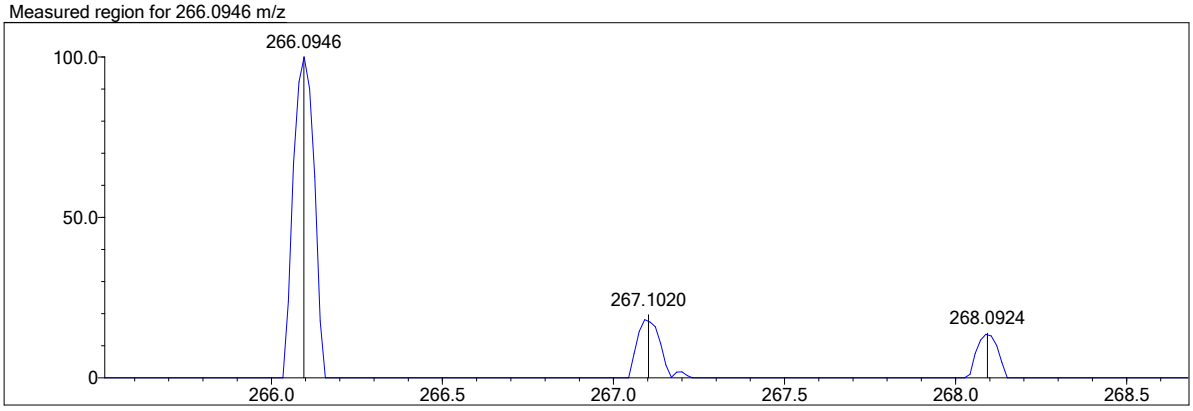
## (2-(3-$^{2}$H-Allyl)-1,1-dioxidotetrahydrothiophen-2-yl)(phenyl)methanone 162



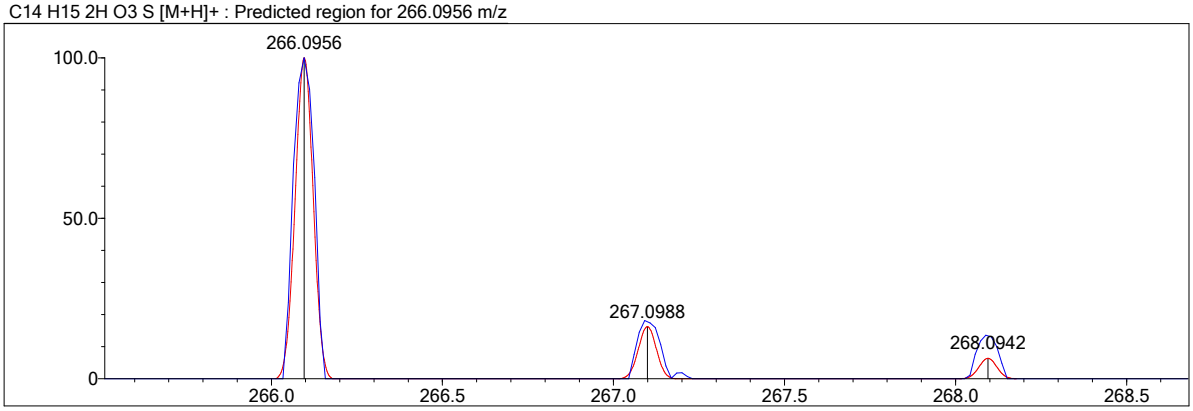

Event#: 1 MS(C+) Ret. Time : 0.253 - 0.063 -> 0.191 Scan# : 33 - 9 -> 25




Measured region for 266.0946 m/z

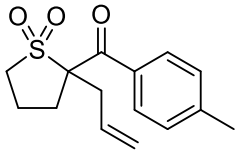



C14 H15 2H O3 S [M+H]+ : Predicted region for 266.0956 m/z

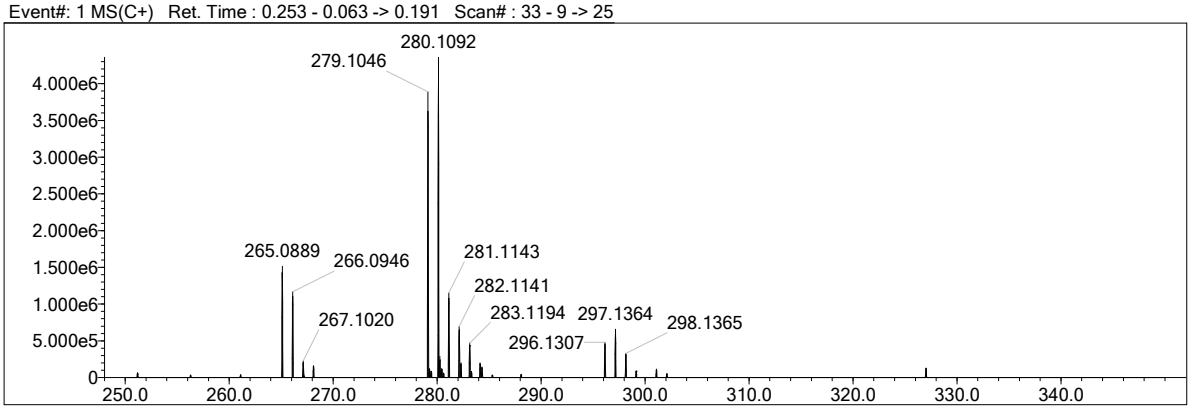



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 66.98 | C14 H15 2H O3 S | [M+H]+ | 266.0946 | 266.0956 | -1.0 | -3.76 | 71.95 | 7.0 |

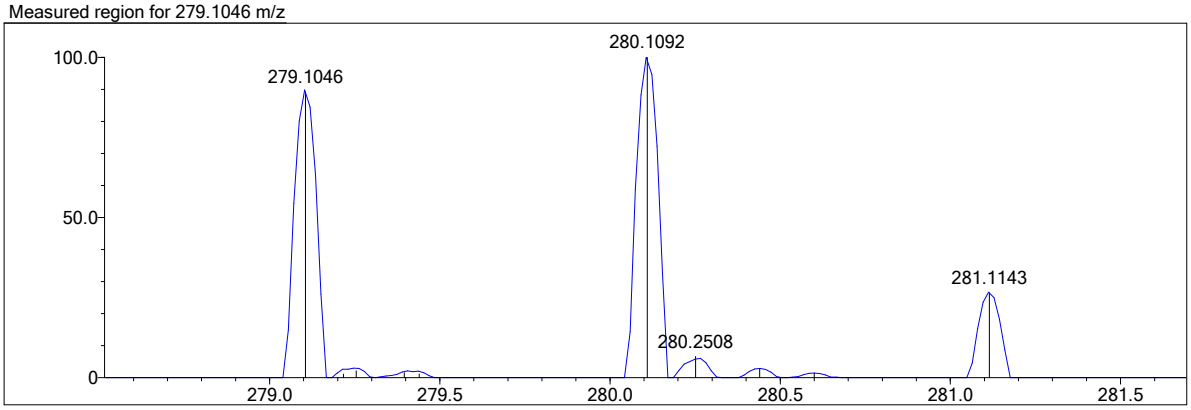
## (2-(Allyl)-1,1-dioxidotetrahydrothiophen-2-yl)(*p*-tolyl)methanone 124



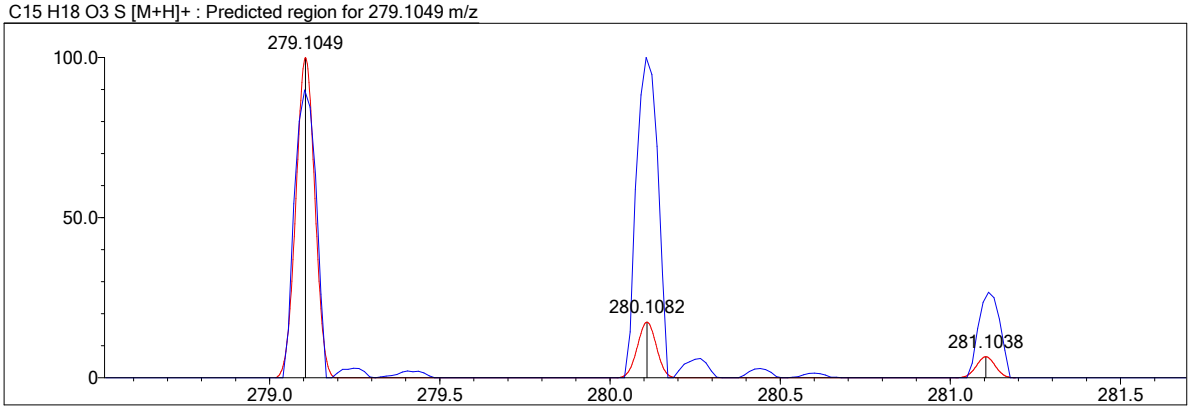
Event#: 1 MS(C+) Ret. Time : 0.253 - 0.063 -> 0.191 Scan# : 33 - 9 -> 25




Measured region for 279.1046 m/z

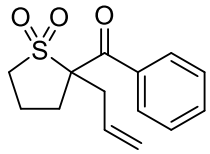



C15 H18 O3 S [M+H]+ : Predicted region for 279.1049 m/z

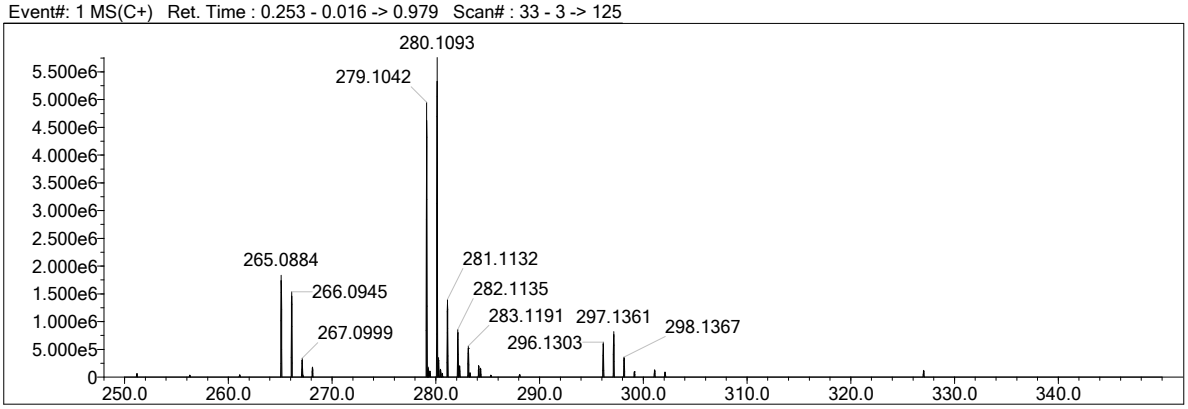



| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 36.81 | C15 H18 O3 S | [M+H]+ | 279.1046 | 279.1049 | -0.3 | -1.07 | 36.88 | 7.0 |

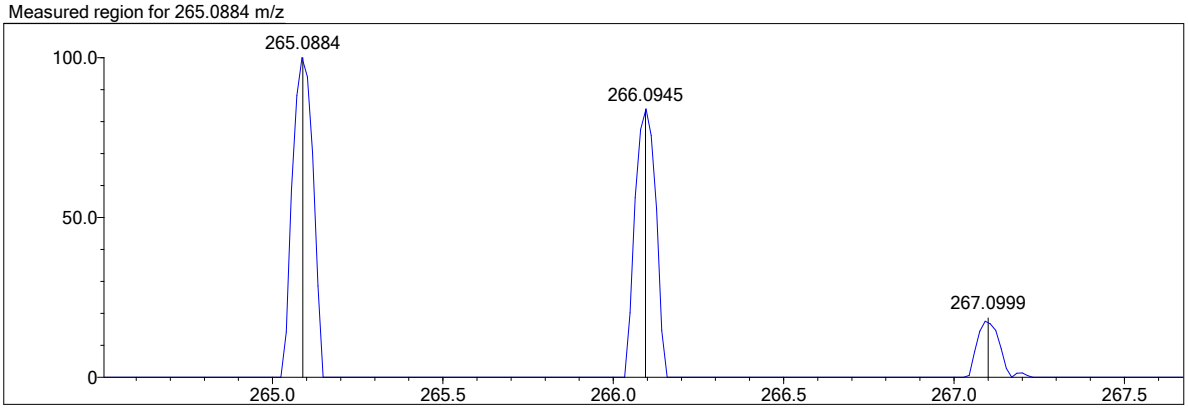
## (2-(Allyl)-1,1-dioxidotetrahydrothiophen-2-yl)(phenyl)methanone 125



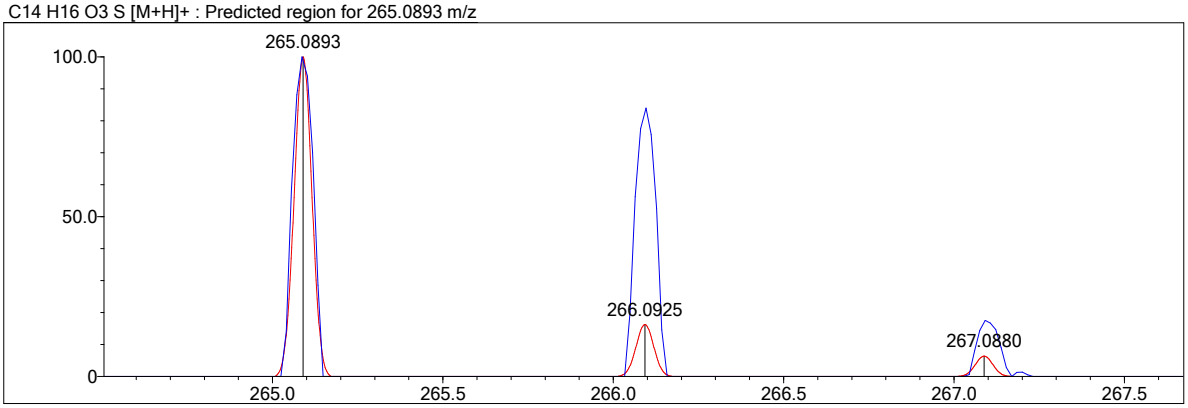
Event#: 1 MS(C+) Ret. Time : 0.253 - 0.016 -> 0.979 Scan# : 33 - 3 -> 125




Measured region for 265.0884 m/z



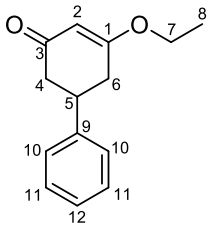

C14 H16 O3 S [M+H]+ : Predicted region for 265.0893 m/z




| Rank | Score | Formula (M) | Ion | Meas. m/z | Pred. m/z | Df. (mDa) | Df. (ppm) | Iso | DBE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 29.80 | C14 H16 O3 S | [M+H]+ | 265.0884 | 265.0893 | -0.9 | -3.40 | 31.71 | 7.0 |

### 3.2.5 Synthesis of Precursors for Relative Stereochemistry Determination

**3-Ethoxy-5-phenyl-cyclohex-2-en-1-one 169**[54]




5-Phenyl-1,3-cyclohexanedione (1.85 g, 9.83 mmol) and *p*-toluenesulfonic acid monohydrate (25.8 mg, 0.14 mmol) were dissolved in a mixture of ethanol (23 mL) and toluene (45 mL), and the mixture was heated to 120 °C with a Dean-Stark trap for 3 hours. The reaction was cooled to room temperature, then concentrated under reduced pressure. The residue was dissolved in $Et_2O$ (30 mL), and the solution was washed with NaOH (2 N, 3 x 25 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **169** (1.87 g, 88%) as a colourless solid. $R_f$ = 0.24 [petrol:EtOAc 4:1].

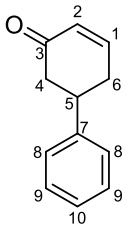
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.37-7.32 (2H, m, **H10**), 7.28-7.23 (3H, m, **H11** and **H12**), 5.44 (1H, d, *J* = 1.0 Hz, **H2**), 4.00-3.88 (2H, m, **H7**), 3.40-3.32 (1H, m, **H5**), 2.72-2.52 (4H, m, **H4** and **H6**), 1.38 (3H, t, *J* = 7.0 Hz, **H8**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 199.2 (**C3**), 177.2 (**C1**), 142.9 (**C9**), 128.8 (**C10**), 127.0 (**C12**), 126.7 (**C11**), 102.6 (**C2**), 64.6 (**C7**), 43.8 (**C4** or **C6**), 39.5 (**C5**), 36.6 (**C4** or **C6**), 14.1 (**C8**).

**HRMS (*m/z*):** (APCI) calcd for $C_{14}H_{16}O_2$ $[M+H]^+$ 217.1223, found 217.1219.

Analytical data matches literature values.[54]

**5-phenylcyclohex-2-en-1-one 170**[54]




A solution of **169** (500 mg, 2.30 mmol) in $Et_2O$ (15 mL) was cooled to 0 °C. Lithium aluminium hydride (68.5 mg, 1.80 mmol) was added in small portions at 0 °C. The mixture was stirred at 0 °C for 30 minutes, then allowed to warm to room temperature and the mixture was stirred for 30 minutes. The reaction was quenched with aq. HCl (1 N, 10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under

reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **170** (181 mg, 46%) as a colourless oil. $R_f$ = 0.40 [petrol:EtOAc 4:1].

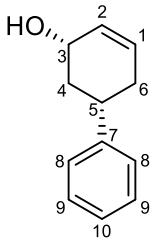
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m, **H8**, **H9** and **H10**), 7.05 (1H, ddd, *J* = 10.0, 5.7, 2.5 Hz, **H1**), 6.17-6.14 (1H, m, **H2**), 3.36 (1H, dddd, *J* = 12.6, 10.2, 5.3, 4.8 Hz, **H5**), 2.75-2.61 (3H, m, **H4a** and **H6**), 2.54 (1H, ddt, *J* = 18.6, 10.7, 2.6 Hz, **H4b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 199.2 (**C3**), 149.4 (**C1**), 143.3 (**C7**), 129.8 (**C2**), 128.8 (**C9**), 127.0 (**C10**), 126.7 (**C8**), 44.9 (**C4**), 41.0 (**C5**), 33.7 (**C6**).

**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{12}O$ $[M+H]^+$ 173.0961, found 173.0965.

Analytical data matches literature values.[54]

### *cis*-5-Phenyl-2-cyclohexen-1-ol 171[54]




A solution of **170** (565 mg, 3.28 mmol) and cerium(III) chloride heptahydrate (1.14 g, 3.05 mmol) in MeOH (30 mL) was cooled to 0 °C. Sodium borohydride (115 mg, 3.05 mmol) was added in small portions at 0 °C. The mixture was stirred at 0 °C for 5 minutes. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [Petrol:EtOAc 3:1] gave **171** (490 mg, 86%) as a colourless solid. $R_f$ = 0.40 [petrol:EtOAc 3:1].

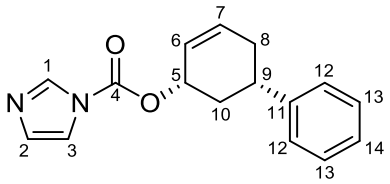
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m, **H9**), 7.25-7.20 (3H, m, **H8** and **H10**), 5.85 (1H, ddt, *J* = 10.0, 4.4, 1.9 Hz, **H1**), 5.78-5.74 (1H, m, **H2**), 4.48 (1H, dddd, *J* = 11.5, 7.8, 4.0, 2.1 Hz, **H3**), 2.92 (1H, dddd, *J* = 13.3, 11.1, 5.2, 2.5 Hz, **H5**), 2.34-2.25 (2H, m, **H4a** and **H6a**), 2.19-2.10 (1H, m, **H6b**), 1.74 (1H, ddd, *J* = 12.7, 12.1, 9.9 Hz, **H4b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 145.5 (**C7**), 131.0 (**C2**), 128.7 (**C1**), 128.6 (**C9**), 126.8 (**C8**), 126.4 (**C10**), 68.6 (**C3**), 39.6 (**C4**), 39.3 (**C5**), 33.8 (**C6**).

**IR:** $\nu_{max}$ (neat): 3275 (O–H, broad), 3080 (C–H), 3062 (C–H), 3023 (C–H), 2931 (C–H), 2917 (C–H), 2892 (C–H), 2838 (C–H).

Analytical data matches literature values.[54]

**(*cis*-5-Phenylcyclohex-2-en-1-yl) imidazole-1-carboxylate 172**



**171** (45 mg, 0.26 mmol) was dissolved in $CH_2Cl_2$ (5 mL) at room temperature. 1,1'-Carbonyldiimidazole (105 mg, 0.65 mmol) was added in portions at room temperature. The suspension was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [Petrol:EtOAc 3:1] gave **172** (63 mg, 90%) as a colourless solid. $R_f$ = 0.24 [petrol:EtOAc 3:1]. **m.p.:** 105–107 °C.

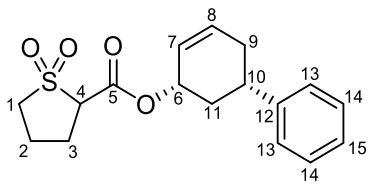
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 8.09 (1H, br s, **H1**), 7.39 (1H, br s, **H2**), 7.35-7.31 (2H, m, **H12**), 7.26-7.22 (3H, m, **H13** and **H14**), 7.06 (1H, br s, **H3**), 6.07 (1H, ddt, *J* = 9.7, 4.6, 2.2 Hz, **H7**), 5.84-5.80 (1H, m, **H6**), 5.75 (1H, dddd, *J* = 11.3, 7.5, 4.2, 2.2 Hz, **H5**), 3.05 (1H, dddd, *J* = 12.9, 10.4, 5.1, 2.6 Hz, **H9**), 2.51-2.36 (2H, m, **H8a** and **H10a**), 2.32-2.23 (1H, m, **H8b**), 2.05 (1H, td, *J* = 12.6, 9.8 Hz, **H10b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 148.4 (**C4**), 144.4 (**C11**), 137.2 (**C1**), 132.2 (**C7**), 130.6 (**C3**), 128.7 (**C12**), 126.8 (**C13**), 126.7 (**C14**), 125.3 (**C6**), 117.1 (**C2**), 75.5 (**C5**), 38.7 (**C9**), 35.0 (**C10**), 33.2 (**C8**).

**HRMS (*m/z*):** Molecular ion not observed.

**IR:** $\nu_{max}$ (neat): 3157 (C–H), 3152 (C–H), 3034 (C–H), 2950 (C–H), 2931 (C–H), 2891 (C–H), 1741 (C=O) $cm^{-1}$.

**(*cis*-5-Phenylcyclohex-2-en-1-yl) 1,1-dioxothiolane-2-carboxylate 173**



Sulfolane (123 mg, 1.02 mmol) was dissolved in THF (10 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 2.1 mL, 2.10 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. A solution of **172** (300 mg, 1.12 mmol) in THF (5 mL) was

added dropwise at –78 °C. The mixture was allowed to reach room temperature and was stirred overnight. The reaction was quenched with aq. HCl (1 N, 10 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **173** (125 mg, 38%) as a 1:1 mixture of diastereoisomers as a colourless oil. $R_f$ = 0.21 [petrol:EtOAc 4:1].

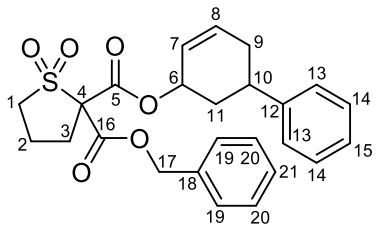
**$^1$H NMR:** (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 7.35-7.30 (2H, m, **H13**), 7.26-7.22 (3H, m, **H14** and **H15**), 5.99 (1H, dddd, *J* = 7.7, 6.2, 5.2, 3.1 Hz, **H7**), 5.80 (d, *J* = 10.2 Hz) and 5.73-5.66 (m) (2H, **H6** and **H8**), 3.92 (1H, q, *J* = 7.4 Hz, **H4**), 3.18-3.06 (2H, m, **H1**), 3.02-2.94 (1H, m, **H10**), 2.55 (1H, sextet, *J* = 8.0 Hz, **H3a**), 2.44-2.32 (4H, m, **H2a**, **H3b**, **H9a** and **H11a**), 2.26-2.10 (2H, m, **H2b** and **H9b**), 2.02-1.92 (1H, m, **H11b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$, mixture of diastereoisomers) δ 165.4 and 165.3 (**C5**), 144.9 and 144.8 (**C12**), 131.3 and 130.8 (**C7**), 128.7 and 128.6 (**C13**), 126.8 and 126.8 (**C14**), 126.6 and 126.5 (**C15**), 126.4 and 126.2 (**C8**), 73.7 and 73.5 (**C6**), 64.9 (**C4**), 51.7 (**C1**), 39.0 and 38.9 (**C10**), 34.9 and 34.7 (**C11**), 33.3 and 33.3 (**C9**), 26.0 and 25.9 (**C3**), 20.4 (**C2**).

**HRMS (*m/z*):** Molecular ion not observed.

**IR:** $\nu_{max}$ (neat): 3157 (C–H), 3142 (C–H), 3034 (C–H), 2950 (C–H), 2931 (C–H), 2891 (C–H), 1741 (C=O) $cm^{-1}$.

**2-Benzyl 2-(*cis*-5-phenylcyclohex-2-en-1-yl) 1,1-dioxothiolane-2,2-dicarboxylate 174**




**173** (58 mg, 0.18 mmol) was dissolved in THF (2 mL) and NaHMDS (1 M in THF, 0.2 mL, 0.20 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzyl chloroformate (27 µL, 0.20 mmol) was added dropwise, and the solution was stirred at room temperature overnight. The reaction was quenched with aq. HCl (1 N, 5 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography

[hexane:EtOAc 9:1–4:1] gave **174** (20 mg, 25%) as a 1:1 mixture of diastereoisomers as a colourless oil. $R_f$ = 0.25 [petrol:EtOAc 4:1].

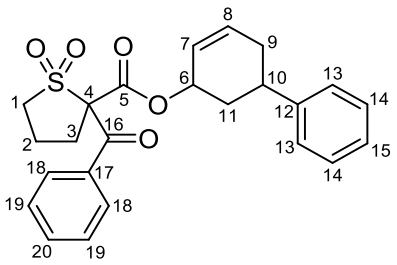
**$^1$H NMR:** (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 7.41-7.15 (10H, m, **H13**, **H14**, **H15**, **H19**, **H20** and **H21**), 5.93 (1H, tdd, *J* = 10.5, 4.4, 1.9 Hz, **H7**), 5.69-5.65 (m) and 5.58-5.54 (m) (2H, **H6** and **H8**), 5.35-5.29 (2H, m, **H17**), 3.37-3.32 (2H, m, **H1**), 2.94 (1H, tdd, *J* = 12.9, 5.1, 3.0 Hz, **H10**), 2.77-2.73 (2H, m, **H3**), 2.30-2.13 (4H, m, **H2** and **H9** or **H11**), 1.84-1.64 (2H, m, **H9** or **H11**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$, mixture of diastereoisomers) δ 164.4 and 164.3 (**C16**), 164.0 and 163.9 (**C5**), 144.7 and 144.6 (**C-Ar**), 134.5 and 134.4 (**C-Ar**), 131.2 and 131.1 (**C7**), 128.7 (**C-Ar**), 128.6 (**C-Ar**), 128.5 and 128.4 (**C-Ar**), 126.8 and 126.8 (**C-Ar**), 126.6 (**C-Ar**), 125.8 (**C-Ar**), 125.6 (**C8**), 75.0 (**C4**), 74.4 and 74.3 (**C6**), 68.7 (**C17**), 50.3 (**C1**), 38.9 and 38.8 (**C10**), 34.4, 34.3 and 33.1 (**C9** and **C11**), 30.0 (**C3**), 17.1 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{25}H_{26}O_6S$ $[M+Na]^+$ 447.1342, found 447.1350.

**IR:** $\nu_{max}$ (neat): 3062 (C–H), 3032 (C–H), 2954 (C–H), 2837 (C–H), 1729 (C=O) $cm^{-1}$.

**(*cis*-5-Phenylcyclohex-2-en-1-yl) 2-benzoyl-1,1-dioxo-thiolane-2-carboxylate 175**



**173** (58 mg, 0.18 mmol) was dissolved in THF (2 mL) and NaHMDS (1 M in THF, 0.2 mL, 0.20 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzoyl chloride (23 µL, 0.20 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 5 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **175** (22 mg, 29%) as a 1:1 mixture of diastereoisomers as a colourless oil. $R_f$ = 0.23 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 7.99-7.96 (2H, m, **H18**), 7.66-7.55 (1H, m, **H20**), 7.48 (2H, td, *J* = 8.0, 1.8 Hz, **H19**), 7.33-7.20 (3H, m, **H14** and **H15**), 7.14-7.11 (2H, m, **H13**), 5.85 (1H, dddd, *J* = 9.8, 5.2, 4.6, 2.2 Hz, **H7**), 5.63 (1H, ddddd, *J* = 8.1, 5.9, 4.0,

3.9, 2.2 Hz, **H6**), 5.36 (1H, tt, *J* = 10.9, 2.3 Hz, **H8**), 3.49-3.34 (2H, m, **H1**), 3.12 (1H, ddt, *J* = 14.5, 8.4, 7.2 Hz, **H3a**), 2.94-2.82 (1H, m, **H10**), 2.75 (1H, quint, *J* = 7.0 Hz, **H3b**), 2.37-2.20 (3H, m, **H2** and **H9a**), 2.15-2.02 (2H, m, **H9b** and **H11a**), 1.57 (1H, dddd, *J* = 13.2, 12.2, 10.0, 3.3 Hz, **H11b**).

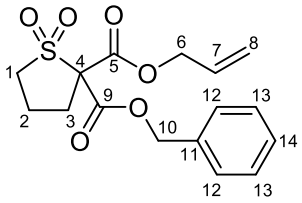
**$^{13}$C NMR:** (100 MHz, $CDCl_3$, mixture of diastereoisomers) δ 188.7 and 188.6 (**C16**), 166.0 and 166.0 (**C5**), 144.6 and 144.5 (**C12**), 135.6 (**C17**), 133.7 (**C20**), 131.6 and 131.4 (**C7**), 130.2 (**C18**), 129.0 and 128.9 (**C19**), 128.6 and 128.5 (**C14**), 126.7 (**C13**), 126.5 (**C15**), 125.2 and 125.1 (**C8**), 77.9 and 77.9 (**C4**), 74.1 and 74.0 (**C6**), 51.8 (**C1**), 38.8 (**C10**), 34.1 and 34.0 (**C11**), 33.2 and 33.2 (**C9**), 31.9 and 31.8 (**C3**), 17.7 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{24}H_{24}O_5S$ $[M+Na]^+$ 447.1237, found 447.1230.

**IR:** $\nu_{max}$ (neat): 3062 (C–H), 3029 (C–H), 2954 (C–H), 1728 (C=O), 1687 (C=O) $cm^{-1}$.

### 3.2.6 Additive Screen for Optimisation of the Pd-DAAA Reaction

**2-Allyl 2-benzyl dihydrothiophene-2,2(3*H*)-dicarboxylate 1,1-dioxide 96**




**117** (1.00 g, 4.90 mmol) was dissolved in THF (50 mL). NaHMDS (1 M in THF, 5.39 mL, 5.39 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzyl chloroformate (0.77 mL, 5.39 mmol) was added dropwise, and the solution was stirred overnight. The reaction was quenched with aq. HCl (1 N, 40 mL). The mixture was extracted with EtOAc (3 x 40 mL), washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 19:1–4:1] gave **96** (1.16 g, 70%) as a colourless oil. $R_f$ = 0.28 [petrol:EtOAc 4:1].

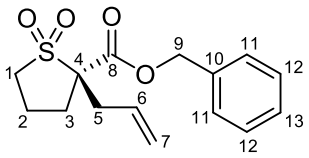
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.39-7.33 (5H, m, **H12**, **H13** and **H14**), 5.79 (1H, dddd, *J* = 16.4, 10.4, 6.6, 5.8 Hz, **H7**), 5.35-5.29 (1H, m, **H8a**), 5.21 (1H, dq, *J* = 10.6, 1.3 Hz, **H8b**), 4.70 (2H, dt, *J* = 5.9, 1.4 Hz, **H6**), 3.33 (2H, t, *J* = 6.4 Hz, **H1**), 2.75-2.72 (2H, m, **H3**), 2.28-2.21 (2H, m, **H2**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.2 (**C9**), 163.9 (**C5**), 134.4 (**C11**), 130.5 (**C7**), 128.6 and 128.3 (**C12** and **C13**), 119.5 (**C8**), 75.1 (**C4**), 68.9 (**C10**), 67.7 (**C6**), 50.3 (**C1**), 30.1 (**C3**), 17.2 (**C2**).

**HRMS (*m/z*):** (ESI) calcd for $C_{16}H_{18}O_6S$ $[M+Na]^+$ 361.0716, found 361.0701.

**IR:** $\nu_{max}$ (neat): 3034 (C–H), 3017 (C–H), 2961 (C–H), 1754 (C=O), 1724 (C=O) $cm^{-1}$.

**(*R*)-Benzyl 2-allyltetrahydrothiophene-2-carboxylate 1,1-dioxide 97**




**96** (50.7 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.00375 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (7.9 mg, 0.00975 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **97** (39.7 mg, 90%) as a yellow oil. $R_f$ = 0.20 [petrol:EtOAc 4:1].

**$^{1}$H NMR:** (400 MHz, $CDCl_3$) δ 7.39-7.33 (5H, m, **H11**, **H12** and **H13**), 5.54 (1H, dddd, *J* = 17.2, 10.0, 7.9, 6.2 Hz, **H6**), 5.29 (1H, d, *J* = 12.9 Hz, **H9a**), 5.19 (1H, d, *J* = 12.0 Hz, **H9b**), 5.14-5.09 (2H, m, **H7**), 3.20 (1H, quint, *J* = 5.8 Hz, **H1a**), 3.14-3.05 (2H, m, **H1b** and **H5a**), 2.80-2.72 (1H, m, **H3a**), 2.14 (1H, dd, *J* = 14.4, 8.2 Hz, **H5b**), 2.30-2.18 (1H, m, **H2a**), 2.13-2.01 (2H, m, **H2b** and **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 167.4 (**C8**), 134.9 (**C10**), 131.0 (**C6**), 128.6 (**C11** or **C12**), 128.5 (**C13**), 128.4 (**C11** or **C12**), 120.6 (**C7**), 70.4 (**C4**), 68.4 (**C9**), 51.4 (**C1**), 37.2 (**C5**), 30.9 (**C3**), 18.4 (**C2**).

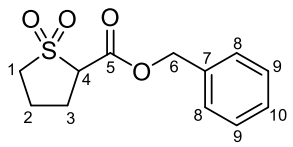
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_4S$ $[M+H]^+$ 295.0999, found 295.0986.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 3034 (C–H), 2954 (C–H), 1733 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALPAK AD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 20.4 min, $t_B$ (minor) = 22.4 min. 86% ee.

$\boldsymbol{[\alpha]_D^{20}}$: –55.1 (*c* 0.118, $CHCl_3$).

**Benzyl tetrahydrothiophene-2-carboxylate 1,1-dioxide 98**



**96** (50.7 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.00375 mmol), (*S,S*)-ANDEN Phenyl Trost ligand (7.9 mg, 0.00975 mmol) and acetic acid (0.86 µL, 0.015 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **98** (33.0 mg, 87%) as a yellow oil. $R_f$ = 0.17 [petrol:EtOAc 4:1].

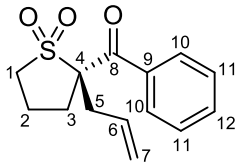
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.42-7.33 (5H, m, **H8**, **H9** and **H10**), 5.26 (2H, q, *J* = 12.5 Hz, **H6**), 3.95 (1H, t, *J* = 8.0 Hz, **H4**), 3.16-3.07 (2H, m, **H1**), 2.63-2.50 (1H, m, **H3a**), 2.45-2.31 (2H, m, **H2a** and **H3b**), 2.23-2.09 (1H, m, **H2b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 165.5 (**C5**), 134.8 (**C7**), 128.6 (**C8** or **C9**), 128.5 (**C10**), 128.4 (**C8** or **C9**), 68.4 (**C6**), 64.7 (**C4**), 51.6 (**C1**), 26.0 (**C3**), 20.4 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{14}O_4S$ $[M+Na]^+$ 277.0505, found 277.0499.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 3034 (C–H), 2954 (C–H), 1735 (C=O) $cm^{-1}$.

**(*R*)-(2-Allyl-1,1-dioxidotetrahydrothiophen-2-yl)(phenyl)methanone 103**



**106** (48.7 mg, 0.15 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (15.9 mg, 0.0195 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **103** (30.8 mg, 86%) as a colourless oil. $R_f$ = 0.27 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 8.02-7.98 (2H, m, **H10**), 7.55 (1H, tt, *J* = 6.1, 1.4 Hz, **H12**), 7.49-7.43 (2H, m, **H11**), 5.32 (1H, dddd, *J* = 16.9, 10.1, 7.8, 6.6 Hz, **H6**), 5.02-4.98 (1H, m, **H7a**), 4.87 (1H, dq, *J* = 16.7, 1.4 Hz, **H7b**), 3.34-3.05 (4H, m, **H1**, **H3a** and **H5a**), 2.63 (1H, dd, *J* = 14.7, 8.1 Hz, **H5b**), 2.33-2.02 (3H, m, **H2** and **H3b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 194.0 (**C8**), 136.2 (**C9**), 132.9 (**C12**), 130.3 (**C6**), 129.5 (**C10**), 128.6 (**C11**), 120.9 (**C7**), 73.9 (**C4**), 53.8 (**C1**), 39.3 (**C5**), 32.6 (**C3**), 18.8 (**C2**).

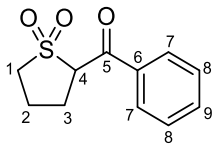
**HRMS (*m/z*):** (APCI) calcd for $C_{14}H_{16}O_3S$ $[M+H]^+$ 265.0893, found 265.0885.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 2950 (C–H), 1675 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 90:10 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 13.4 min, $t_B$ (major) = 18.0 min. 72% ee.

**$[\alpha]_D^{20}$**: –44.9 (*c* 0.345, $CHCl_3$).

### (1,1-Dioxidotetrahydrothiophen-2-yl)(phenyl)methanone 178




**106** (48.7 mg, 0.15 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), (*S,S*)-ANDEN Phenyl Trost ligand (15.9 mg, 0.0195 mmol) and acetic acid (0.86 µL, 0.015 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **178** (30.0 mg, 89%) as a yellow oil. $R_f$ = 0.12 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 8.09-8.05 (2H, m, **H7**), 7.66-7.60 (1H, m, **H9**), 7.55-7.49 (2H, m, **H8**), 4.88 (1H, t, *J* = 7.7 Hz, **H4**), 3.25-3.07 (2H, m, **H1**), 2.92-2.79 (1H, m, **H3a**), 2.46-2.15 (3H, m, **H2** and **H3b**).

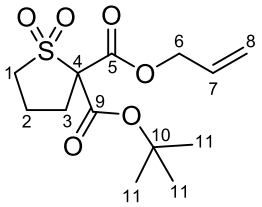
**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 189.9 (**C5**), 136.3 (**C6**), 134.3 (**C9**), 129.1 and 129.0 (**C7** and **C8**), 65.4 (**C4**), 52.7 (**C1**), 26.1 (**C3**), 20.7 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{12}O_3S$ $[M+H]^+$ 225.0580, found 225.0570.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 2974 (C–H), 2950 (C–H), 1679 (C=O) $cm^{-1}$.

### 3.2.7 Synthesis of 5-Membered Cyclic Sulfone Precursors

#### 2-Allyl 2-(*t*-butyl) dihydrothiophene-2,2(3H)-dicarboxylate 1,1-dioxide 182



**117** (200 mg, 0.98 mmol) was dissolved in THF (15 mL). NaHMDS (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Boc anhydride (250 µL, 1.08 mmol) was added dropwise, and the mixture was stirred overnight. The reaction was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **182** (101 mg, 34%) as a colourless oil. $\boldsymbol{R_f}$ = 0.29 [petrol:EtOAc 4:1].

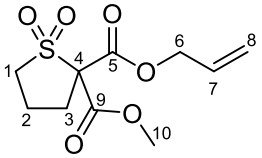
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.99-5.86 (1H, m, **H7**), 5.40 (1H, dq, *J* = 17.3, 1.4 Hz, **H8a**), 5.27 (1H, dq, *J* = 10.7, 1.4 Hz, **H8b**), 4.76-4.72 (2H, m, **H6**), 3.29 (2H, t, *J* = 7.6 Hz, **H1**), 2.66 (2H, td, *J* = 7.3, 2.7 Hz, **H3**), 2.20 (2H, quint, *J* = 7.6 Hz, **H2**), 1.48 (9H, s, **H11**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 164.5 (**C5**), 163.0 (**C9**), 130.8 (**C7**), 119.4 (**C8**), 84.9 (**C10**), 75.5 (**C4**), 67.3 (**C6**), 50.2 (**C1**), 29.9 (**C3**), 27.7 (**C11**), 16.9 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{13}H_{20}O_6S$ $[M+H]^+$ 305.1053, found 305.1039.

**IR:** $\nu_{max}$ (neat): 2980 (C–H), 1730 (C=O) $cm^{-1}$.

#### 2-Allyl 2-methyl dihydrothiophene-2,2(3H)-dicarboxylate 1,1-dioxide 183



**117** (200 mg, 0.98 mmol) was dissolved in THF (15 mL). NaHMDS (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Methyl chloroformate (83 µL, 1.08 mmol) was added dropwise, and the mixture was stirred

overnight. The reaction was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **183** (141 mg, 55%) as a yellow oil. $R_f$ = 0.18 [petrol:EtOAc 4:1].

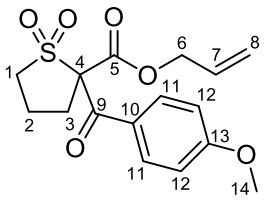
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.92 (1H, ddt, *J* = 16.1, 10.5, 5.8 Hz, **H7**), 5.39 (1H, dq, *J* = 17.2, 1.5 Hz, **H8a**), 5.29 (1H, dq, *J* = 10.4, 1.2 Hz, **H8b**), 4.77 (2H, dt, *J* = 5.7, 1.3 Hz, **H6**), 3.88 (3H, s, **H10**), 3.34 (2H, t, *J* = 7.2 Hz, **H1**), 2.73 (2H, td, *J* = 7.2, 2.3 Hz, **H3**), 2.26 (2H, quint, *J* = 7.2 Hz, **H2**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 164.9 (**C9**), 164.1 (**C5**), 130.7 (**C7**), 119.5 (**C8**), 75.0 (**C4**), 67.5 (**C6**), 53.9 (**C10**), 50.2 (**C1**), 30.1 (**C3**), 17.1 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{10}H_{14}O_6S$ $[M+H]^+$ 263.0584, found 263.0577.

**IR:** $\nu_{max}$ (neat): 2957 (C–H), 1733 (C=O) $cm^{-1}$.

### Allyl 2-(4-methoxybenzoyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 184



**117** (200 mg, 0.98 mmol) was dissolved in THF (15 mL), and NaHMDS (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise. The mixture was stirred at room temperature for 30 minutes. 4-Methoxybenzoyl chloride (150 µL, 1.08 mmol) was added dropwise, and the mixture was heated to 80 °C overnight. The solution was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **184** (109 mg, 33%) as a yellow oil. $R_f$ = 0.14 [petrol:EtOAc 4:1].

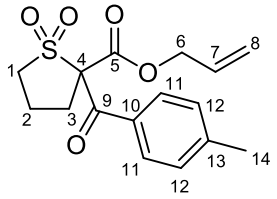
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.96 (2H, dt, *J* = 9.7, 2.8 Hz, **H11**), 6.98-6.92 (2H, m, **H12**), 5.77-5.64 (1H, m, **H7**), 5.23-5.14 (2H, m, **H8**), 4.64 (2H, dt, *J* = 5.9, 1.2 Hz, **H6**), 3.87 (3H, s, **H14**), 3.50-3.32 (2H, m Hz, **H1**), 3.17 (1H, quint, *J* = 8.1 Hz, **H3a**), 2.68 (1H, quint, *J* = 6.9 Hz, **H3b**), 2.37-2.19 (2H, m, **H2**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 185.9 (**C9**), 166.3 (**C5**), 164.0 (**C13**), 131.7 (**C11**), 130.3 (**C7**), 128.2 (**C10**), 119.9 (**C8**), 113.9 (**C12**), 77.7 (**C4**), 67.2 (**C6**), 55.5 (**C14**), 51.9 (**C1**), 31.9 (**C3**), 17.6 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_6S$ $[M+H]^+$ 339.0897, found 339.0889.

**IR:** $\nu_{max}$ (neat): 3065 (C–H), 2956 (C–H), 1733 (C=O), 1675 (C=O) $cm^{-1}$.

### Allyl 2-(*p*-toluoyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 185



**117** (100 mg, 0.49 mmol) was dissolved in THF (6 mL) and NaHMDS (1 M in THF, 0.54 mL, 0.54 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Benzoyl chloride (71 µL, 0.54 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The mixture was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 6 mL). The mixture was extracted with EtOAc (3 x 6 mL), washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **185** (79 mg, 50%) as a colourless solid. $R_f$ = 0.14 [petrol:EtOAc 4:1]. **m.p.:** 64–66 °C.

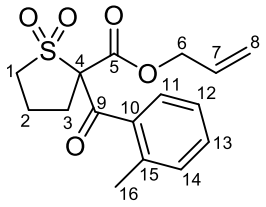
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.4 Hz, **H12**), 7.24 (2H, d, *J* = 8.0 Hz, **H11**), 5.65 (1H, dddd, *J* = 16.7, 10.7, 6.2, 6.0 Hz, **H7**), 5.19-5.11 (2H, m, **H8**), 4.61 (2H, dt, *J* = 5.9, 1.2 Hz, **H6**), 3.46-3.31 (2H, m, **H1**), 3.11 (1H, quint, *J* = 6.9 Hz, **H3a**), 2.68 (1H, quint, *J* = 7.3 Hz, **H3b**), 2.38 (3H, s, **H14**), 2.33-2.16 (2H, m, **H2**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 187.7 (**C9**), 166.5 (**C5**), 145.1 (**C13**), 133.1 (**C10**), 130.2 (**C7**), 129.4 (**C11**), 129.2 (**C12**), 119.9 (**C8**), 77.7 (**C4**), 67.3 (**C6**), 51.8 (**C1**), 31.9 (**C3**), 21.7 (**C14**), 17.6 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_5S$ $[M+H]^+$ 323.0948, found 323.0944.

**IR:** $\nu_{max}$ (neat): 3076 (C–H), 3022 (C–H), 2993 (C–H), 1739 (C=O), 1679 (C=O) $cm^{-1}$.

**Allyl 2-(*o*-toluoyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 186**



**117** (200 mg, 0.98 mmol) was dissolved in THF (15 mL) and NaHMDS (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. *o*-Toluoyl chloride (140 µL, 1.08 mmol) was added dropwise, and the solution was heated to 80 °C overnight. The reaction was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **186** (133 mg, 42%) as a colourless solid. $R_f$ = 0.20 [petrol:EtOAc 4:1]. **m.p.:** 74–75 °C.

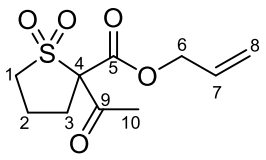
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.37-7.31 (2H, m, **H12** and **H13**), 7.25-7.15 (2H, m, **H11** and **H14**), 5.45 (1H, ddt, *J* = 16.4, 10.4, 6.1 Hz, **H7**), 5.15-5.04 (2H, m, **H8**), 4.56-4.40 (2H, m, **H6**), 3.53-3.43 (1H, m, **H1a**), 3.34 (1H, quint, *J* = 6.3 Hz, **H1b**), 3.01 (1H, quint, *J* = 7.5 Hz, **H3a**), 2.82-2.72 (1H, m, **H3b**), 2.43 (3H, s, **H16**), 2.34-2.24 (2H, m, **H2**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 195.3 (**C9**), 165.0 (**C5**), 138.2 (**C15**), 136.9 (**C10**), 131.8 (**C14**), 131.5 (**C12**), 130.2 (**C7**), 126.0 (**C13**), 125.3 (**C11**), 119.6 (**C8**), 79.9 (**C4**), 67.4 (**C6**), 51.2 (**C1**), 31.9 (**C3**), 20.4 (**C16**), 17.6 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_5S$ $[M+Na]^+$ 345.0767, found 345.0759.

**IR:** $\nu_{max}$ (neat): 3071 (C–H), 3022 (C–H), 2956 (C–H), 1744 (C=O), 1694 (C=O) $cm^{-1}$.

**Allyl 2-acetyltetrahydrothiophene-2-carboxylate 1,1-dioxide 187**



**117** (200 mg, 0.98 mmol) was dissolved in THF (15 mL) and NaHMDS (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Acetyl chloride (77 µL, 1.08 mmol) was added dropwise, and the solution was heated to 80 °C

overnight. The reaction was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **187** (121 mg, 50%) as a yellow oil. $R_f$ = 0.26 [petrol:EtOAc 4:1].

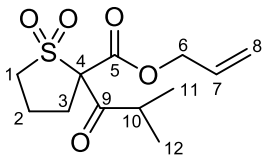
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.93 (1H, ddt, *J* = 16.7, 9.9, 5.8 Hz, **H7**), 5.39 (1H, dq, *J* = 17.4, 1.4 Hz, **H8a**), 5.32 (1H, dq, *J* = 10.4, 1.1 Hz, **H8b**), 4.76 (2H, dq, *J* = 5.6, 0.9 Hz, **H6**), 3.38-3.17 (2H, m, **H1**), 2.83 (1H, ddd, *J* = 14.4, 8.2, 6.5 Hz, **H3a**), 2.58-2.48 (4H, m, **H3b** and **H10**), 2.33-2.08 (2H, m, **H2**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 195.5 (**C9**), 164.9 (**C5**), 130.4 (**C7**), 120.3 (**C8**), 79.9 (**C4**), 67.7 (**C6**), 51.2 (**C1**), 29.4 (**C10**), 28.7 (**C3**), 17.4 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{10}H_{14}O_5S$ $[M+H]^+$ 247.0635, found 247.0625.

**IR:** $\nu_{max}$ (neat): 2956 (C–H), 1718 (C=O) $cm^{-1}$.

### Allyl 2-(2-methylpropanoyl)-1,1-dioxo-thiolane-2-carboxylate 188




**117** (250 mg, 1.12 mmol) was dissolved in THF (20 mL) and NaHMDS (1 M in THF, 1.35 mL, 1.35 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Isobutyryl chloride (140 µL, 1.35 mmol) was added dropwise, and the mixture was heated to 80 °C overnight. The reaction was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **188** (184 mg, 60%) as a yellow oil. $R_f$ = 0.33 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.96 (1H, ddt, *J* = 16.6, 10.5, 6.1 Hz, **H7**), 5.42 (1H, dd, *J* = 17.3, 1.2 Hz, **H8a**), 5.32 (1H, d, *J* = 10.5 Hz, **H8b**), 4.77 (2H, d, *J* = 5.9 Hz, **H6**), 3.35-3.16 (3H, m, **H1** and **H10**), 2.76 (1H, quint, *J* = 7.7 Hz, **H3a**), 2.60 (1H, quint, *J* = 7.4 Hz, **H3b**), 2.19 (2H, quint, *J* = 7.1 Hz, **H2**), 1.18 (3H, d, *J* = 6.5 Hz) and 1.10 (3H, d, *J* = 6.9 Hz) (**H11** and **H12**).

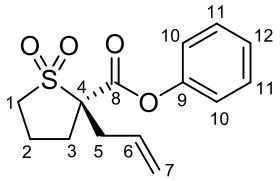
**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 203.6 (**C9**), 164.7 (**C5**), 130.4 (**C7**), 120.6 (**C8**), 80.2 (**C4**), 67.7 (**C6**), 50.7 (**C1**), 39.7 (**C10**), 29.0 (**C3**), 20.5 and 19.5 (**C11** and **C12**), 17.0 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{18}O_5S$ $[M+H]^+$ 275.0948, found 275.0943.

**IR:** $\nu_{max}$ (neat): 2978 (C–H), 2877 (C–H), 1735 (C=O), 1718 (C=O) $cm^{-1}$.

### 3.2.8 5-Membered Sulfone Pd-DAAA Reaction Products

#### (*R*)-Phenyl 2-allyltetrahydrothiophene-2-carboxylate 1,1-dioxide 121




**104** (48.7 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.00375 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (7.9 mg, 0.00975 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **121** (38.5 mg, 90%) as a yellow oil. $R_f$ = 0.20 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.42-7.36 (2H, m, **H11**), 7.25 (1H, tt, *J* = 7.2, 1.3 Hz, **H12**), 7.15 (2H, d, *J* = 9.1 Hz, **H10**), 5.79 (1H, dddd, *J* = 17.1, 10.2, 7.3, 6.7 Hz, **H6**), 5.37-5.26 (2H, m, **H7**), 3.33-3.24 (2H, m, **H1a** and **H5a**), 3.19-3.10 (1H, m, **H1b**), 2.93-2.82 (1H, m, **H3a**), 2.54 (1H, dd, *J* = 14.0, 7.7 Hz, **H5b**), 2.39-2.25 (1H, m, **H2a**), 2.21-2.08 (2H, m, **H2b** and **H3b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 166.6 (**C8**), 150.7 (**C9**), 130.8 (**C6**), 129.7 (**C11**), 126.3 (**C12**), 121.4 (**C10**), 120.9 (**C7**), 70.2 (**C4**), 51.6 (**C1**), 37.4 (**C5**), 31.2 (**C3**), 18.5 (**C2**).

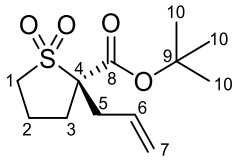
**HRMS (*m/z*):** (APCI) calcd for $C_{14}H_{16}O_4S$ $[M+H]^+$ 281.0842, found 281.0832.

**IR:** $\nu_{max}$ (neat): 3079 (C–H), 2952 (C–H), 1750 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 90:10 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 14.5 min, $t_B$ (minor) = 17.2 min. 94% ee.

$[\alpha]_D^{20}$: –68.5 (*c* 0.073, $CHCl_3$).

**(*R*)-*t*-Butyl 2-allyl tetrahydrothiophene-2-carboxylate 1,1-dioxide 190**



**182** (43 mg, 0.14 mmol), $Pd_2(dba)_3$ (3.2 mg, 0.0035 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (7.4 mg, 0.0091 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **190** (34 mg, 94%) as a colourless oil. $\boldsymbol{R_f}$ = 0.32 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.63 (1H, dddd, *J* = 17.1, 10.0, 7.8, 6.5 Hz, **H6**), 5.23-5.16 (2H, m, **H7**), 3.21-3.14 (1H, m, **H1a**), 3.09-3.02 (2H, m, **H1b** and **H5a**), 2.73-2.68 (1H, m, **H3a**), 2.37 (1H, dd, *J* = 14.4, 8.3 Hz, **H5b**), 2.27-2.17 (1H, m, **H2a**), 2.10-1.96 (2H, m, **H2b** and **H3b**), 1.50 (9H, s, **H10**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 166.6 (**C8**), 132.0 (**C6**), 120.2 (**C7**), 84.6 (**C9**), 71.4 (**C4**), 52.1 (**C1**), 38.2 (**C5**), 31.5 (**C3**), 28.5 (**C10**), 19.1 (**C2**).

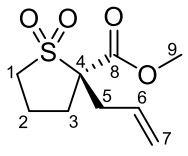
**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{20}O_4S$ $[M+Na]^+$ 283.0975, found 283.0970.

**IR:** $\nu_{max}$ (neat): 3081 (C–H), 2978 (C–H), 1728 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 7.89 min, $t_B$ (major) = 8.83 min. 38% ee.

$\boldsymbol{[\alpha]_D^{20}}$: –75.0 (*c* 0.10, $CHCl_3$).

**(*R*)-Methyl 2-allyl tetrahydrothiophene-2-carboxylate 1,1-dioxide 191**



**183** (77 mg, 0.29 mmol), $Pd_2(dba)_3$ (6.7 mg, 0.0073 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (15.3 mg, 0.091 mmol) were stirred in 1,4-dioxane (2 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **191** (58 mg, 92%) as a colourless oil. $\boldsymbol{R_f}$ = 0.32 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.61 (1H, dddd, *J* = 17.3, 9.9, 7.9, 6.3 Hz, **H6**), 5.24-5.16 (2H, m, **H7**), 3.84 (3H, s, **H9**), 3.25-3.18 (1H, m, **H1a**), 3.13-3.05 (2H, m, **H1b** and **H5a**), 2.80-2.73 (1H, m, **H3a**), 2.42 (1H, dd, *J* = 14.1, 7.9 Hz, **H5b**), 2.31-2.20 (1H, m, **H2a**), 2.14-2.02 (2H, m, **H2b** and **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 168.0 (**C8**), 131.2 (**C6**), 120.7 (**C7**), 70.3 (**C4**), 53.5 (**C9**), 51.4 (**C1**), 37.1 (**C5**), 30.8 (**C3**), 18.5 (**C2**).

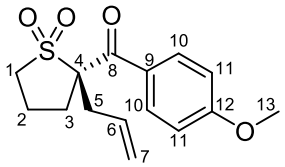
**HRMS (*m/z*):** (APCI) calcd for $C_9H_{14}O_4S$ $[M+H]^+$ 219.0686, found 219.0680.

**IR:** $\nu_{max}$ (neat): 3081 (C–H), 3006 (C–H), 2954 (C–H), 1735 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 17.3 min, $t_B$ (major) = 19.0 min. 70% ee.

**$[\alpha]_D^{20}$**: –56.7 (*c* 0.30, $CHCl_3$).

### (*R*)-(2-Allyl-1,1-dioxidotetrahydrothiophen-2-yl)(4-methoxyphenyl)methanone 192




**184** (77 mg, 0.23 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (24.3 mg, 0.030 mmol) were stirred in 1,4-dioxane (2 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **192** (62 mg, 92%) as a colourless oil. $R_f$ = 0.19 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 9.9 Hz, **H10**), 6.95 (2H, d, *J* = 9.7 Hz, **H11**), 5.39-5.29 (1H, m, **H6**), 5.02 (1H, d, *J* = 9.8 Hz, **H7a**), 4.92 (1H, dd, *J* = 16.7, 1.4 Hz, **H7b**), 3.90 (3H, s, **H13**), 3.34-3.18 (3H, m, **H1** and **H5a**), 3.10 (1H, ddd, *J* = 14.2, 7.7, 5.4 Hz, **H3a**), 2.64 (1H, dd, *J* = 14.2, 7.7 Hz, **H5b**), 2.29-2.04 (3H, m, **H2** and **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 191.8 (**C8**), 163.7 (**C12**), 132.1 (**C10**), 130.4 (**C6**), 128.8 (**C9**), 120.6 (**C7**), 113.7 (**C11**), 74.0 (**C4**), 55.5 (**C13**), 53.9 (**C1**), 39.7 (**C5**), 32.5 (**C3**), 18.6 (**C2**).

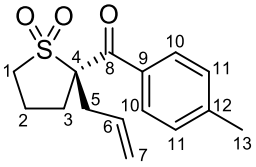
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_3S$ $[M+H]^+$ 295.0999, found 295.0986.

**IR:** $\nu_{max}$ (neat): 3079 (C–H), 3006 (C–H), 2950(C–H), 2842 (C–H), 1668 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 90:10 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 23.0 min, $t_B$ (major) = 33.5 min. 10% ee.

$[\alpha]_D^{20}$: –7.4 (*c* 0.336, $CHCl_3$).

**(*R*)-(2-Allyl-1,1-dioxidotetrahydrothiophen-2-yl)(*p*-tolyl)methanone 124**




**185** (30 mg, 0.093 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (9.8 mg, 0.012 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **124** (23 mg, 89%) as a colourless solid. $R_f$ = 0.22 [petrol:EtOAc 4:1]. **m.p.:** 81–82 °C.

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.6 Hz, **H11**), 7.26 (2H, d, *J* = 7.9 Hz, **H10**), 5.41-5.27 (1H, m, **H6**), 5.00 (1H, dt, *J* = 10.1, 0.9 Hz, **H7a**), 4.90 (1H, dq, *J* = 16.8, 1.4 Hz, **H7b**), 3.36-3.05 (4H, m, **H1**, **H3a** and **H5a**), 2.63 (1H, dd, *J* = 14.6, 7.9 Hz, **H5b**), 2.40 (3H, s, **H13**), 2.32-2.01 (3H, m, **H2** and **H3b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 193.0 (**C8**), 143.9 (**C12**), 133.4 (**C9**), 130.3 (**C6**), 129.7 (**C11**), 129.2 (**C10**), 120.7 (**C7**), 73.9 (**C4**), 53.9 (**C1**), 39.6 (**C5**), 32.5 (**C3**), 21.7 (**C13**), 18.8 (**C2**).

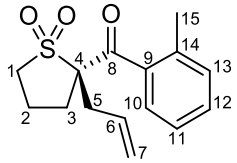
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_3S$ $[M+H]^+$ 279.1049, found 279.1041.

**IR:** $\nu_{max}$ (neat): 3066 (C–H), 2954 (C–H), 2926 (C–H), 2854 (C–H), 1675 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 21.2 min, $t_B$ (major) = 33.4 min. 62% ee.

$[\alpha]_D^{20}$: –68.8 (*c* 0.109, $CHCl_3$).

**(*R*)-(2-Allyl-1,1-dioxidotetrahydrothiophen-2-yl)(*o*-tolyl)methanone 193**




**186** (77 mg, 0.24 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (25.4 mg, 0.031 mmol) were stirred in 1,4-dioxane (2 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **193** (63 mg, 95%) as a colourless oil. $\boldsymbol{R_f}$ = 0.23 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 8.4 Hz, **H10**), 7.34 (1H, t, *J* = 8.1 Hz, **H11**), 7.30-7.25 (2H, m, **H12** and **H13**), 5.41 (1H, ddt, *J* = 17.1, 10.1, 7.4 Hz, **H6**), 5.04 (1H, dd, *J* = 9.7, 0.8 Hz, **H7a**), 4.86 (1H, dd, *J* = 19.9, 4.2 Hz, **H7b**), 3.30-3.22 (1H, m, **H1a**), 3.19-3.11 (2H, m, **H1b** and **H5a**), 2.96-2.87 (1H, m, **H3a**), 2.55 (1H, ddd, *J* = 14.4, 7.7, 0.9 Hz, **H5b**), 2.35-2.25 (4H, m, **H2a** and **H15**), 2.16-2.08 (2H, m, **H2b** and **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 198.4 (**C8**), 138.1 (**C14**), 136.7 (**C9**), 131.8 (**C13**), 130.9 (**C11**), 130.3 (**C6**), 127.0 (**C10**), 125.2 (**C12**), 120.9 (**C7**), 74.4 (**C4**), 52.4 (**C1**), 38.5 (**C5**), 32.6 (**C3**), 20.7 (**C15**), 18.8 (**C2**).

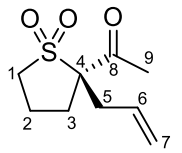
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_3S$ $[M+H]^+$ 279.1049, found 279.1044.

**IR:** $\nu_{max}$ (neat): 3062 (C–H), 2954 (C–H), 2928 (C–H), 1685 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 16.7 min, $t_B$ (major) = 22.8 min. 10% ee.

$\boldsymbol{[\alpha]_D^{20}}$: –2.0 (*c* 0.510, $CHCl_3$).

**(*R*)-(2-Allyl-1,1-dioxidotetrahydrothiophen-2-yl)(methyl)methanone 194**



**187** (55 mg, 0.22 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (23.2 mg, 0.029 mmol) were stirred in 1,4-dioxane (1.5 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **194** (40 mg, 90%) as a yellow oil. $R_f$ = 0.21 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.56-5.45 (1H, m, **H6**), 5.23-5.16 (2H, m, **H7**), 3.17-3.00 (3H, m, **H1** and **H5a**), 2.79 (1H, quint, *J* = 6.2 Hz, **H3a**), 2.57 (1H, dd, *J* = 15.4, 7.7 Hz, **H5b**), 2.34 (3H, s, **H9**), 2.19-1.99 (2H, m, **H2**), 1.90 (1H, quint, *J* = 7.3 Hz, **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 200.8 (**C8**), 130.8 (**C6**), 120.9 (**C7**), 74.2 (**C4**), 51.6 (**C1**), 36.9 (**C5**), 29.3 (**C3**), 28.0 (**C9**), 17.9 (**C2**).

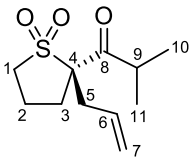
**HRMS (*m/z*):** (APCI) calcd for $C_9H_{14}O_3S$ $[M+H]^+$ 203.0736, found 203.0737.

**IR:** $\nu_{max}$ (neat): 3082 (C–H), 2954 (C–H), 1713 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 15.5 min, $t_B$ (major) = 16.9 min. 20% ee.

$[\alpha]_D^{20}$: –23.2 (*c* 0.345, $CHCl_3$).

**(*R*)-1-(2-Allyl-1,1-dioxo-thiolan-2-yl)-2-methyl-propan-1-one 195**



**188** (50 mg, 0.18 mmol), $Pd_2(dba)_3$ (8.2 mg, 0.0091 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (19 mg, 0.023 mmol) were stirred in 1,4-dioxane (2 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **195** (40 mg, 97%) as a yellow oil. $R_f$ = 0.29 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.49 (1H, dddd, *J* = 17.2, 9.7, 8.4, 5.4 Hz, **H6**), 5.24-5.16 (2H, m, **H7**), 3.24-3.04 (4H, m, **H1**, **H5a** and **H9**), 2.79-2.70 (1H, m, **H3a**), 2.63 (1H, dd, *J* = 15.3, 8.6 Hz, **H5b**), 2.20-1.95 (3H, m, **H2** and **H3b**), 1.18 (3H, d, *J* = 6.6 Hz) and 1.15 (3H, d, *J* = 6.8 Hz) (**H10** and **H11**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 208.0 (**C8**), 130.8 (**C6**), 120.8 (**C7**), 75.0 (**C4**), 51.6 (**C1**), 38.2 (**C9**), 36.3 (**C5**), 28.6 (**C3**), 20.5 and 19.8 (**C10** and **H11**), 17.6 (**C2**).

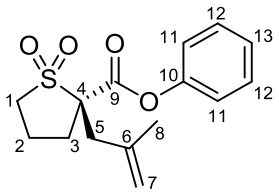
**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{18}O_3S$ $[M+H]^+$ 231.1049, found 231.1042.

**IR:** $\nu_{max}$ (neat): 3083 (C–H), 2976 (C–H), 2939 (C–H), 2876 (C–H), 1709 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 10.5 min, $t_B$ (major) = 12.6 min. 88% ee.

**$[\alpha]_D^{20}$**: –173.1 (*c* 0.182, $CHCl_3$).

### (*R*)-Phenyl 2-(2-methylallyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 119




**129** (30 mg, 0.089 mmol), $Pd_2(dba)_3$ (2.1 mg, 0.0025 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (4.7 mg, 0.0058 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 19:1–4:1] gave **119** (16 mg, 62%) as a colourless oil. $R_f$ = 0.21 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.42-7.35 (2H, m, **H12**), 7.28-7.22 (1H, m, **H13**), 7.18-7.13 (2H, m, **H11**), 4.99 (1H, s, **H7a**), 4.86 (1H, s, **H7b**), 3.36-3.23 (2H, m, **H1a** and **H5a**), 3.18-3.09 (1H, m, **H1b**), 2.99-2.89 (1H, m, **H3a**), 2.55 (1H, d, *J* = 14.7 Hz, **H5b**), 2.38-2.07 (3H, m, **H2** and **H3b**), 1.82 (3H, s, **H8**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 167.1 (**C9**), 150.7 (**C10**), 139.7 (**C6**), 129.5 (**C12**), 126.4 (**C13**), 121.4 (**C11**), 115.4 (**C7**), 70.1 (**C4**), 51.5 (**C1**), 40.4 (**C5**), 31.1 (**C3**), 23.4 (**C8**), 18.7 (**C2**).

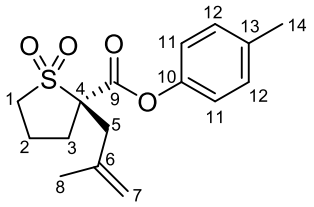
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_4S$ $[M+H]^+$ 295.0999, found 295.0999.

**IR:** $\nu_{max}$ (neat): 3075 (C–H), 2948 (C–H), 1752 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 18.9 min, $t_B$ (minor) = 20.9 min. 82% ee.

$[\alpha]_D^{20}$: –217.4 (*c* 0.046, $CHCl_3$).

### (*R*)-(*p*-Tolyl) 2-(2-methylallyl)tetrahydrothiophene-2-carboxylate 1,1-dioxide 118




**105** (30 mg, 0.085 mmol), $Pd_2(dba)_3$ (2.1 mg, 0.0021 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (4.5 mg, 0.0055 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 19:1–4:1] gave **118** (16 mg, 60%) as a colourless oil. $R_f$ = 0.25 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 9.0 Hz, **H12**), 7.02 (2H, t, *J* = 8.8 Hz, **H11**), 4.98 (1H, s, **H7a**), 4.85 (1H, s, **H7b**), 3.35-3.22 (2H, m, **H1a** and **H5a**), 3.18-3.08 (1H, m, **H1b**), 2.97-2.88 (1H, m, **H3a**), 2.54 (1H, dd, *J* = 15.0, 0.7 Hz, **H5b**), 2.34 (3H, s, **H14**), 2.32-2.07 (3H, m, **H2** and **H3b**), 1.81 (3H, s, **H8**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 167.0 (**C9**), 148.5 (**C10**), 139.7 (**C6**), 136.3 (**C13**), 130.2 (**C12**), 121.2 (**C11**), 115.3 (**C7**), 70.0 (**C4**), 51.4 (**C1**), 40.4 (**C5**), 31.1 (**C3**), 23.3 (**C8**), 20.9 (**C14**), 18.6 (**C2**).

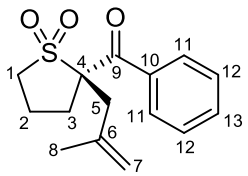
**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{20}O_4S$ $[M+H]^+$ 309.1155, found 309.1145.

**IR:** $\nu_{max}$ (neat): 3075 (C–H), 3032 (C–H), 2948 (C–H), 1750 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 18.6 min, $t_B$ (minor) = 21.6 min. 86% ee.

$[\alpha]_D^{20}$: –100.0 (*c* 0.10, $CHCl_3$).

**(*R*)-(2-(2-Methylallyl)-1,1-dioxidotetrahydrothiophen-2-yl)(phenyl)methanone 123**



**130** (30 mg, 0.093 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (9.8 mg, 0.012 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 19:1–4:1] gave **123** (17 mg, 65%) as a colourless oil. $R_f$ = 0.27 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 8.01-7.99 (2H, m, **H12**), 7.54 (1H, tt, *J* = 6.2, 1.4 Hz, **H13**), 7.48-7.43 (2H, m, **H11**), 4.77 (1H, s, **H7a**), 4.58 (1H, s, **H7b**), 3.37 (1H, d, *J* = 15.0 Hz, **H5a**), 3.32-3.13 (3H, m, **H1** and **H3a**), 2.73 (1H, d, *J* = 15.6 Hz, **H5b**), 2.35-2.09 (3H, m, **H2** and **H3b**), 1.41 (3H, s, **H8**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 194.9 (**C9**), 139.2 (**C6**), 136.1 (**C10**), 132.8 (**C13**), 129.6 (**C12**), 128.4 (**C11**), 115.9 (**C7**), 73.9 (**C4**), 53.4 (**C1**), 42.5 (**C5**), 32.6 (**C3**), 23.2 (**C8**), 19.0 (**C2**).

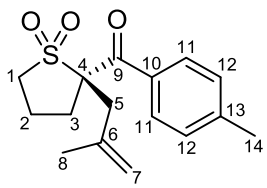
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_3S$ $[M+H]^+$ 279.1049, found 279.1043.

**IR:** $\nu_{max}$ (neat): 3067 (C–H), 2950 (C–H), 1675 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 18.3 min, $t_B$ (major) = 26.6 min. 14% ee.

**$[\alpha]_D^{20}$**: –83.3 (*c* 0.054, $CHCl_3$).

**(*R*)-(2-(2-methylallyl)-1,1-dioxidotetrahydrothiophen-2-yl)(*p*-tolyl)methanone 122**



**107** (30 mg, 0.089 mmol), $Pd_2(dba)_3$ (4.1 mg, 0.005 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (9.8 mg, 0.012 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 19:1–4:1] gave **122** (15 mg, 59%) as a colourless oil. $R_f$ = 0.27 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.5 Hz, **H12**), 7.25 (2H, d, *J* = 8.0 Hz, **H11**), 4.77 (1H, s, **H7a**), 4.59 (1H, s, **H7b**), 3.38 (1H, d, *J* = 15.1 Hz, **H5a**), 3.31-3.10 (3H, m, **H1** and **3a**), 2.73 (1H, dd, *J* = 15.1, 0.9 Hz, **H5b**), 2.39 (3H, s, **H14**), 2.30-2.08 (3H, m, **H2** and **H3b**), 1.42 (3H, s, **H8**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 194.3 (**C9**), 143.7 (**C13**), 139.5 (**C6**), 133.6 (**C10**), 130.0 (**C12**), 129.0 (**C11**), 116.1 (**C7**), 73.8 (**C4**), 53.4 (**C1**), 42.6 (**C5**), 32.5 (**C3**), 23.1 (**C8**), 21.7 (**C14**), 18.9 (**C2**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{20}O_3S$ $[M+H]^+$ 293.1206, found 293.1202.

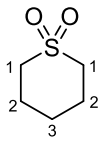
**IR:** $\nu_{max}$ (neat): 3067 (C–H), 2950 (C–H), 2924 (C–H), 2854 (C–H), 1664 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 19.3 min, $t_B$ (major) = 32.1 min. 10% ee.

**$[\alpha]_D^{20}$**: –66.4 (*c* 0.10, $CHCl_3$).

### 3.2.9 Synthesis of 6-Membered Cyclic Sulfone Precursors

**Thiane 1,1-dioxide 197**[55]




Tetrahydrothiopyran (2.02 mL, 19.6 mmol) and potassium permanganate (6.18 g, 39.1 mmol) were added to a 3:1 mixture of $H_2O$:$CH_2Cl_2$ (200 mL). The reaction mixture was stirred vigorously at room temperature overnight. The mixture was filtered under reduced pressure and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic phase was washed with aq. $Na_2S_2O_3$ (10 %, 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **197** (2.604 g, 99%) as a colourless solid.

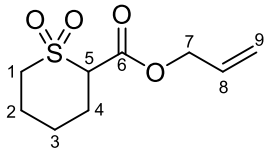
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 2.98 (4H, t, *J* = 6.0 Hz, **H1**), 2.13-2.05 (4H, m, **H2**), 1.67-1.59 (2H, m, **H3**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 52.2 (**C1**), 24.3 (**C2**), 23.9 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_5H_{10}O_2S$ $[M+H]^+$ 135.0474, found 135.0468.

Analytical data matches literature values.[55]

**Allyl 1,1-dioxothiane-2-carboxylate 198**



**197** (2.00 g, 14.9 mmol) was dissolved in THF (120 mL) and the solution was cooled to –78 °C. LiHMDS (1 M in THF, 29.8 mL, 29.8 mmol) was added dropwise at –78 °C. The solution was stirred at –78 °C for 1 hour. Allyl chloroformate (1.75 mL, 16.4 mmol) was added dropwise at –78 °C. The mixture was allowed to reach room temperature and was stirred overnight. The reaction was quenched with aq. HCl (1 N, 40 mL), and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [Petrol:EtOAc 4:1] gave **198** (2.27 g, 70%) as a yellow oil. $\boldsymbol{R_f}$ = 0.17 [petrol:EtOAc 4:1].

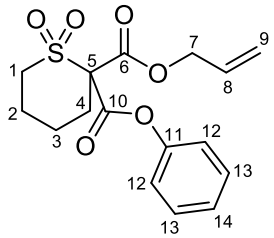
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.92 (1H, ddt, *J* = 17.2, 10.3, 5.7 Hz, **H8**), 5.38 (1H, dq, *J* = 17.1, 1.4 Hz, **H9a**), 5.29 (1H, dq, *J* = 10.4, 1.1 Hz, **H9b**), 4.71 (2H, d, *J* = 5.7 Hz, **H7**), 3.88 (1H, ddd, *J* = 6.5, 4.7, 1.9 Hz, **H5**), 3.48-3.39 (1H, m, **H1a**), 3.03-2.94 (1H, m, **H1b**), 2.41-2.25 (2H, m, **H4**), 2.15-2.07 (2H, m, **H2**), 1.98-1.84 (1H, m, **H3a**), 1.66-1.55 (1H, m, **H3b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 165.6 (**C6**), 131.0 (**C8**), 119.5 (**C9**), 66.8 (**C7**), 65.0 (**C5**), 51.0 (**C1**), 28.0 (**C4**), 24.2 (**C2**), 20.7 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_9H_{14}O_4S$ $[M+H]^+$ 219.0686, found 219.0677.

**IR:** $\nu_{max}$ (neat): 2939 (C–H), 2870 (C–H),1731 (C=O) $cm^{-1}$.

**2-Allyl 2-phenyl 1,1-dioxothiane-2,2-dicarboxylate 200**



**198** (300 mg, 1.37 mmol) was dissolved in THF (20 mL). NaHMDS (1 M in THF, 1.51 mL, 1.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Phenyl chloroformate (190 µL, 1.51 mmol) was added dropwise, and the mixture was stirred overnight. The reaction was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under

reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **200** (195 mg, 43%) as a yellow oil. $R_f$ = 0.22 [petrol:EtOAc 4:1].

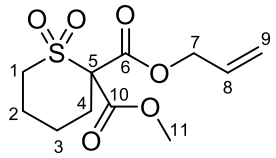
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.41 (2H, t, *J* = 7.7 Hz, **H13**), 7.28 (1H, t, *J* = 7.4 Hz, **H14**), 7.14 (2H, d, *J* = 7.9 Hz, **H12**), 5.94 (1H, ddt, *J* = 22.8, 13.8, 7.5 Hz, **H8**), 5.40 (1H, dq, *J* = 23.0, 2.0 Hz, **H9a**), 5.31 (1H, dq, *J* = 13.9, 1.5 Hz, **H9b**), 4.73 (2H, d, *J* = 7.7 Hz, **H7**), 3.60-3.54 (1H, m, **H1a**), 3.46-3.40 (1H, m, **H1b**), 2.67 (2H, q, *J* = 6.4 Hz, **H4**), 2.13 (2H, quint, *J* = 5.5 Hz, **H2**), 1.78 (2H, quint, *J* = 5.5 Hz, **H3**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 163.6 (**C6**), 162.8 (**C10**), 150.1 (**C11**), 130.5 (**C8**), 129.6 (**C13**), 126.7 (**C14**), 121.2 (**C12**), 120.0 (**C9**), 76.5 (**C5**), 67.7 (**C7**), 52.1 (**C1**), 32.5 (**C4**), 24.1 (**C2**), 20.0 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_{16}H_{18}O_6S$ $[M+H]^+$ 339.0897, found 339.0884.

**IR:** $\nu_{max}$ (neat): 3017 (C–H), 2985 (C–H), 2946 (C–H), 2872 (C–H), 1767 (C=O), 1737 (C=O) $cm^{-1}$.

### 2-Allyl 2-methyl 1,1-dioxothiane-2,2-dicarboxylate 201




**198** (300 mg, 1.37 mmol) was dissolved in THF (20 mL). NaHMDS (1 M in THF, 1.51 mL, 1.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Methyl chloroformate (120 µL, 1.51 mmol) was added dropwise, and the mixture was stirred overnight. The reaction was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave 227 mg of a 1:1 mixture of **201** and **198**, corresponding to 155 mg, 41% of **201** as a yellow oil. $R_f$ = 0.20 [petrol:EtOAc 4:1].

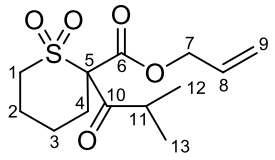
**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 5.97-5.86 (1H, m, **H8**), 5.39 (1H, dq, *J* = 17.2, 1.5 Hz, **H9a**), 5.30 (1H, dd, *J* = 10.5, 1.1 Hz, **H9b**), 4.76 (2H, dt, *J* = 5.6, 1.3 Hz, **H7**), 3.88 (3H, s, **H11**), 3.48-3.39 (2H, m, **H1**), 2.55 (2H, t, *J* = 5.8 Hz, **H4**), 2.14-2.06 (2H, m, **H2**), 1.73-1.69 (2H, m, **H3**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 164.4 (**C10**), 163.8 (**C6**), 130.6 (**C8**), 119.5 (**C9**), 76.4 (**C5**), 67.4 (**C7**), 53.9 (**C11**), 51.9 (**C1**), 32.5 (**C4**), 24.0 (**C2**), 19.9 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{16}O_6S$ $[M+H]^+$ 277.0740, found 277.0735.

**IR:** $\nu_{max}$ (neat): 2939 (C–H), 2870 (C–H), 1733 (C=O) $cm^{-1}$.

### Allyl 2-(2-methylpropanoyl)-1,1-dioxo-thiane-2-carboxylate 202




**198** (300 mg, 1.37 mmol) was dissolved in THF (20 mL) and NaHMDS (1 M in THF, 1.51 mL, 1.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Isobutyryl chloride (150 µL, 1.51 mmol) was added dropwise, and the mixture was heated to 80 °C overnight. The reaction was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **202** (191 mg, 48%) as a yellow oil. $R_f$ = 0.32 [petrol:EtOAc 4:1].

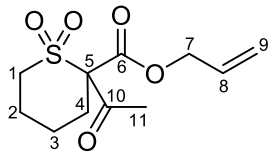
**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.92 (1H, ddt, *J* = 16.5, 10.4, 6.1 Hz, **H8**), 5.40 (1H, dq, *J* = 17.3, 1.4 Hz, **H9a**), 5.32 (1H, dd, *J* = 10.3, 1.2 Hz, **H9b**), 4.75 (2H, tt, *J* = 6.8, 1.2 Hz, **H7**), 3.66-3.59 (1H, m, **H1a**), 3.22 (1H, dt, *J* = 14.2, 4.8 Hz, **H1b**), 3.08 (1H, septet, *J* = 6.8 Hz, **H11**), 2.50 (1H, ddd, *J* = 15.1, 11.3, 3.3 Hz, **H4a**), 2.39 (1H, ddd, *J* = 15.4, 6.3, 3.3 Hz, **H4b**), 2.09-2.02 (2H, m, **H2**), 1.77-1.68 (1H, m, **H3a**), 1.59-1.50 (1H, m, **H3b**), 1.18 (3H, d, *J* = 6.5 Hz) and 1.14 (3H, d, *J* = 6.7 Hz) (**H12** and **H13**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 202.4 (**C10**), 165.2 (**C6**), 130.5 (**C8**), 120.8 (**C9**), 81.3 (**C4**), 67.5 (**C7**), 52.4 (**C1**), 40.6 (**C11**), 31.3 (**C4**), 24.0 (**C2**), 20.7, 19.9 and 19.9 (**C3**, **C11** and **C12**).

**HRMS (*m/z*):** (APCI) calcd for $C_{13}H_{20}O_5S$ $[M+H]^+$ 289.1104, found 289.1097.

**IR:** $\nu_{max}$ (neat): 2976 (C–H), 2939 (C–H), 2876 (C–H), 1744 (C=O), 1716 (C=O) $cm^{-1}$.

**Allyl 2-acetyl-1,1-dioxo-thiane-2-carboxylate 203**



**198** (300 mg, 1.37 mmol) was dissolved in THF (20 mL) and NaHMDS (1 M in THF, 1.51 mL, 1.51 mmol) was added dropwise. The solution was stirred at room temperature for 30 minutes. Acetyl chloride (110 µL, 1.51 mmol) was added dropwise, and the mixture was heated to 80 °C overnight. The reaction was allowed to cool to room temperature and was quenched with aq. HCl (1 N, 15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 9:1–4:1] gave **203** (132 mg, 37%) as a yellow oil. $R_f$ = 0.33 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.95-5.84 (1H, m, **H8**), 5.39 (1H, dq, *J* = 17.0, 1.4 Hz, **H9a**), 5.33 (1H, dq, *J* = 10.4, 1.1 Hz, **H9b**), 4.76 (2H, dq, *J* = 5.7, 1.5 Hz, **H7**), 3.69-3.60 (1H, m, **H1a**), 3.18 (1H, dt, *J* = 13.7, 4.3 Hz, **H1b**), 2.53-2.33 (5H, m, **H4** and **H11**), 2.13-2.01 (2H, m, **H2**), 1.83-1.73 (1H, m, **H3a**), 1.69-1.54 (1H, m, **H3b**).

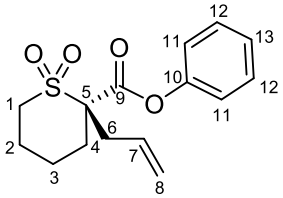
**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 194.2 (**C10**), 165.2 (**C6**), 130.2 (**C8**), 120.4 (**C9**), 80.6 (**C5**), 67.5 (**C7**), 52.2 (**C1**), 31.2 (**C4**), 29.7 (**C11**), 23.9 (**C2**), 19.8 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_{11}H_{16}O_5S$ $[M+H]^+$ 261.0791, found 261.0786.

**IR:** $\nu_{max}$ (neat): 2939 (C–H), 2870 (C–H), 1718 (C=O) $cm^{-1}$.

### 3.2.10 6-Membered Sulfone Pd-DAAA Reaction Products

**(*R*)-phenyl 2-allyl-1,1-dioxo-thiane-2-carboxylate 205**



**200** (40 mg, 0.12 mmol), $Pd_2(dba)_3$ (2.7 mg, 0.003 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (6.3 mg, 0.0078 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2

hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **205** (34 mg, 96%) as a yellow oil. $R_f$ = 0.21 [petrol:EtOAc 4:1].

**$^1$H NMR:** (400 MHz, $CDCl_3$) δ 7.45-7.39 (2H, m, **H11**), 7.29 (1H, tt, *J* = 6.9, 1.1 Hz, **H13**), 7.15-7.12 (2H, m, **H12**), 5.97 (1H, dddd, *J* = 16.8, 10.2, 8.6, 6.2 Hz, **H7**), 5.36-5.28 (2H, m, **H8**), 3.51-3.40 (1H, m, **H1a**), 3.33 (1H, ddt, *J* = 14.1, 6.0, 1.4 Hz, **H6a**), 3.14 (1H, dt, *J* = 14.1, 5.1 Hz, **H1b**), 2.77 (1H, dd, *J* = 14.4, 8.4 Hz, **H6b**), 2.47 (1H, ddd, *J* = 14.8, 6.4, 3.5 Hz, **H4a**), 2.22-2.11 (3H, m, **H2** and **H4b**), 1.95-1.85 (1H, m, **H3a**), 1.82-1.73 (1H, m, **H3b**).

**$^{13}$C NMR:** (100 MHz, $CDCl_3$) δ 167.1 (**C9**), 150.3 (**C10**), 130.8 (**C7**), 129.6 (**C11**), 126.6 (**C13**), 121.4 (**C12**), 120.8 (**C8**), 71.0 (**C5**), 50.4 (**C1**), 35.6 (**C6**), 33.1 (**C4**), 24.0 (**C2**), 20.4 (**C3**).

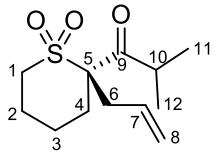
**HRMS (*m/z*):** (APCI) calcd for $C_{15}H_{18}O_4S$ $[M+H]^+$ 295.0999, found 295.0985.

**IR:** $\nu_{max}$ (neat): 3079 (C–H), 2935 (C–H), 2856 (C–H), 1750 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALPAK AD-H, 1 mL/min, 90:10 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 11.8 min, $t_B$ (minor) = 14.5 min. 64% ee.

**$[\alpha]_D^{20}$**: –55.1 (*c* 0.245, $CHCl_3$).

### (*R*)-1-(2-allyl-1,1-dioxo-thian-2-yl)-2-methyl-propan-1-one 207




**202** (40 mg, 0.14 mmol), $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (14.8 mg, 0.018 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **207** (32 mg, 94%) as a yellow oil. $R_f$ = 0.22 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.49 (1H, dddd, *J* = 16.7, 10.0, 8.5, 5.6 Hz, **H7**), 5.24-5.16 (2H, m, **H8**), 3.48 (1H, septet, *J* = 6.9 Hz, **H10**), 3.27-3.00 (3H, m, **H1** and **H6a**), 2.74 (1H, dd, *J* = 15.2, 8.5 Hz, **H6b**), 2.28 (1H, ddd, *J* = 14.8, 10.2, 3.8 Hz, **H4a**), 2.11-2.00 (3H, m, **H2** and **H4b**), 1.78-1.66 (1H, m, **H3a**), 1.63-1.50 (1H, m, **H3b**), 1.16 (3H, d, *J* = 6.6 Hz) and 1.13 (3H, d, *J* = 6.6 Hz) (**H11** and **H12**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 209.4 (**C9**), 130.3 (**C7**), 120.5 (**C8**), 75.7 (**C5**), 50.9 (**C1**), 37.3 (**C10**), 34.6 (**C6**), 29.6 (**C4**), 24.1 (**C2**), 30.4 and 20.2 (**C11** and **C12**), 19.7 (**C3**).

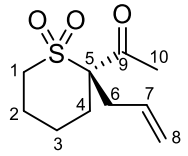
**HRMS (*m/z*):** (APCI) calcd for $C_{12}H_{20}O_3S$ $[M+H]^+$ 245.1206, found 245.1208.

**IR:** $\nu_{max}$ (neat): 2973 (C–H), 2937 (C–H), 2874 (C–H), 1709 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALPAK AD-H, 1 mL/min, 90:10 hexane:*i*-PrOH, 30.0 °C, $t_A$ (minor) = 7.3 min, $t_B$ (major) = 7.8 min. 88% ee.

**$[\alpha]_D^{20}$**: –167.5 (*c* 0.20, $CHCl_3$).

**(*R*)-1-(2-Allyl-1,1-dioxo-thian-2-yl)ethanone 208**




**203** (40 mg, 0.15 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.010 mmol) and (*S,S*)-ANDEN Phenyl Trost ligand (15.8 mg, 0.020 mmol) were stirred in 1,4-dioxane (1 mL) at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [hexane:EtOAc 4:1] gave **208** (30 mg, 93%) as a yellow oil. $R_f$ = 0.20 [petrol:EtOAc 4:1].

**$^1$H NMR:** (300 MHz, $CDCl_3$) δ 5.62-5.49 (1H, m, **H7**), 5.24-5.17 (2H, m, **H8**), 3.22-2.99 (3H, m, **H1** and **H6a**), 2.69 (1H, dd, *J* = 14.4, 7.7 Hz, **H6b**), 2.43 (3H, s, **H10**), 2.32 (1H, ddd, *J* = 14.7, 9.3, 3.5 Hz, **H4a**), 2.10-1.98 (3H, m, **H2** and **H4b**), 1.85-1.72 (1H, m, **H3a**), 1.66-1.54 (1H, m, **H3b**).

**$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 201.7 (**C9**), 129.8 (**C7**), 120.7 (**C8**), 75.2 (**C5**), 50.6 (**C1**), 35.0 (**C6**), 30.1 (**C4**), 28.9 (**C2**), 20.0 (**C3**).

**HRMS (*m/z*):** (APCI) calcd for $C_{10}H_{16}O_3S$ $[M+H]^+$ 217.0893, found 217.0884.

**IR:** $\nu_{max}$ (neat): 2941 (C–H), 2868 (C–H), 1709 (C=O) $cm^{-1}$.

**Chiral HPLC:** CHIRALCEL OD-H, 1 mL/min, 95:5 hexane:*i*-PrOH, 30.0 °C, $t_A$ (major) = 16.3 min, $t_B$ (minor) = 17.9 min. 32% ee.

**$[\alpha]_D^{20}$**: –55.1 (*c* 0.336, $CHCl_3$).

### 3.2.11 Chiral HPLC Traces

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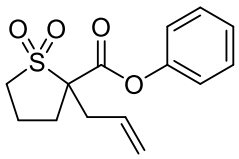
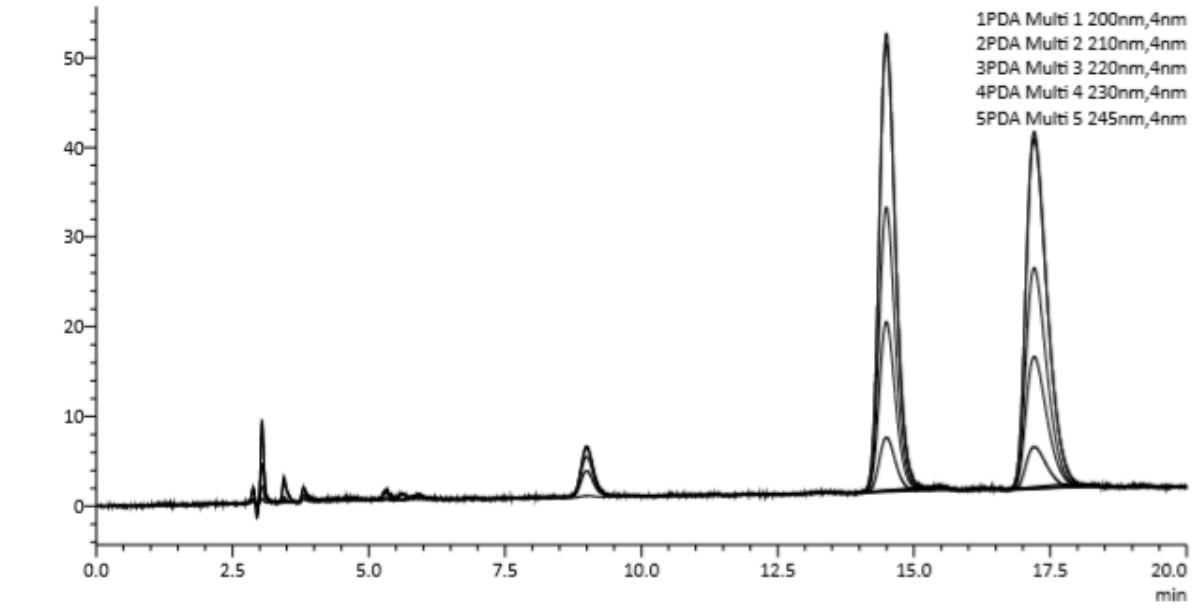
## Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-011-2 |
| Sample ID | : EPB-011-RAC-181121-002 |
| Data File | : EPB-011-2-RAC-181121-002.lcd |
| Batch File | : Batch-181120-002.lcb |
| Vial# | : 2 |
| Injecti o Volume | : 5 |
| Method File | : Method_181120.lcm |
| Date Acquired | : 21/11/2018 11:38:59 |
| Date Processed | : 21/11/2018 13:49:46 |



**121**

Chromatogram
EPB-011-2 EPB-011-2-RAC-181121-002.lcd




Peak Table

PDA Ch1 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.496 | 1055507 | 50.081 | M |
| | 2 | 17.206 | 1052095 | 49.919 | M |
| | Total | | 2107602 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.496 | 1079097 | 49.965 | M |
| | 2 | 17.206 | 1080602 | 50.035 | M |
| | Total | | 2159699 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.495 | 666365 | 50.052 | M |
| | 2 | 17.206 | 664983 | 49.948 | M |
| | Total | | 1331349 | 100.000 | |

PDA Ch4 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.496 | 392858 | 50.043 | M |
| | 2 | 17.207 | 392187 | 49.957 | M |
| | Total | | 785045 | 100.000 | |

PDA Ch5 245nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.497 | 127130 | 50.196 | M |
| | 2 | 17.208 | 126135 | 49.804 | M |
| | Total | | 253265 | 100.000 | |

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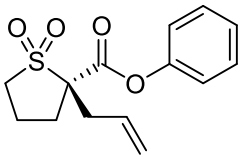
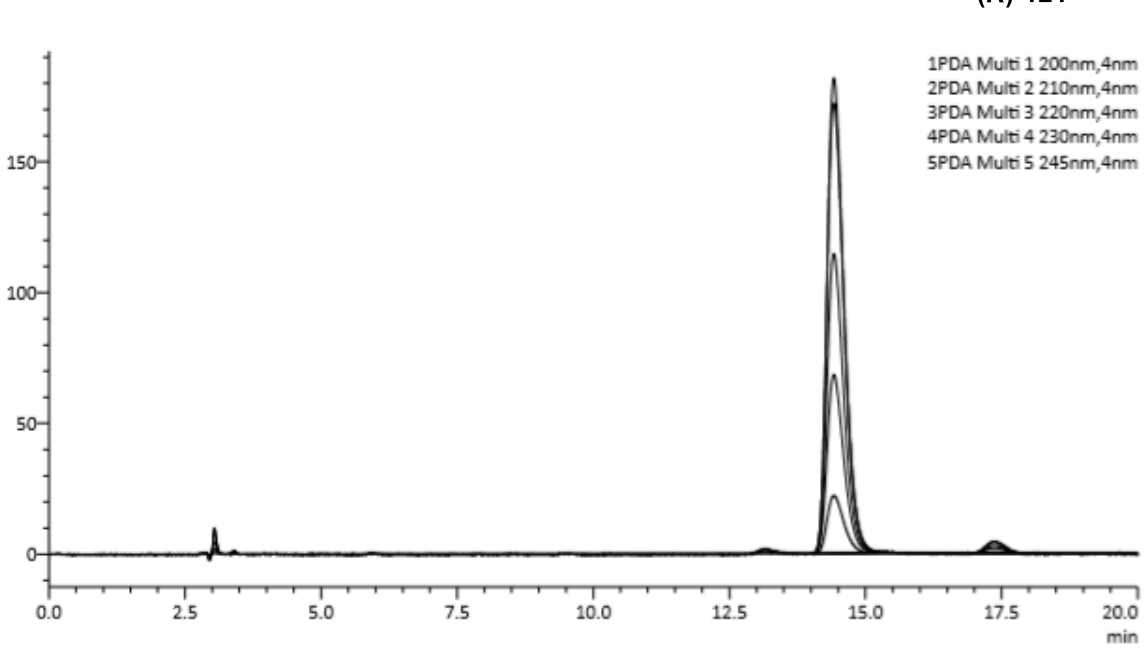
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-013-2 |
| Sample ID | : EPB-013-2-NOADD-181121-002 |
| Data File | : EPB-013-2-NOADD-181121-002.lcd |
| Batch File | : Batch-181120-002.lcb |
| Vial# | : 4 |
| Injecti ø Volume | : 5 |
| Method File | : Method_181120.lcm |
| Date Acquired | : 21/11/2018 12:19:41 |
| Date Processed | : 21/11/2018 13:58:48 |



**(*R*)-121**

Chromatogram
EPB-013-2 EPB-013-2-NOADD-181121-002.lcd




Peak Table

PDA Ch1 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.420 | 3779047 | 96.894 | M |
| | 2 | 17.378 | 121146 | 3.106 | SV |
| | Total | | 3900193 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.420 | 3982461 | 97.011 | S |
| | 2 | 17.366 | 122720 | 2.989 | |
| | Total | | 4105180 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.420 | 2475480 | 96.999 | |
| | 2 | 17.364 | 76580 | 3.001 | |
| | Total | | 2552060 | 100.000 | |

PDA Ch4 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.420 | 1471840 | 97.091 | |
| | 2 | 17.370 | 44099 | 2.909 | |
| | Total | | 1515939 | 100.000 | |

PDA Ch5 245nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 14.420 | 476872 | 97.445 | |
| | 2 | 17.372 | 12504 | 2.555 | |
| | Total | | 489376 | 100.000 | |

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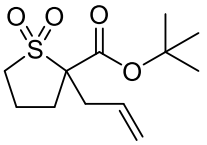
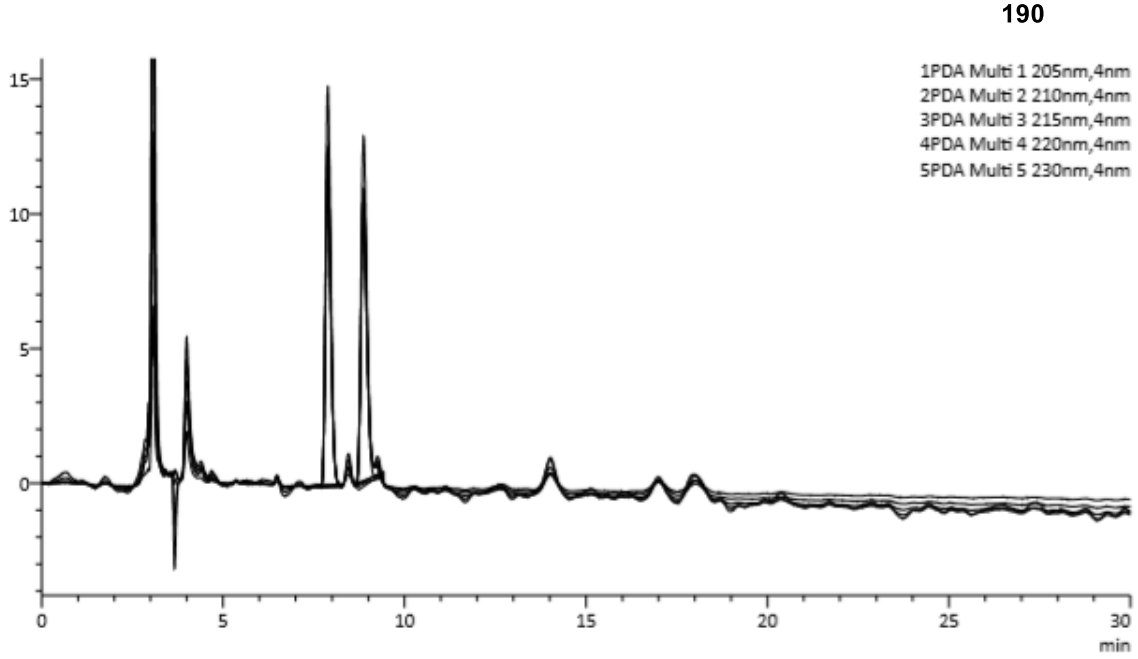
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-133A-2-RAC |
| Sample ID | : EPB-133A-2-RAC |
| Data File | : EPB-133A-2-RAC-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 3 |
| Injecti o Volume | : 7 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/09/2019 13:39:47 |
| Date Processed | : 09/09/2019 08:35:37 |



**190**

Chromatogram
EPB-133A-2-RAC EPB-133A-2-RAC-001.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.886 | 153650 | 49.300 | M |
| | 2 | 8.873 | 158013 | 50.700 | M |
| | Total | | 311664 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.886 | 131536 | 49.548 | |
| | 2 | 8.873 | 133938 | 50.452 | M |
| | Total | | 265474 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.886 | 124978 | 50.157 | M |
| | 2 | 8.873 | 124194 | 49.843 | M |
| | Total | | 249172 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.886 | 129103 | 49.682 | M |
| | 2 | 8.873 | 130756 | 50.318 | M |
| | Total | | 259859 | 100.000 | |

PDA Ch5 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.886 | 115529 | 50.303 | M |
| | 2 | 8.873 | 114136 | 49.697 | M |
| | Total | | 229666 | 100.000 | |

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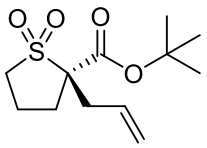
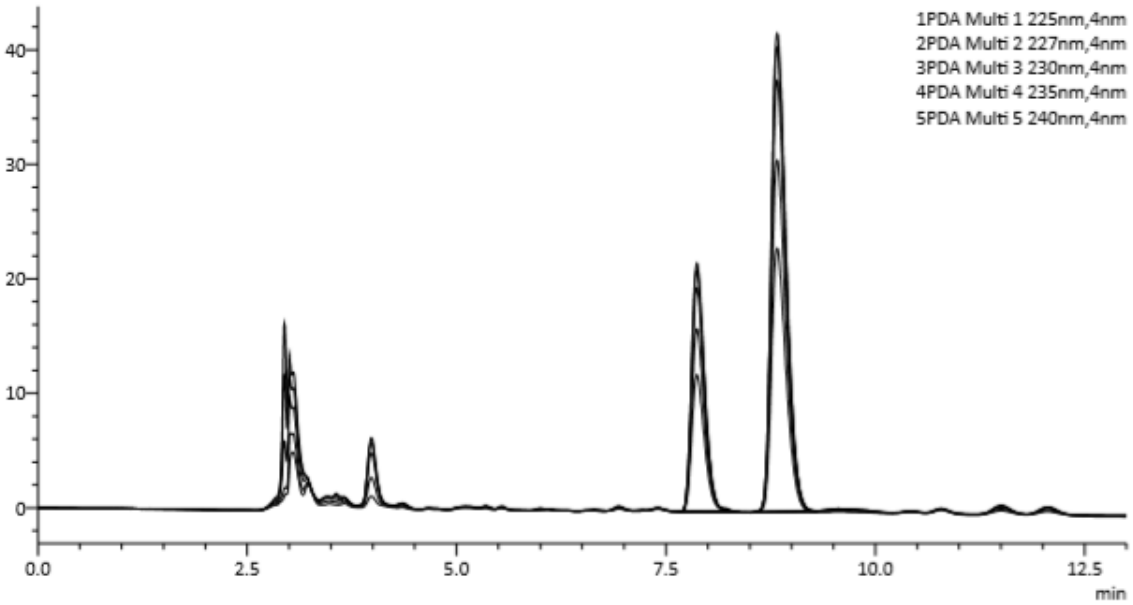
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-133B |
| Sample ID | : EPB-133B |
| Data File | : EPB-133B.lcd |
| Batch File | : BATCH190909.lcb |
| Vial# | : 9 |
| Injecti ɑ Volume | : 11 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 09/09/2019 15:26:19 |
| Date Processed | : 10/09/2019 09:18:16 |



(*R*)-**190**

Chromatogram
EPB-133B EPB-133B.lcd




Peak Table

PDA Ch1 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.870 | 234661 | 31.223 | |
| | 2 | 8.829 | 516900 | 68.777 | |
| | Total | | 751561 | 100.000 | |

PDA Ch2 227nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.870 | 227648 | 31.212 | |
| | 2 | 8.829 | 501720 | 68.788 | |
| | Total | | 729368 | 100.000 | |

PDA Ch3 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.870 | 211211 | 31.226 | |
| | 2 | 8.829 | 465181 | 68.774 | |
| | Total | | 676392 | 100.000 | |

PDA Ch4 235nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.870 | 173378 | 31.323 | |
| | 2 | 8.829 | 380135 | 68.677 | |
| | Total | | 553512 | 100.000 | |

PDA Ch5 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 7.870 | 129034 | 31.148 | M |
| | 2 | 8.829 | 285220 | 68.852 | |
| | Total | | 414254 | 100.000 | |

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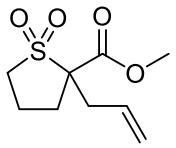
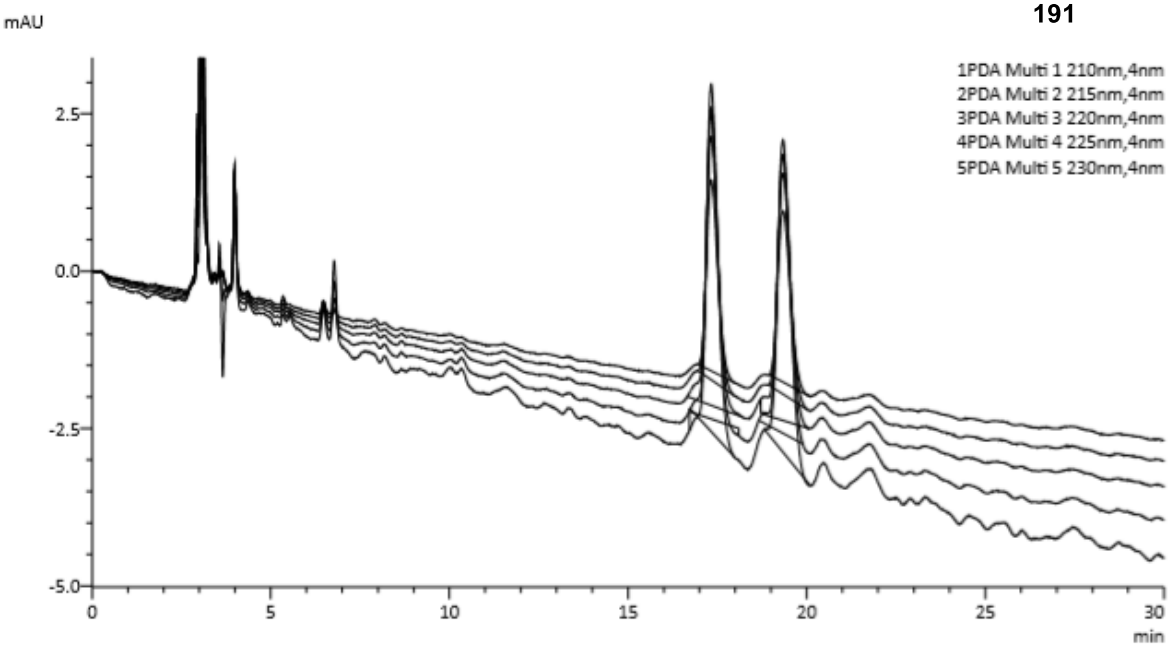
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-134A-2-RAC |
| Sample ID | : EPB-134A-2-RAC |
| Data File | : EPB-134A-2-RAC-002.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 4 |
| Injecti o Volume | : 5 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/09/2019 21:37:27 |
| Date Processed | : 09/09/2019 12:33:28 |



**191**

Chromatogram
EPB-134A-2-RAC EPB-134A-2-RAC-002.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.330 | 118663 | 49.087 | M |
| | 2 | 19.340 | 123079 | 50.913 | M |
| | Total | | 241743 | 100.000 | |

PDA Ch2 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.331 | 111417 | 49.850 | M |
| | 2 | 19.340 | 112087 | 50.150 | M |
| | Total | | 223505 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.331 | 109921 | 49.606 | M |
| | 2 | 19.340 | 111669 | 50.394 | M |
| | Total | | 221590 | 100.000 | |

PDA Ch4 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.330 | 84331 | 49.602 | |
| | 2 | 19.340 | 85683 | 50.398 | |
| | Total | | 170014 | 100.000 | |

PDA Ch5 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.331 | 66421 | 49.899 | |
| | 2 | 19.341 | 66690 | 50.101 | |
| | Total | | 133111 | 100.000 | |

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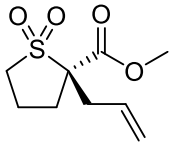
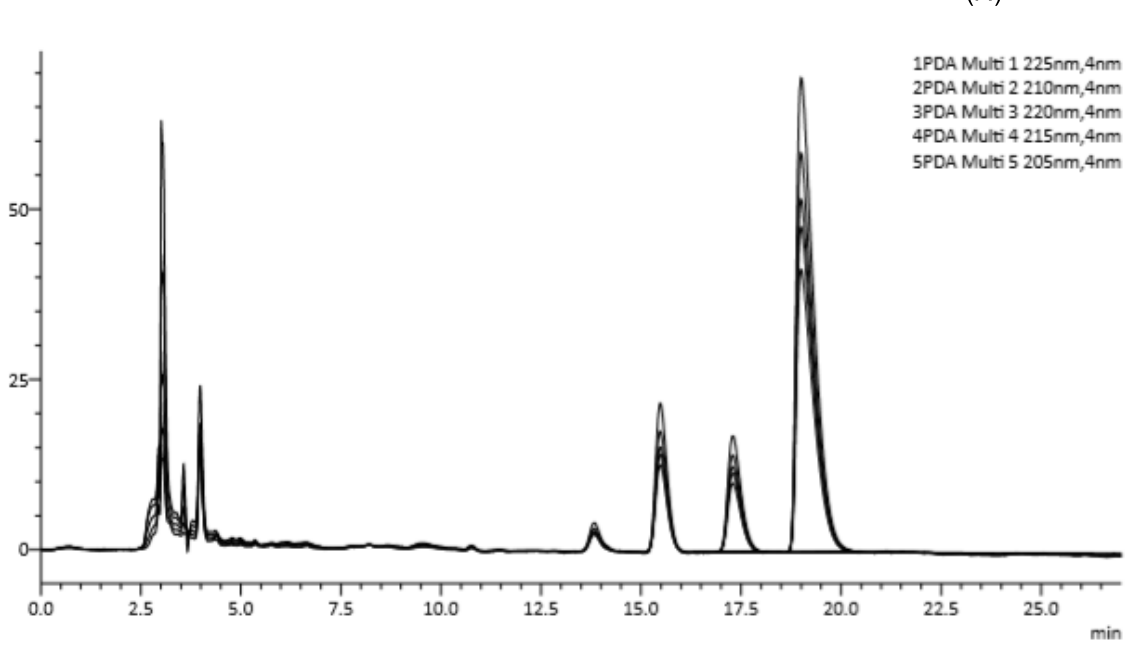
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-134B |
| Sample ID | : EPB-134B |
| Data File | : EPB-134B.lcd |
| Batch File | : BATCH190909.lcb |
| Vial# | : 10 |
| Injecti o Volume | : 10 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 09/09/2019 16:12:05 |
| Date Processed | : 10/09/2019 09:20:33 |



(*R*)-**191**

Chromatogram
EPB-134B EPB-134B.lcd




Peak Table

PDA Ch1 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.297 | 230644 | 15.533 | |
| | 2 | 19.004 | 1254228 | 84.467 | |
| | Total | | 1484871 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.297 | 330845 | 15.686 | |
| | 2 | 19.004 | 1778351 | 84.314 | |
| | Total | | 2109197 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.297 | 266072 | 15.563 | |
| | 2 | 19.004 | 1443524 | 84.437 | |
| | Total | | 1709596 | 100.000 | |

PDA Ch4 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.297 | 290227 | 15.611 | |
| | 2 | 19.004 | 1568848 | 84.389 | |
| | Total | | 1859076 | 100.000 | |

PDA Ch5 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 17.297 | 399603 | 15.891 | |
| | 2 | 19.004 | 2115058 | 84.109 | |
| | Total | | 2514661 | 100.000 | |

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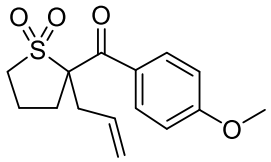
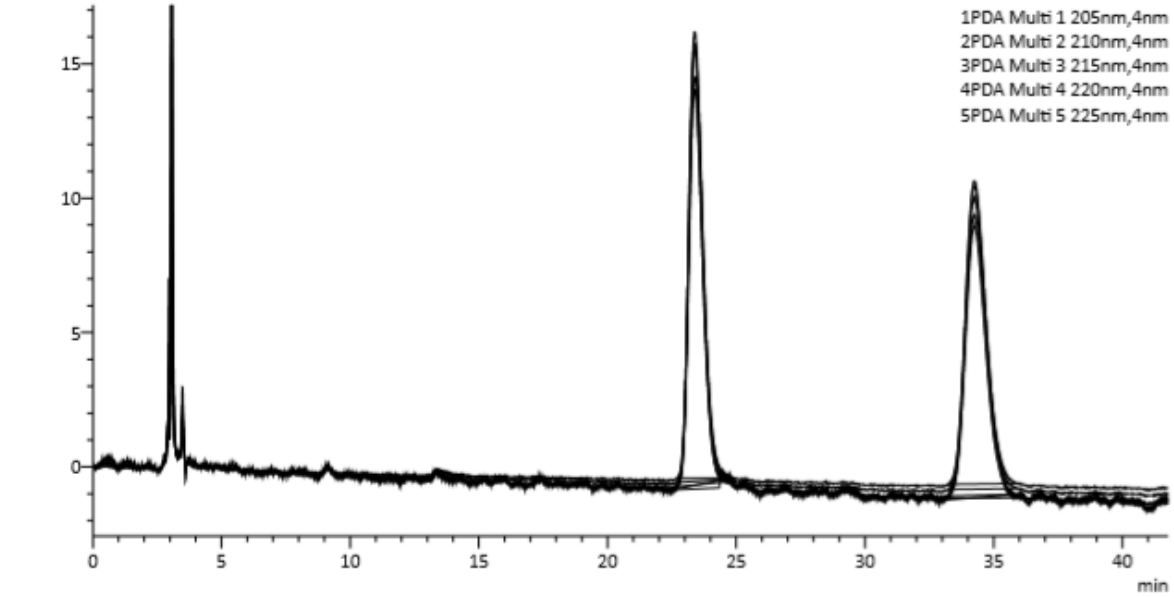
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-136A-2-90:10-002 |
| Sample ID | : EPB-136A-2-90:10-002 |
| Data File | : EPB-136A-2-90.10-002.lcd |
| Batch File | : BATCH.lcb |
| Vial# | : 3 |
| Injecti o Volume | : 11 |
| Method File | : Method_181214.lcm |
| Date Acquired | : 12/09/2019 11:57:20 |
| Date Processed | : 12/09/2019 15:55:13 |



**192**

Chromatogram
EPB-136A-2-90:10-002 EPB-136A-2-90.10-002.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 23.393 | 635470 | 49.847 | M |
| | 2 | 34.254 | 639363 | 50.153 | V |
| | Total | | 1274833 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 23.393 | 557490 | 49.306 | |
| | 2 | 34.255 | 573192 | 50.694 | |
| | Total | | 1130681 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 23.389 | 582959 | 49.739 | |
| | 2 | 34.259 | 589084 | 50.261 | |
| | Total | | 1172043 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 23.389 | 647650 | 49.909 | |
| | 2 | 34.253 | 650000 | 50.091 | |
| | Total | | 1297650 | 100.000 | |

PDA Ch5 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 23.388 | 631884 | 50.167 | |
| | 2 | 34.254 | 627681 | 49.833 | |
| | Total | | 1259565 | 100.000 | |

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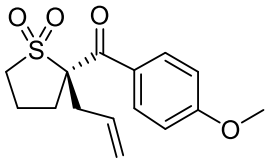
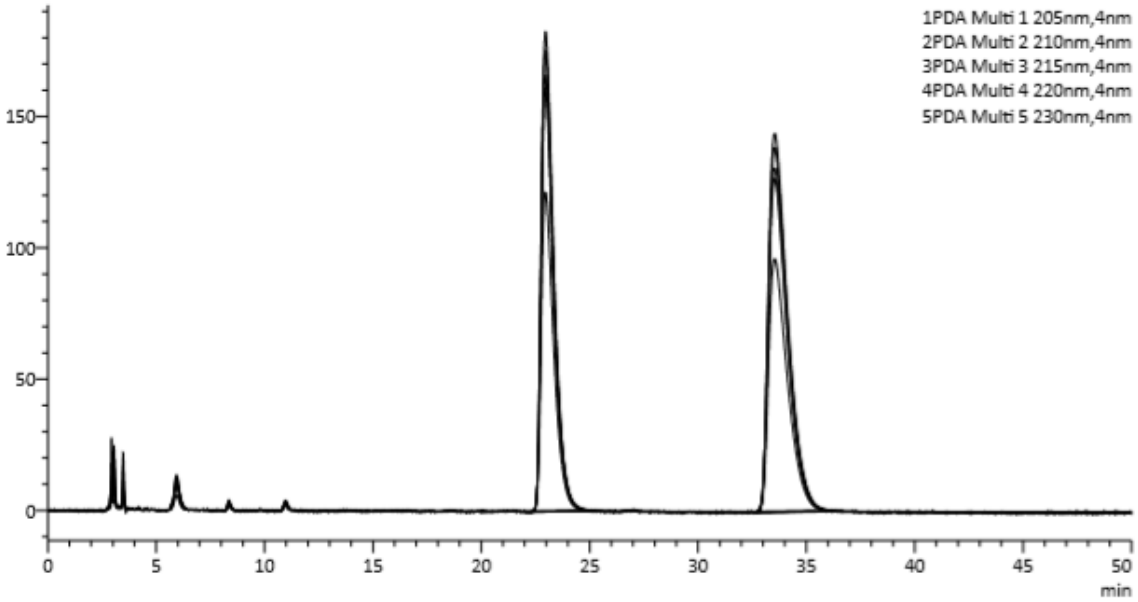
# Chiral HPLC Analysis

Sample Name : EPB-136B-2-90:10
Sample ID : EPB-136B-2-90:10
Data File : EPB-136B-2-90.10.lcd
Batch File : BATCH.lcb
Vial# : 5
Injecti o Volume : 10
Method File : Method_181214.lcm
Date Acquired : 12/09/2019 13:29:51
Date Processed : 12/09/2019 15:54:34



(*R*)-**192**

Chromatogram
EPB-136B-2-90:10 EPB-136B-2-90.10.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 22.966 | 7188263 | 45.527 | M |
| | 2 | 33.540 | 8600821 | 54.473 | M |
| | Total | | 15789084 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 22.967 | 6588259 | 45.634 | |
| | 2 | 33.541 | 7848875 | 54.366 | |
| | Total | | 14437134 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 22.967 | 6775519 | 45.581 | |
| | 2 | 33.541 | 8089400 | 54.419 | |
| | Total | | 14864918 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 22.967 | 7470700 | 45.652 | |
| | 2 | 33.540 | 8893698 | 54.348 | |
| | Total | | 16364398 | 100.000 | |

PDA Ch5 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 22.967 | 4976701 | 45.544 | |
| | 2 | 33.541 | 5950520 | 54.456 | |
| | Total | | 10927221 | 100.000 | |

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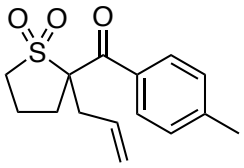
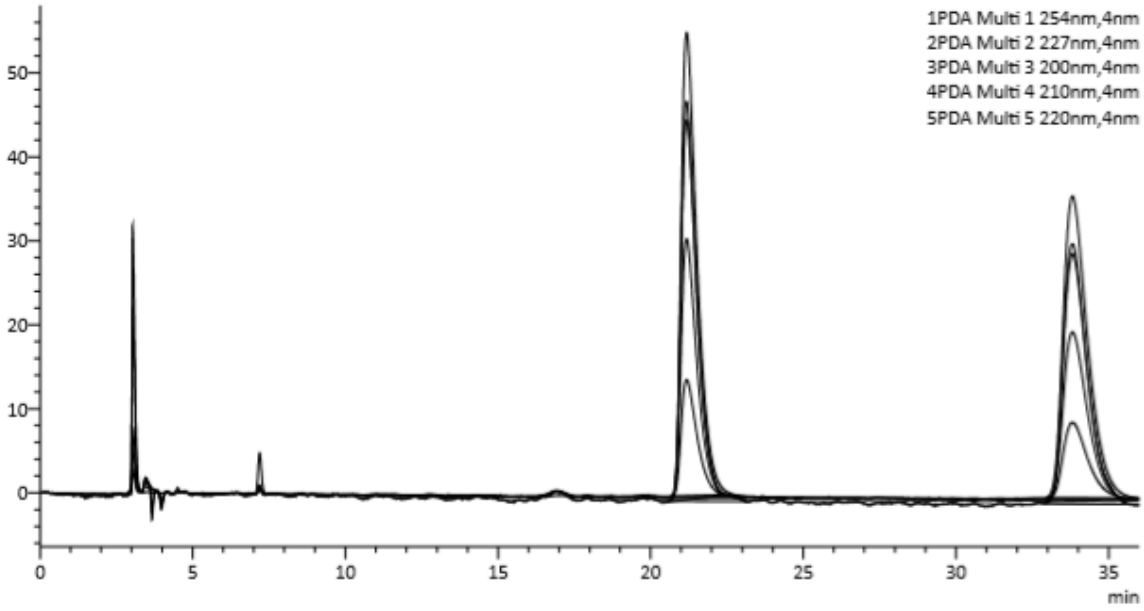
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-094A-2-RAC |
| Sample ID | : EPB-094A-2-RAC-001 |
| Data File | : EPB-094A-2-RAC-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 8 |
| Injecti o Volume | : 2 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 16:41:58 |
| Date Processed | : 24/08/2019 13:29:28 |



**124**

Chromatogram
EPB-094A-2-RAC EPB-094A-2-RAC-001.lcd




Peak Table

PDA Ch1 254nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.180 | 2044803 | 50.265 | |
| | 2 | 33.815 | 2023220 | 49.735 | |
| | Total | | 4068023 | 100.000 | |

PDA Ch2 227nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.180 | 502134 | 49.950 | |
| | 2 | 33.816 | 503131 | 50.050 | |
| | Total | | 1005265 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.181 | 1640861 | 49.711 | |
| | 2 | 33.822 | 1659963 | 50.289 | |
| | Total | | 3300823 | 100.000 | |

PDA Ch4 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.179 | 1774063 | 50.626 | |
| | 2 | 33.818 | 1730198 | 49.374 | |
| | Total | | 3504261 | 100.000 | |

PDA Ch5 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.181 | 1145113 | 50.319 | |
| | 2 | 33.817 | 1130611 | 49.681 | |
| | Total | | 2275724 | 100.000 | |

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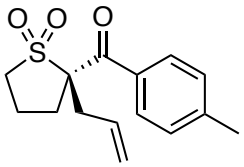
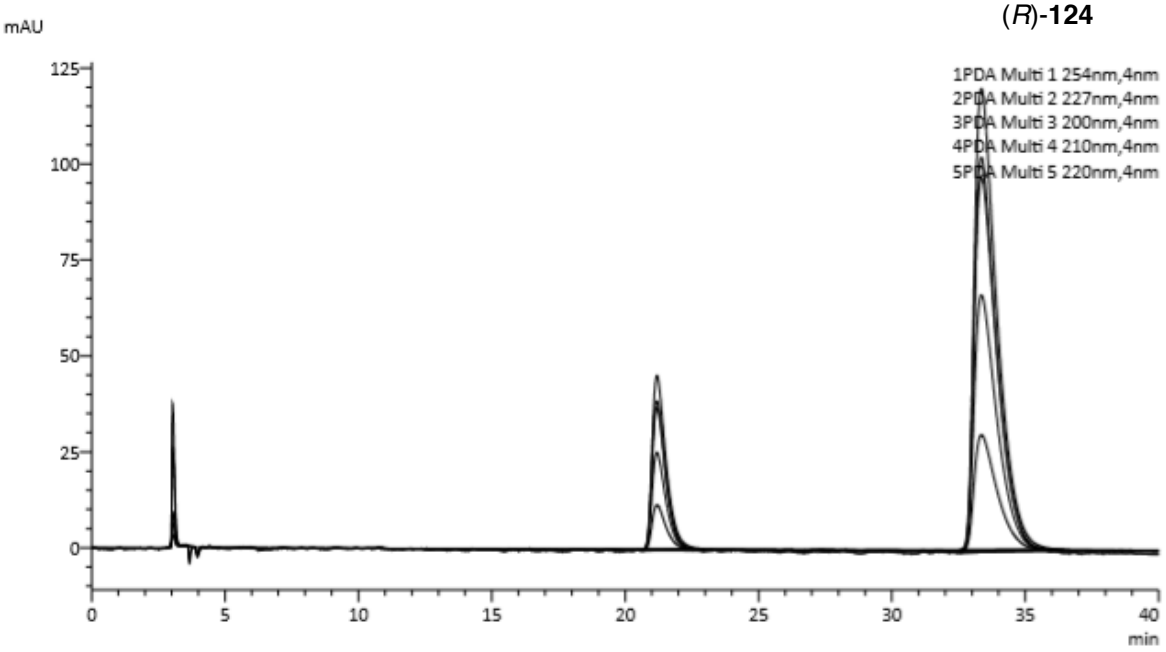
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-094B-2 |
| Sample ID | : EPB-094B-2-001 |
| Data File | : EPB-094B-2-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 9 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 20:10:56 |
| Date Processed | : 22/08/2019 20:50:57 |



(*R*)-**124**

Chromatogram
EPB-094B-2 EPB-094B-2-001.lcd




Peak Table

PDA Ch1 254nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.193 | 1656494 | 18.718 | |
| | 2 | 33.358 | 7193028 | 81.282 | |
| | Total | | 8849522 | 100.000 | |

PDA Ch2 227nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.194 | 420115 | 18.900 | |
| | 2 | 33.360 | 1802727 | 81.100 | |
| | Total | | 2222842 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.196 | 1333343 | 18.652 | M |
| | 2 | 33.358 | 5815244 | 81.348 | M |
| | Total | | 7148587 | 100.000 | |

PDA Ch4 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.193 | 1432633 | 18.839 | |
| | 2 | 33.360 | 6171832 | 81.161 | |
| | Total | | 7604464 | 100.000 | |

PDA Ch5 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 21.193 | 930910 | 18.895 | |
| | 2 | 33.359 | 3995913 | 81.105 | |
| | Total | | 4926823 | 100.000 | |

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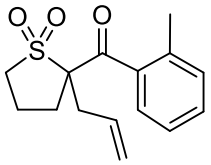
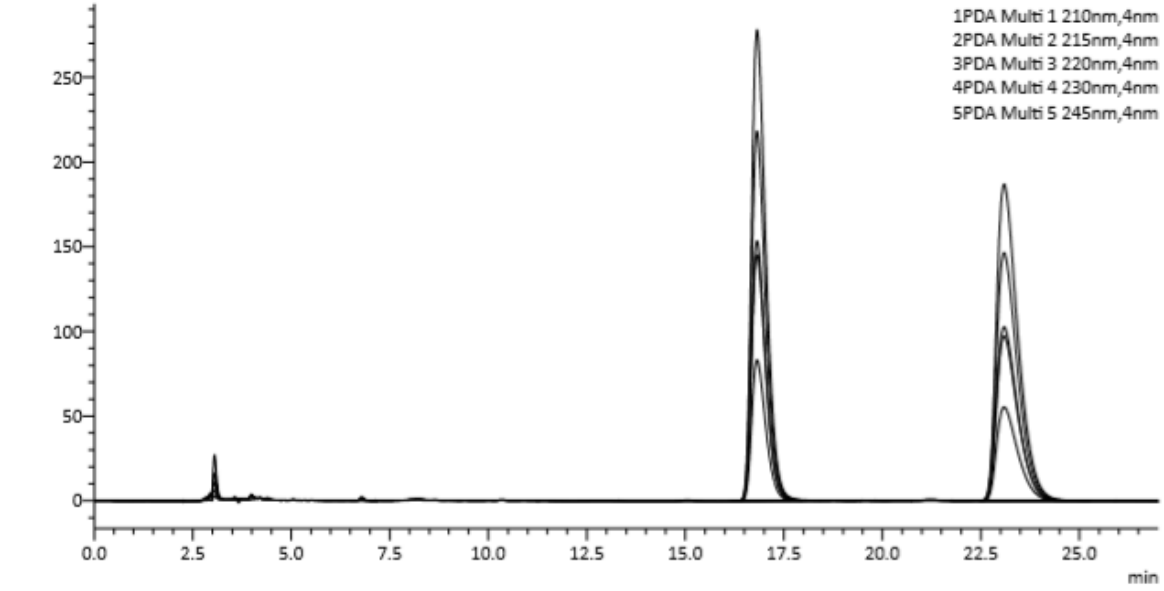
# Chiral HPLC Analysis

Sample Name : EPB-137A
Sample ID : EPB-137A
Data File : EPB-137A.lcd
Batch File : BATCH190909.lcb
Vial# : 7
Injecti o Volume : 7
Method File : Basicmethod2-25min.lcm
Date Acquired : 09/09/2019 16:42:35
Date Processed : 09/09/2019 17:09:37



**193**

Chromatogram
EPB-137A EPB-137A.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.822 | 7122659 | 50.029 | |
| | 2 | 23.090 | 7114282 | 49.971 | |
| | Total | | 14236942 | 100.000 | |

PDA Ch2 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.822 | 5582531 | 50.051 | |
| | 2 | 23.090 | 5571144 | 49.949 | |
| | Total | | 11153675 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.822 | 3910325 | 50.049 | |
| | 2 | 23.090 | 3902711 | 49.951 | |
| | Total | | 7813036 | 100.000 | |

PDA Ch4 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.822 | 2105448 | 50.152 | |
| | 2 | 23.090 | 2092648 | 49.848 | |
| | Total | | 4198096 | 100.000 | |

PDA Ch5 245nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.822 | 3671092 | 49.891 | |
| | 2 | 23.090 | 3687085 | 50.109 | |
| | Total | | 7358176 | 100.000 | |

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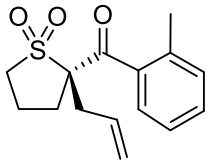
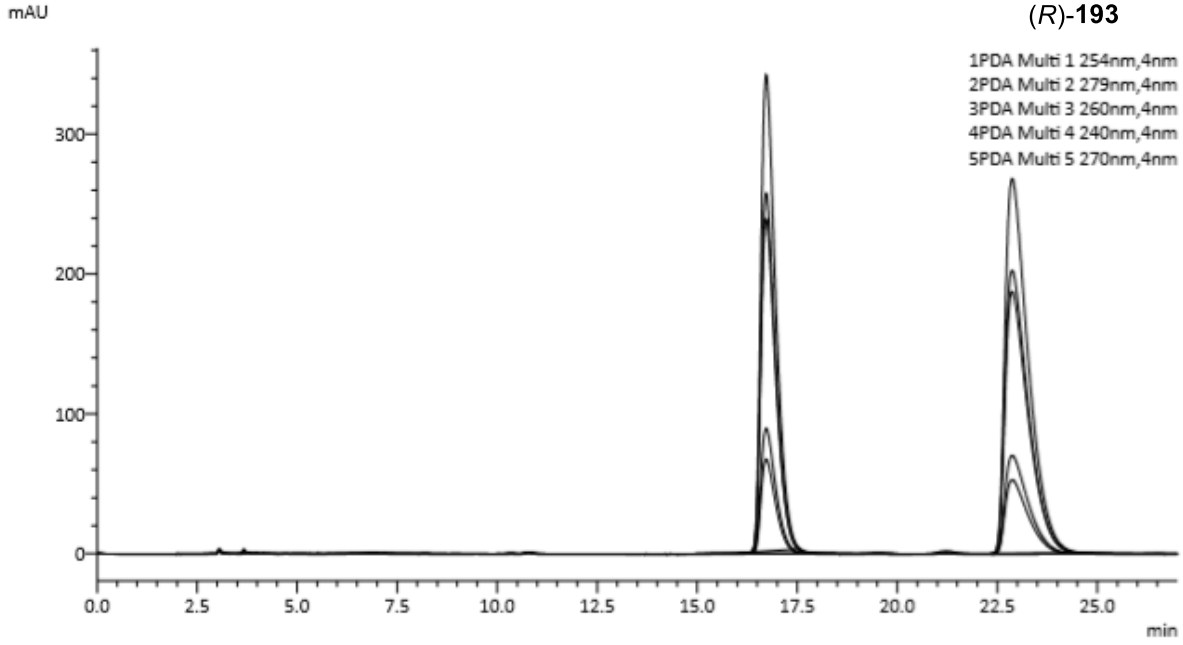
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-137B |
| Sample ID | : EPB-137B |
| Data File | : EPB-137B.lcd |
| Batch File | : BATCH190909.lcb |
| Vial# | : 13 |
| Injecti o Volume | : 7 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 09/09/2019 17:13:03 |
| Date Processed | : 10/09/2019 09:21:23 |



(*R*)-**193**

Chromatogram
EPB-137B EPB-137B.lcd




Peak Table

PDA Ch1 254nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.723 | 8818932 | 44.805 | M |
| | 2 | 22.872 | 10863775 | 55.195 | M |
| | Total | | 19682707 | 100.000 | |

PDA Ch2 279nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.724 | 1773230 | 45.060 | |
| | 2 | 22.873 | 2162031 | 54.940 | |
| | Total | | 3935260 | 100.000 | |

PDA Ch3 260nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.723 | 6815703 | 45.121 | |
| | 2 | 22.872 | 8289558 | 54.879 | |
| | Total | | 15105261 | 100.000 | |

PDA Ch4 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.723 | 6283244 | 45.111 | |
| | 2 | 22.873 | 7645044 | 54.889 | |
| | Total | | 13928288 | 100.000 | |

PDA Ch5 270nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.724 | 2370293 | 45.234 | |
| | 2 | 22.873 | 2869732 | 54.766 | |
| | Total | | 5240026 | 100.000 | |

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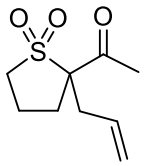
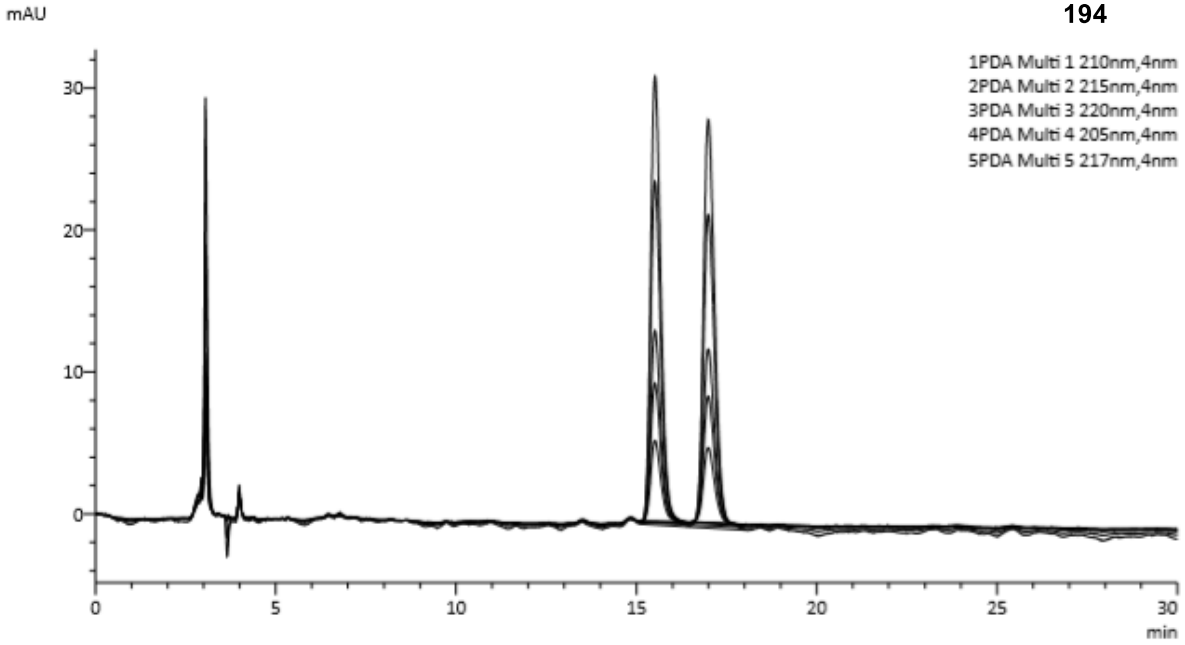
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-138A-2-RAC |
| Sample ID | : EPB-138A-2-RAC |
| Data File | : EPB-138A-2-RAC001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 8 |
| Injecti o Volume | : 5 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/09/2019 23:39:26 |
| Date Processed | : 09/09/2019 12:35:44 |



**194**

Chromatogram
EPB-138A-2-RAC EPB-138A-2-RAC001.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.519 | 478971 | 49.914 | |
| | 2 | 16.997 | 480618 | 50.086 | V |
| | Total | | 959588 | 100.000 | |

PDA Ch2 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.519 | 267218 | 49.993 | |
| | 2 | 16.997 | 267292 | 50.007 | |
| | Total | | 534510 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.520 | 114637 | 50.086 | |
| | 2 | 16.996 | 114243 | 49.914 | |
| | Total | | 228880 | 100.000 | |

PDA Ch4 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.519 | 629938 | 49.854 | |
| | 2 | 16.996 | 633636 | 50.146 | V |
| | Total | | 1263574 | 100.000 | |

PDA Ch5 217nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.519 | 193969 | 49.935 | |
| | 2 | 16.997 | 194473 | 50.065 | |
| | Total | | 388442 | 100.000 | |

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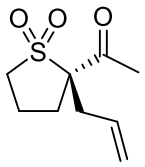
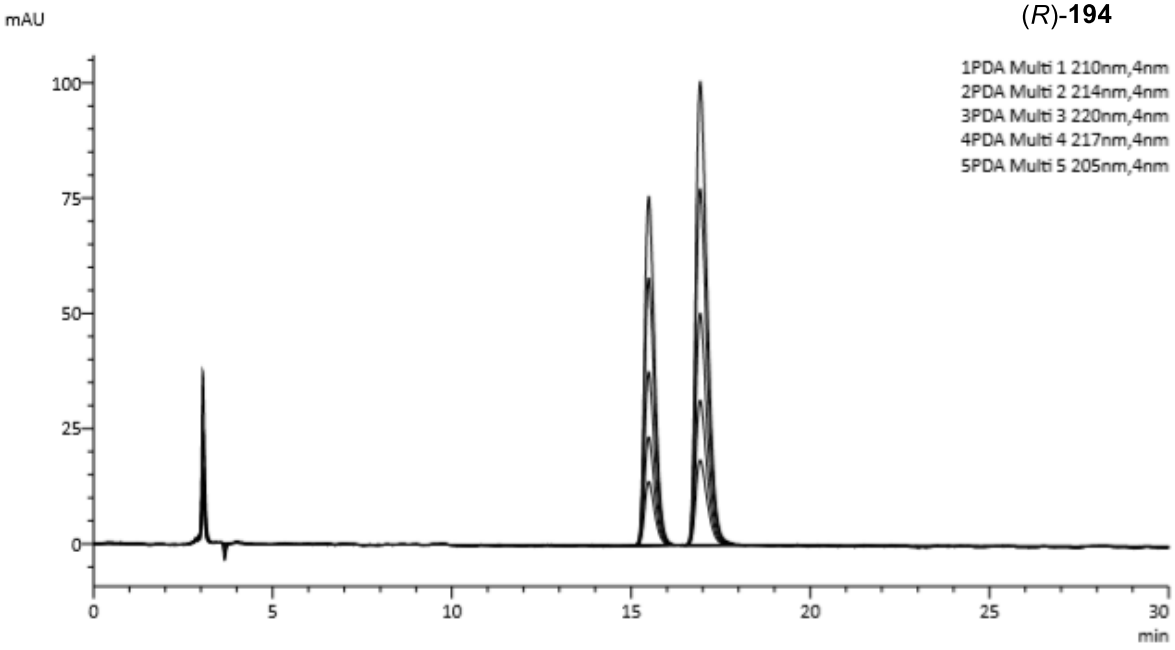
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-138B |
| Sample ID | : EPB-138B |
| Data File | : EPB-138B.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 14 |
| Injecti o Volume | : 7 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/09/2019 19:45:48 |
| Date Processed | : 09/09/2019 15:06:19 |



(*R*)-**194**

Chromatogram
EPB-138B EPB-138B.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.495 | 1146211 | 39.595 | |
| | 2 | 16.929 | 1748620 | 60.405 | |
| | Total | | 2894831 | 100.000 | |

PDA Ch2 214nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.495 | 744319 | 39.637 | |
| | 2 | 16.930 | 1133519 | 60.363 | |
| | Total | | 1877838 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.495 | 272001 | 39.598 | |
| | 2 | 16.931 | 414909 | 60.402 | |
| | Total | | 686909 | 100.000 | |

PDA Ch4 217nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.495 | 464432 | 39.617 | |
| | 2 | 16.930 | 707863 | 60.383 | |
| | Total | | 1172294 | 100.000 | |

PDA Ch5 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 15.495 | 1505581 | 39.736 | |
| | 2 | 16.929 | 2283353 | 60.264 | |
| | Total | | 3788934 | 100.000 | |

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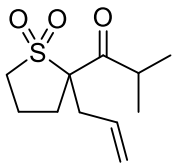
# Chiral HPLC Analysis

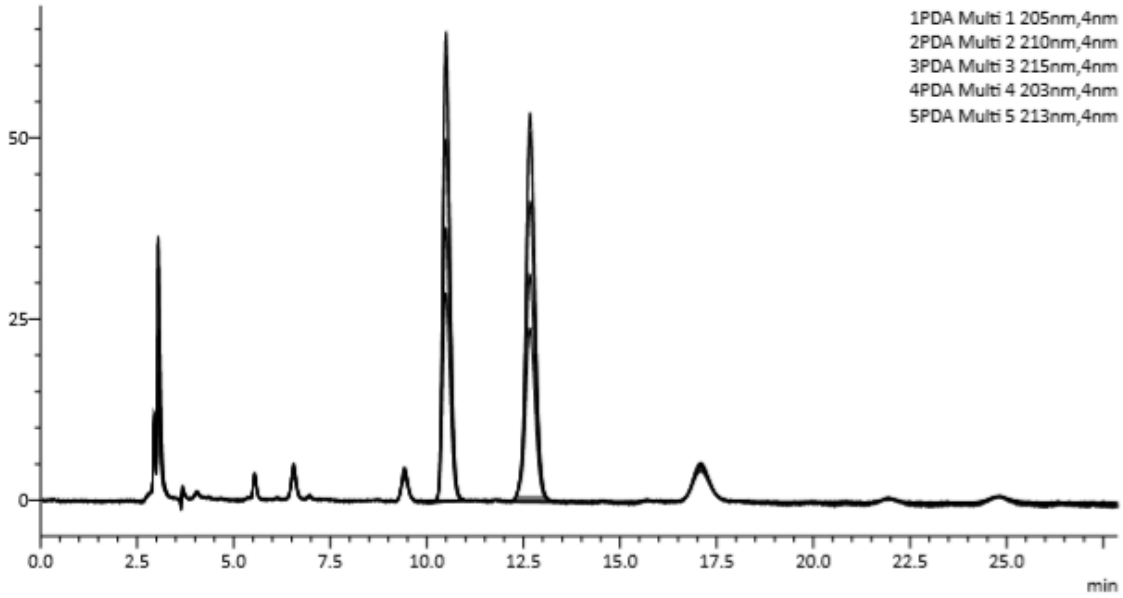
| | |
|---|---|
| Sample Name | : EPB-143A |
| Sample ID | : EPB-143A |
| Data File | : EPB-143A.lcd |
| Batch File | : BATCH021019.lcb |
| Vial# | : 4 |
| Injecti o Volume | : 5 |
| Method File | : Method_181214.lcm |
| Date Acquired | : 15/10/2019 14:34:06 |
| Date Processed | : 15/10/2019 15:05:00 |



**195**

Chromatogram
EPB-143A EPB-143A.lcd

mAU




1PDA Multi 1 205nm,4nm
2PDA Multi 2 210nm,4nm
3PDA Multi 3 215nm,4nm
4PDA Multi 4 203nm,4nm
5PDA Multi 5 213nm,4nm

Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.494 | 863172 | 48.302 | |
| | 2 | 12.669 | 923864 | 51.698 | |
| | Total | | 1787035 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.494 | 665175 | 48.274 | M |
| | 2 | 12.669 | 712730 | 51.726 | M |
| | Total | | 1377905 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.494 | 381893 | 49.287 | M |
| | 2 | 12.668 | 392934 | 50.713 | M |
| | Total | | 774827 | 100.000 | |

PDA Ch4 203nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.494 | 821947 | 48.335 | S |
| | 2 | 12.670 | 878559 | 51.665 | |
| | Total | | 1700506 | 100.000 | |

PDA Ch5 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.494 | 501154 | 47.948 | |
| | 2 | 12.668 | 544054 | 52.052 | |
| | Total | | 1045208 | 100.000 | |

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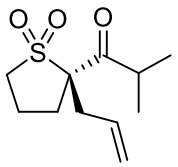
# Chiral HPLC Analysis

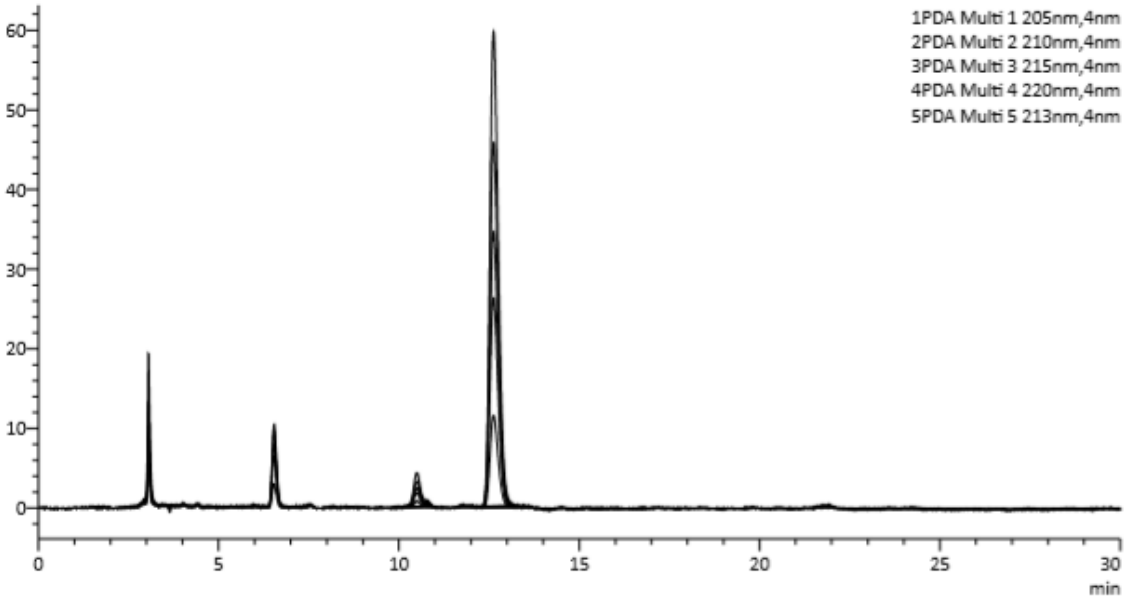
| | |
|---|---|
| Sample Name | : EPB-143B |
| Sample ID | : EPB-143B |
| Data File | : EPB-143B.lcd |
| Batch File | : BATCH021019.lcb |
| Vial# | : 15 |
| Injecti o Volume | : 5 |
| Method File | : Method_181214.lcm |
| Date Acquired | : 15/10/2019 20:36:01 |
| Date Processed | : 16/10/2019 08:15:11 |



(*R*)-**195**

Chromatogram
EPB-143B EPB-143B.lcd

mAU




1PDA Multi 1 205nm,4nm
2PDA Multi 2 210nm,4nm
3PDA Multi 3 215nm,4nm
4PDA Multi 4 220nm,4nm
5PDA Multi 5 213nm,4nm

Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.499 | 67405 | 6.523 | |
| | 2 | 12.626 | 965887 | 93.477 | |
| | Total | | 1033292 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.501 | 48652 | 6.142 | |
| | 2 | 12.626 | 743481 | 93.858 | |
| | Total | | 792133 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.501 | 24351 | 5.395 | M |
| | 2 | 12.626 | 426997 | 94.605 | |
| | Total | | 451347 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.499 | 10354 | 5.234 | M |
| | 2 | 12.626 | 187464 | 94.766 | |
| | Total | | 197818 | 100.000 | |

PDA Ch5 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 10.501 | 33741 | 5.668 | M |
| | 2 | 12.626 | 561549 | 94.332 | |
| | Total | | 595289 | 100.000 | |

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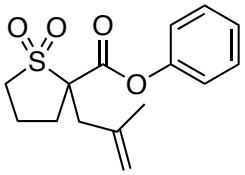
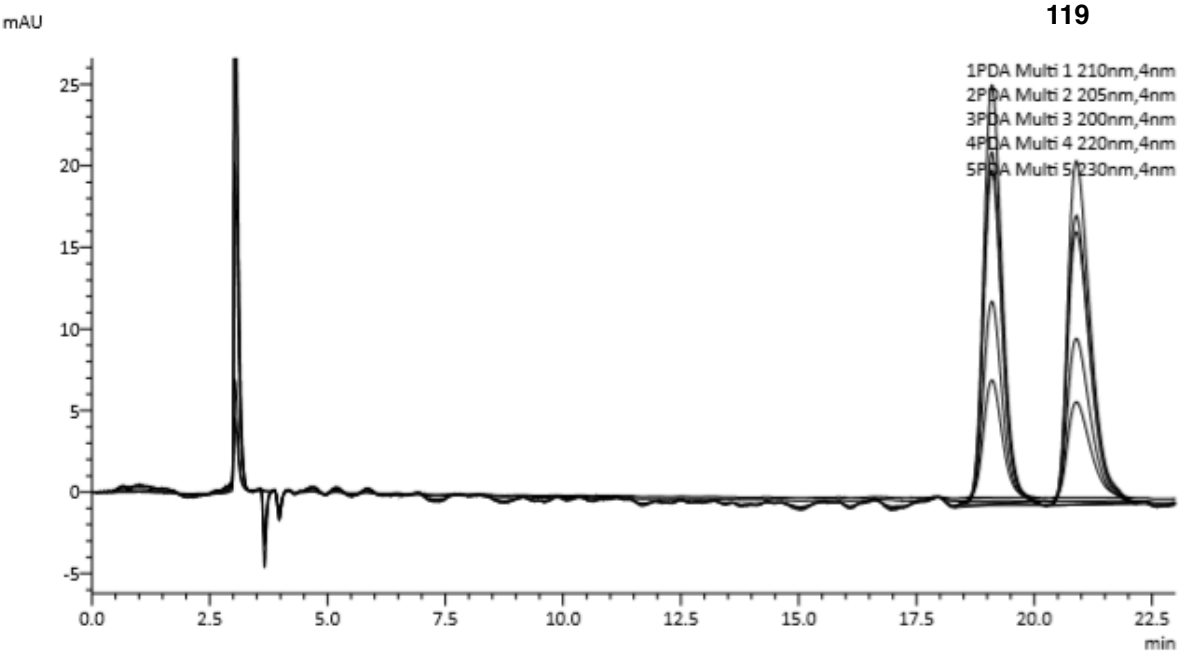
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-095A-2-RAC |
| Sample ID | : EPB-095A-2-RAC-001 |
| Data File | : EPB-095A-2-RAC-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 10 |
| Injecti o Volume | : 2 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 17:18:28 |
| Date Processed | : 22/08/2019 17:41:30 |



**119**

Chromatogram
EPB-095A-2-RAC EPB-095A-2-RAC-001.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.104 | 578011 | 50.418 | |
| | 2 | 20.896 | 568425 | 49.582 | |
| | Total | | 1146436 | 100.000 | |

PDA Ch2 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.104 | 720879 | 50.138 | M |
| | 2 | 20.897 | 716910 | 49.862 | M |
| | Total | | 1437790 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.104 | 599964 | 49.980 | S |
| | 2 | 20.901 | 600438 | 50.020 | |
| | Total | | 1200402 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.104 | 339534 | 50.203 | |
| | 2 | 20.895 | 336782 | 49.797 | |
| | Total | | 676316 | 100.000 | |

PDA Ch5 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.105 | 199953 | 50.201 | |
| | 2 | 20.897 | 198355 | 49.799 | |
| | Total | | 398308 | 100.000 | |

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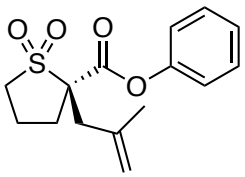
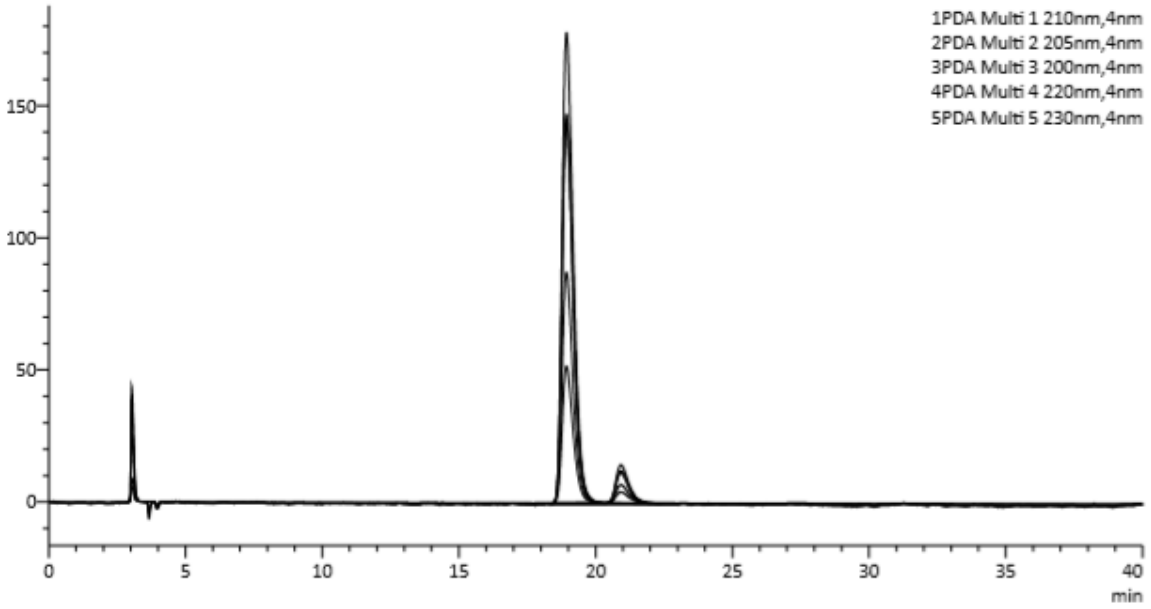
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-095B-2 |
| Sample ID | : EPB-095B-2-001 |
| Data File | : EPB-095B-2-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 11 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 20:51:24 |
| Date Processed | : 24/08/2019 13:45:29 |



(*R*)-**119**

Chromatogram
EPB-095B-2 EPB-095B-2-001.lcd




Peak Table

PDA Ch1 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.937 | 4142882 | 91.187 | |
| | 2 | 20.928 | 400380 | 8.813 | V |
| | Total | | 4543262 | 100.000 | |

PDA Ch2 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.937 | 5160225 | 90.656 | |
| | 2 | 20.928 | 531858 | 9.344 | SV |
| | Total | | 5692083 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.937 | 4279243 | 90.959 | |
| | 2 | 20.920 | 425358 | 9.041 | V |
| | Total | | 4704601 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.937 | 2497453 | 91.047 | |
| | 2 | 20.926 | 245594 | 8.953 | V |
| | Total | | 2743046 | 100.000 | |

PDA Ch5 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.937 | 1458880 | 91.496 | M |
| | 2 | 20.927 | 135599 | 8.504 | M |
| | Total | | 1594479 | 100.000 | |

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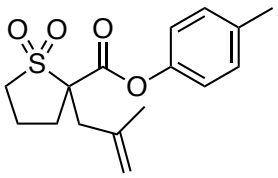
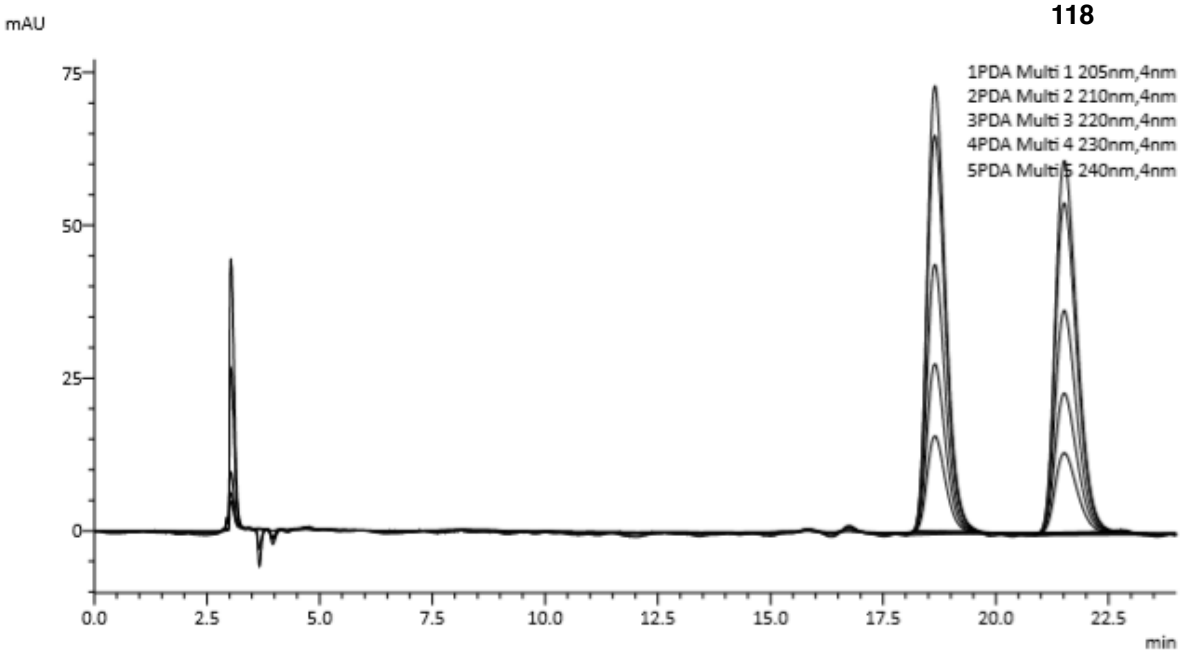
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-097-2-RAC |
| Sample ID | : EPB-097-2-RAC-001 |
| Data File | : EPB-097-2-RAC-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 14 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 18:19:25 |
| Date Processed | : 22/08/2019 18:43:27 |



**118**

Chromatogram
EPB-097-2-RAC EPB-097-2-RAC-001.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.649 | 2129845 | 50.020 | M |
| | 2 | 21.518 | 2128163 | 49.980 | M |
| | Total | | 4258007 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.648 | 1861533 | 50.349 | M |
| | 2 | 21.517 | 1835750 | 49.651 | |
| | Total | | 3697284 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.648 | 1278810 | 50.239 | |
| | 2 | 21.517 | 1266666 | 49.761 | |
| | Total | | 2545476 | 100.000 | |

PDA Ch4 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.648 | 785038 | 50.419 | M |
| | 2 | 21.517 | 771991 | 49.581 | |
| | Total | | 1557028 | 100.000 | |

PDA Ch5 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.648 | 448302 | 50.364 | M |
| | 2 | 21.517 | 441826 | 49.636 | |
| | Total | | 890127 | 100.000 | |

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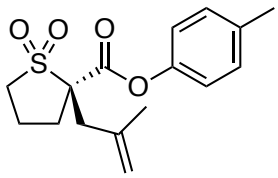
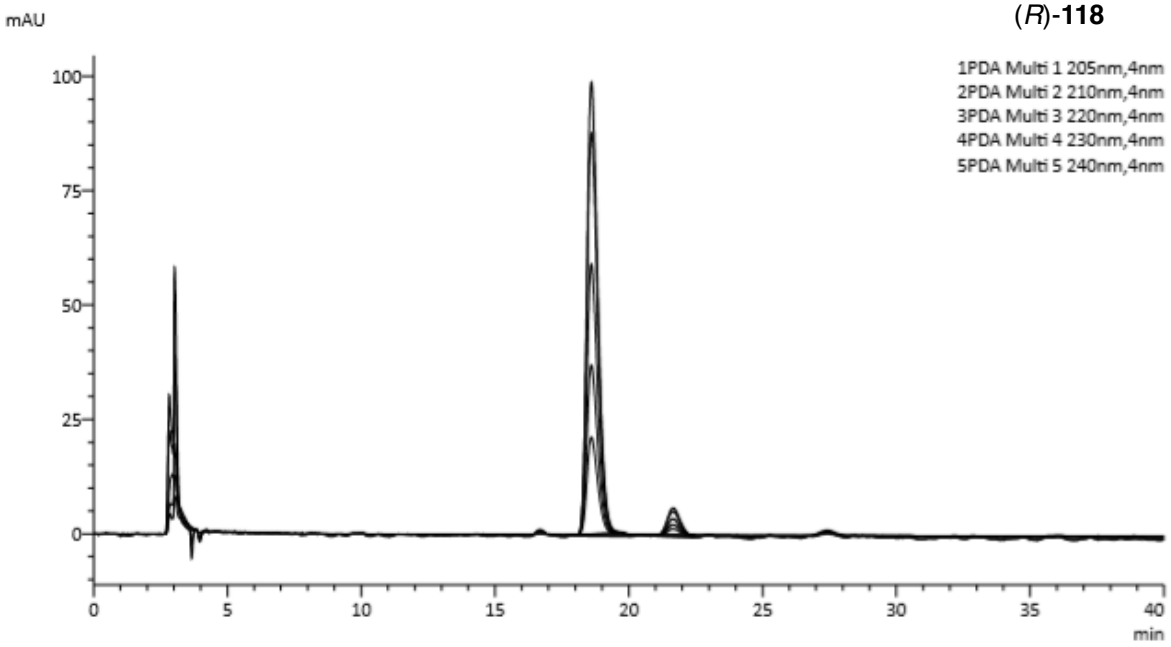
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-099-2 |
| Sample ID | : EPB-099-2-001 |
| Data File | : EPB-099-2-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 16 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 22:12:25 |
| Date Processed | : 22/08/2019 22:52:27 |



(*R*)-**118**

Chromatogram
EPB-099-2 EPB-099-2-001.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.606 | 2896495 | 92.992 | |
| | 2 | 21.653 | 218268 | 7.008 | |
| | Total | | 3114763 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.606 | 2556662 | 93.212 | |
| | 2 | 21.657 | 186173 | 6.788 | |
| | Total | | 2742836 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.606 | 1713545 | 93.421 | |
| | 2 | 21.653 | 120667 | 6.579 | |
| | Total | | 1834212 | 100.000 | |

PDA Ch4 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.606 | 1052191 | 93.398 | |
| | 2 | 21.655 | 74370 | 6.602 | |
| | Total | | 1126561 | 100.000 | |

PDA Ch5 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.606 | 598004 | 93.321 | |
| | 2 | 21.657 | 42802 | 6.679 | |
| | Total | | 640806 | 100.000 | |

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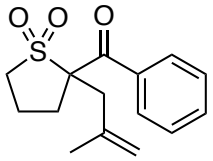
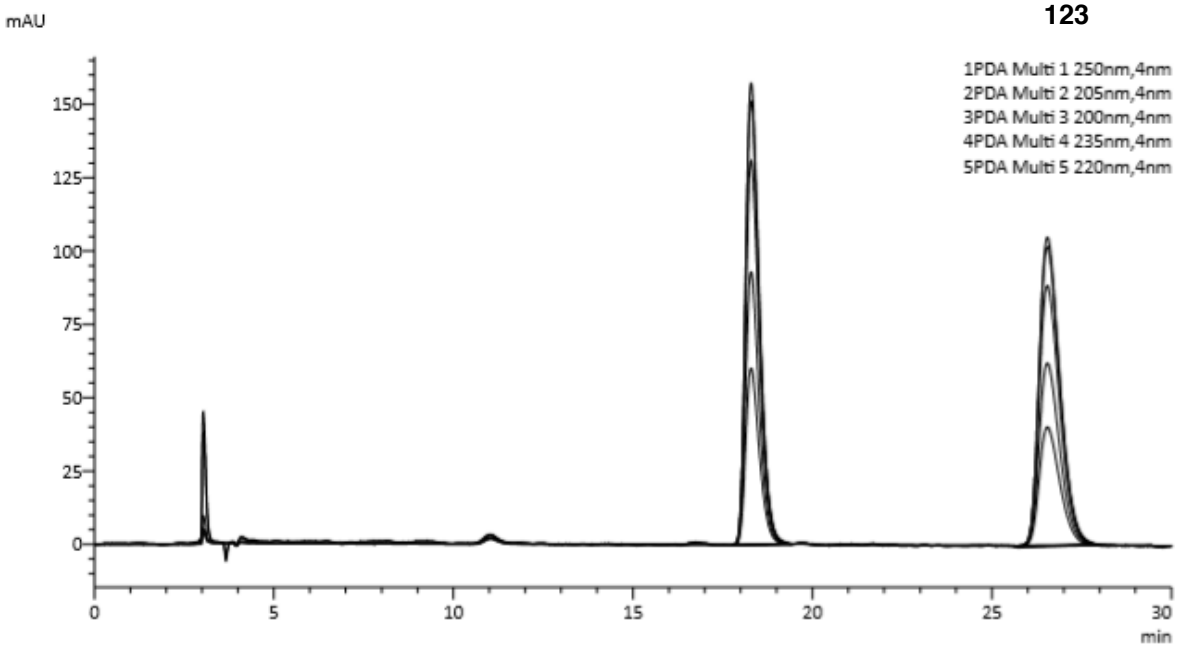
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-096A-2-RAC |
| Sample ID | : EPB-096A-2-RAC-001 |
| Data File | : EPB-096A-2-RAC-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 12 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 17:48:55 |
| Date Processed | : 22/08/2019 18:18:57 |



**123**

Chromatogram
EPB-096A-2-RAC EPB-096A-2-RAC-001.lcd




Peak Table

PDA Ch1 250nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.294 | 4215101 | 49.786 | |
| | 2 | 26.546 | 4251315 | 50.214 | |
| | Total | | 8466415 | 100.000 | |

PDA Ch2 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.295 | 4108553 | 49.861 | |
| | 2 | 26.546 | 4131477 | 50.139 | M |
| | Total | | 8240030 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.295 | 3571655 | 49.555 | |
| | 2 | 26.547 | 3635788 | 50.445 | M |
| | Total | | 7207443 | 100.000 | |

PDA Ch4 235nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.294 | 2496136 | 49.793 | |
| | 2 | 26.546 | 2516907 | 50.207 | |
| | Total | | 5013043 | 100.000 | |

PDA Ch5 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.295 | 1629589 | 49.736 | |
| | 2 | 26.546 | 1646872 | 50.264 | |
| | Total | | 3276461 | 100.000 | |

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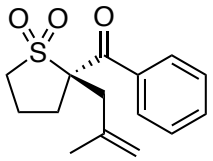
# Chiral HPLC Analysis

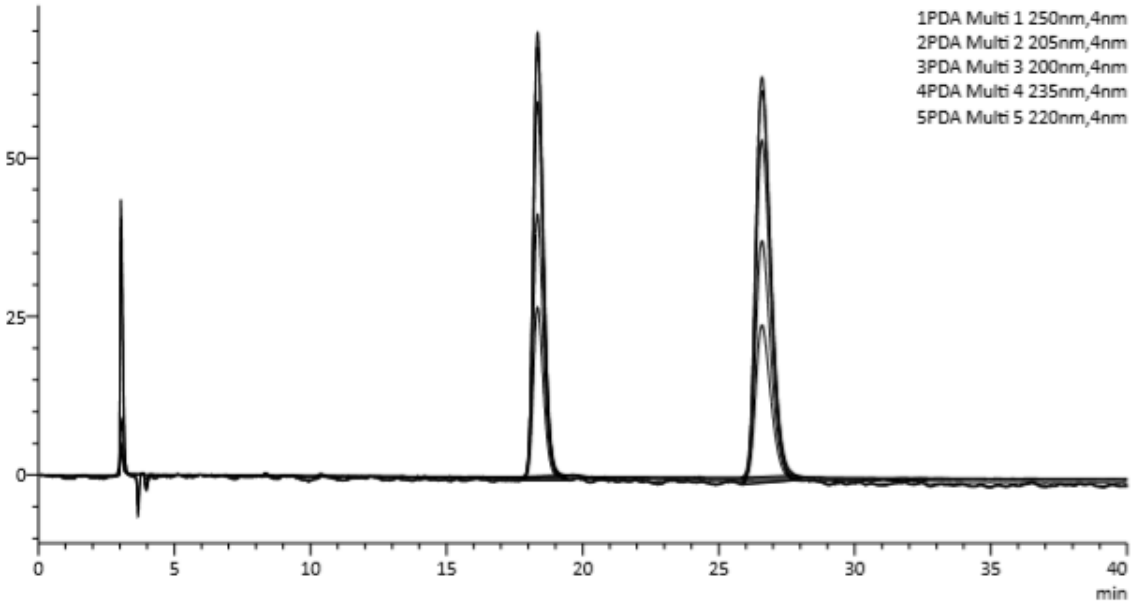
Sample Name : EPB-096B-2
Sample ID : EPB-096B-2-001
Data File : EPB-096B-2-001.lcd
Batch File : 22082019 batch.lcb
Vial# : 13
Injecti o Volume : 3
Method File : Basicmethod2-25min.lcm
Date Acquired : 22/08/2019 21:31:55
Date Processed : 22/08/2019 22:11:57



(*R*)-**123**

Chromatogram
EPB-096B-2 EPB-096B-2-001.lcd

mAU




Peak Table

PDA Ch1 250nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.348 | 1849665 | 42.713 | M |
| | 2 | 26.593 | 2480761 | 57.287 | M |
| | Total | | 4330426 | 100.000 | |

PDA Ch2 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.348 | 1836753 | 42.935 | |
| | 2 | 26.594 | 2441259 | 57.065 | |
| | Total | | 4278012 | 100.000 | |

PDA Ch3 200nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.349 | 1601216 | 42.897 | |
| | 2 | 26.594 | 2131488 | 57.103 | |
| | Total | | 3732704 | 100.000 | |

PDA Ch4 235nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.348 | 1096843 | 42.607 | |
| | 2 | 26.593 | 1477469 | 57.393 | |
| | Total | | 2574312 | 100.000 | |

PDA Ch5 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 18.348 | 717993 | 42.673 | |
| | 2 | 26.594 | 964564 | 57.327 | |
| | Total | | 1682557 | 100.000 | |

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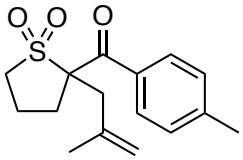
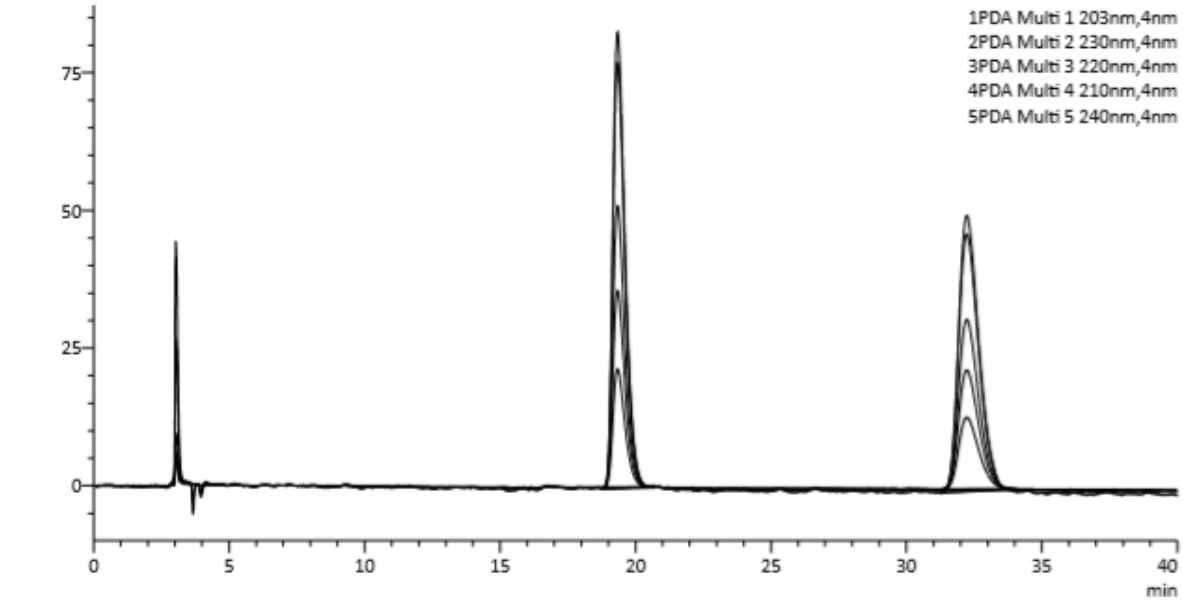
# Chiral HPLC Analysis

Sample Name : EPB-098-2-RAC
Sample ID : EPB-098-2-RAC-001
Data File : EPB-098-2-RAC-001.lcd
Batch File : 22082019 batch.lcb
Vial# : 15
Injecti o Volume : 3
Method File : Basicmethod2-25min.lcm
Date Acquired : 22/08/2019 18:49:55
Date Processed : 22/08/2019 19:29:57



**122**

Chromatogram
EPB-098-2-RAC EPB-098-2-RAC-001.lcd




Peak Table

PDA Ch1 203nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.340 | 2601867 | 49.853 | |
| | 2 | 32.232 | 2617187 | 50.147 | |
| | Total | | 5219054 | 100.000 | |

PDA Ch2 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.339 | 674359 | 49.745 | |
| | 2 | 32.232 | 681280 | 50.255 | |
| | Total | | 1355640 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.339 | 1618039 | 49.889 | |
| | 2 | 32.231 | 1625220 | 50.111 | |
| | Total | | 3243259 | 100.000 | |

PDA Ch4 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.339 | 2436296 | 50.114 | |
| | 2 | 32.231 | 2425209 | 49.886 | M |
| | Total | | 4861504 | 100.000 | |

PDA Ch5 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.340 | 1127131 | 49.951 | |
| | 2 | 32.232 | 1129360 | 50.049 | |
| | Total | | 2256491 | 100.000 | |

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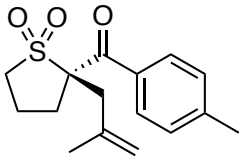
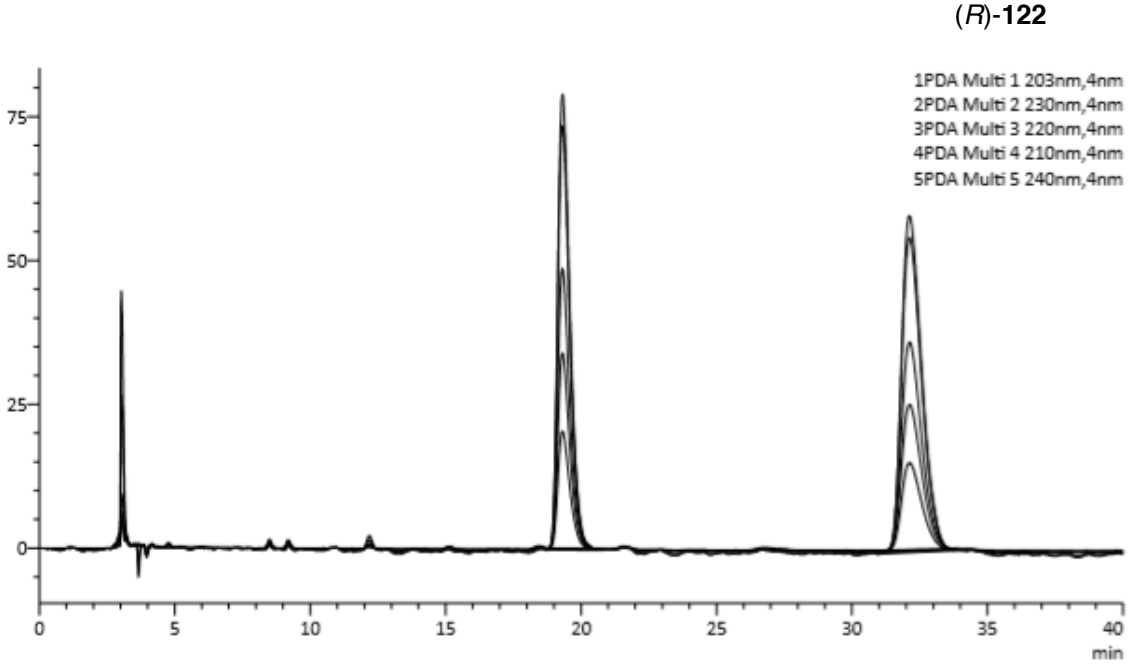
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-100-2 |
| Sample ID | : EPB-100-2-001 |
| Data File | : EPB-100-2-001.lcd |
| Batch File | : 22082019 batch.lcb |
| Vial# | : 18 |
| Injecti o Volume | : 3 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 22/08/2019 23:33:24 |
| Date Processed | : 23/08/2019 00:13:26 |



(*R*)-**122**

Chromatogram
EPB-100-2 EPB-100-2-001.lcd




Peak Table

PDA Ch1 203nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.316 | 2475728 | 44.818 | |
| | 2 | 32.122 | 3048262 | 55.182 | |
| | Total | | 5523989 | 100.000 | |

PDA Ch2 230nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.316 | 636369 | 44.745 | |
| | 2 | 32.126 | 785857 | 55.255 | |
| | Total | | 1422225 | 100.000 | |

PDA Ch3 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.315 | 1522064 | 44.667 | |
| | 2 | 32.126 | 1885487 | 55.333 | |
| | Total | | 3407551 | 100.000 | |

PDA Ch4 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.315 | 2299177 | 44.781 | |
| | 2 | 32.124 | 2835106 | 55.219 | |
| | Total | | 5134283 | 100.000 | |

PDA Ch5 240nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 19.315 | 1059602 | 44.668 | |
| | 2 | 32.125 | 1312589 | 55.332 | |
| | Total | | 2372192 | 100.000 | |

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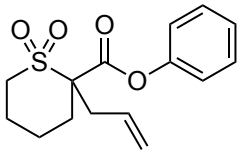
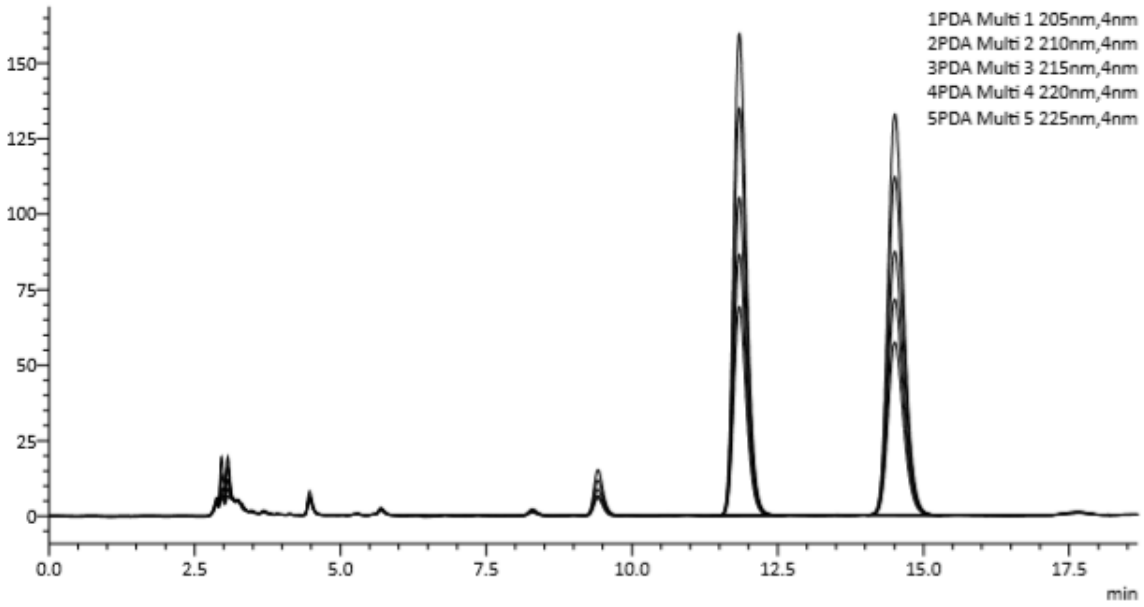
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-155A |
| Sample ID | : EPB-155A |
| Data File | : EPB-155A.lcd |
| Batch File | : BATCH251019.lcb |
| Vial# | : 2 |
| Injecti ɑ Volume | : 7 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/11/2019 09:13:33 |
| Date Processed | : 06/11/2019 09:32:14 |



**205**

Chromatogram
EPB-155A EPB-155A.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.842 | 2475257 | 49.410 | |
| | 2 | 14.510 | 2534347 | 50.590 | |
| | Total | | 5009603 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.842 | 2078273 | 49.382 | |
| | 2 | 14.510 | 2130290 | 50.618 | |
| | Total | | 4208563 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.842 | 1617316 | 49.413 | |
| | 2 | 14.510 | 1655722 | 50.587 | |
| | Total | | 3273038 | 100.000 | |

PDA Ch4 220nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.842 | 1325361 | 49.484 | |
| | 2 | 14.510 | 1352997 | 50.516 | |
| | Total | | 2678357 | 100.000 | |

PDA Ch5 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.842 | 1059799 | 49.455 | |
| | 2 | 14.510 | 1083153 | 50.545 | |
| | Total | | 2142952 | 100.000 | |

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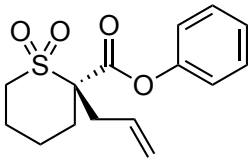
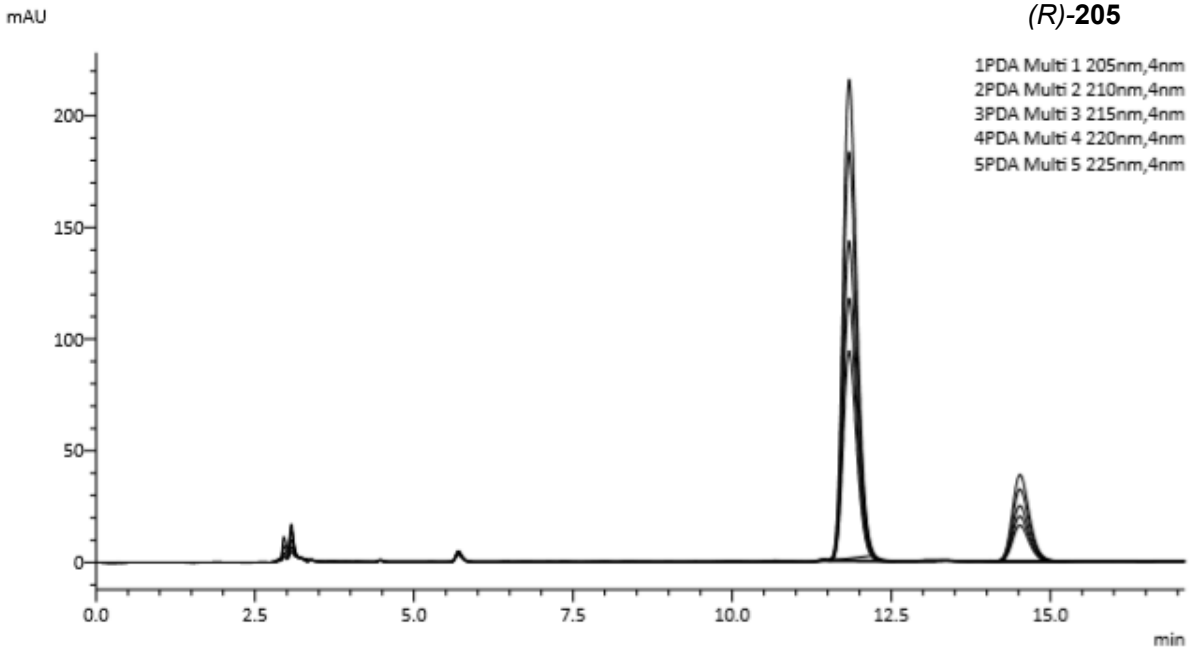
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-155B |
| Sample ID | : EPB-155B |
| Data File | : EPB-155B.lcd |
| Batch File | : BATCH251019.lcb |
| Vial# | : 4 |
| Injecti o Volume | : 7 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 06/11/2019 10:33:41 |
| Date Processed | : 07/11/2019 10:47:33 |



*(R)*-**205**

Chromatogram
EPB-155B EPB-155B.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.838 | 3327288 | 82.030 | |
| | 2 | 14.524 | 728896 | 17.970 | |
| | Total | | 4056183 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.838 | 2834427 | 82.332 | M |
| | 2 | 14.524 | 608273 | 17.668 | |
| | Total | | 3442700 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.838 | 2192733 | 82.375 | |
| | 2 | 14.523 | 469155 | 17.625 | |
| | Total | | 2661888 | 100.000 | |

PDA Ch4 220nm

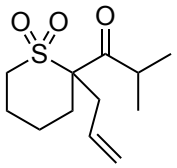
| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.838 | 1737259 | 82.033 | M |
| | 2 | 14.523 | 380507 | 17.967 | M |
| | Total | | 2117766 | 100.000 | |

PDA Ch5 225nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 11.838 | 1438541 | 82.470 | |
| | 2 | 14.524 | 305769 | 17.530 | |
| | Total | | 1744311 | 100.000 | |

# Chiral HPLC Analysis

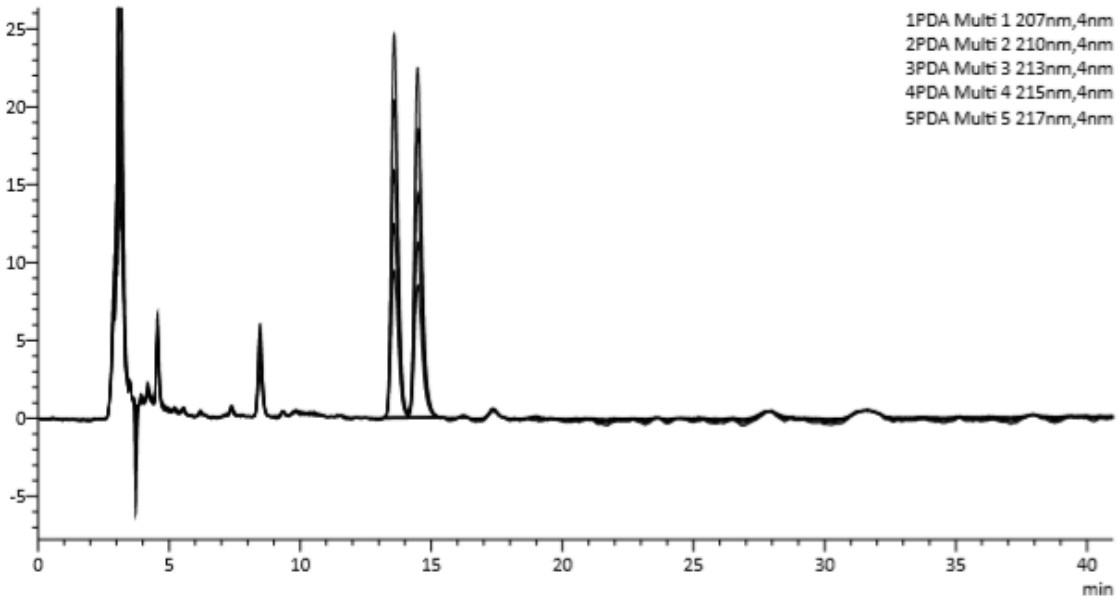
Sample Name : EPB-157A
Sample ID : EPB-157A
Data File : EPB-157A.lcd
Batch File : BATCH251019.lcb
Vial# : 4
Injecti o Volume : 8
Method File : Basicmethod2-25min.lcm
Date Acquired : 05/11/2019 12:23:48
Date Processed : 05/11/2019 14:01:45



**207**

Chromatogram
EPB-157A EPB-157A.lcd

mAU




1PDA Multi 1 207nm,4nm
2PDA Multi 2 210nm,4nm
3PDA Multi 3 213nm,4nm
4PDA Multi 4 215nm,4nm
5PDA Multi 5 217nm,4nm

Peak Table

PDA Ch1 207nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.586 | 457061 | 49.834 | |
| | 2 | 14.481 | 460109 | 50.166 | V |
| | Total | | 917170 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.586 | 377951 | 49.844 | |
| | 2 | 14.480 | 380320 | 50.156 | V |
| | Total | | 758271 | 100.000 | |

PDA Ch3 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.586 | 294452 | 49.840 | |
| | 2 | 14.480 | 296348 | 50.160 | V |
| | Total | | 590800 | 100.000 | |

PDA Ch4 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.586 | 230688 | 49.826 | |
| | 2 | 14.480 | 232302 | 50.174 | V |
| | Total | | 462991 | 100.000 | |

PDA Ch5 217nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.586 | 174949 | 49.852 | |
| | 2 | 14.481 | 175991 | 50.148 | V |
| | Total | | 350940 | 100.000 | |

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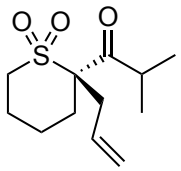
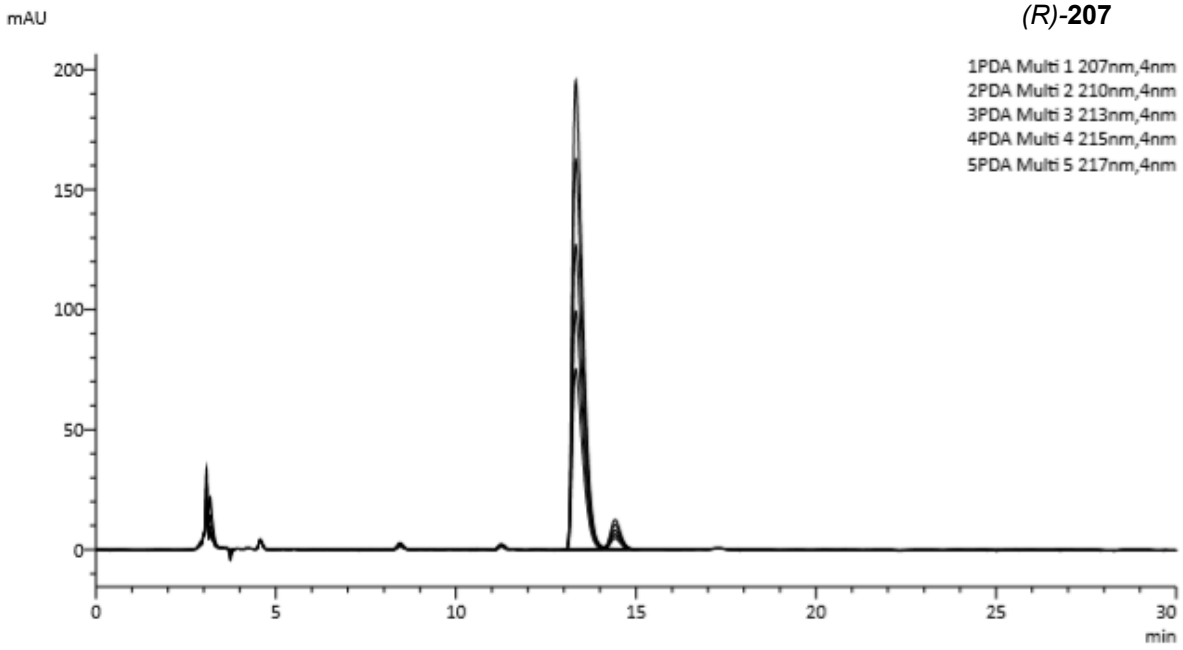
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-157B |
| Sample ID | : EPB-157B |
| Data File | : EPB-157B.lcd |
| Batch File | : BATCH251019.lcb |
| Vial# | : 13 |
| Injecti o Volume | : 10 |
| Method File | : Basicmethod2-25min.lcm |
| Date Acquired | : 05/11/2019 20:56:57 |
| Date Processed | : 06/11/2019 07:09:30 |



*(R)*-**207**

Chromatogram
EPB-157B EPB-157B.lcd




Peak Table

PDA Ch1 207nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.329 | 3986333 | 94.026 | |
| | 2 | 14.421 | 253259 | 5.974 | V |
| | Total | | 4239592 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.329 | 3311160 | 94.060 | |
| | 2 | 14.421 | 209094 | 5.940 | V |
| | Total | | 3520254 | 100.000 | |

PDA Ch3 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.329 | 2581247 | 94.067 | |
| | 2 | 14.421 | 162800 | 5.933 | V |
| | Total | | 2744047 | 100.000 | |

PDA Ch4 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.329 | 1999997 | 94.738 | M |
| | 2 | 14.421 | 111079 | 5.262 | |
| | Total | | 2111076 | 100.000 | |

PDA Ch5 217nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 13.329 | 1528747 | 94.066 | |
| | 2 | 14.421 | 96437 | 5.934 | V |
| | Total | | 1625184 | 100.000 | |

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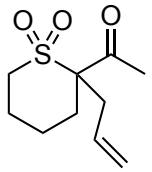
# Chiral HPLC Analysis

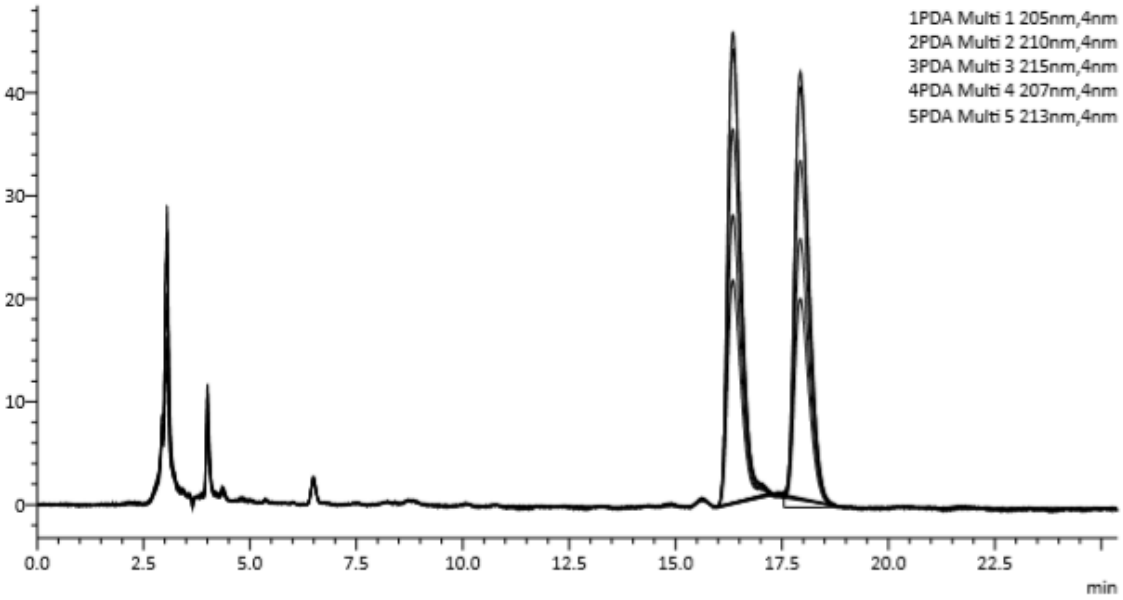
Sample Name : EPB-159A
Sample ID : EPB-159A
Data File : EPB-159A.lcd
Batch File : BATCH021019.lcb
Vial# : 9
Injecti o Volume : 5
Method File : Method_181214.lcm
Date Acquired : 15/10/2019 17:38:20
Date Processed : 15/10/2019 18:41:49



**208**

Chromatogram
EPB-159A EPB-159A.lcd

mAU




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.349 | 1029280 | 50.785 | M |
| | 2 | 17.933 | 997442 | 49.215 | M |
| | Total | | 2026722 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.349 | 806603 | 50.793 | M |
| | 2 | 17.933 | 781416 | 49.207 | |
| | Total | | 1588018 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.350 | 476986 | 50.610 | M |
| | 2 | 17.933 | 465484 | 49.390 | |
| | Total | | 942470 | 100.000 | |

PDA Ch4 207nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.349 | 995414 | 49.739 | M |
| | 2 | 17.932 | 1005856 | 50.261 | |
| | Total | | 2001271 | 100.000 | |

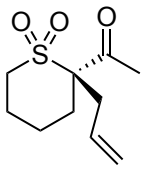
PDA Ch5 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.349 | 622847 | 50.843 | M |
| | 2 | 17.933 | 602185 | 49.157 | |
| | Total | | 1225032 | 100.000 | |

Department of Chemistry | Lancaster University

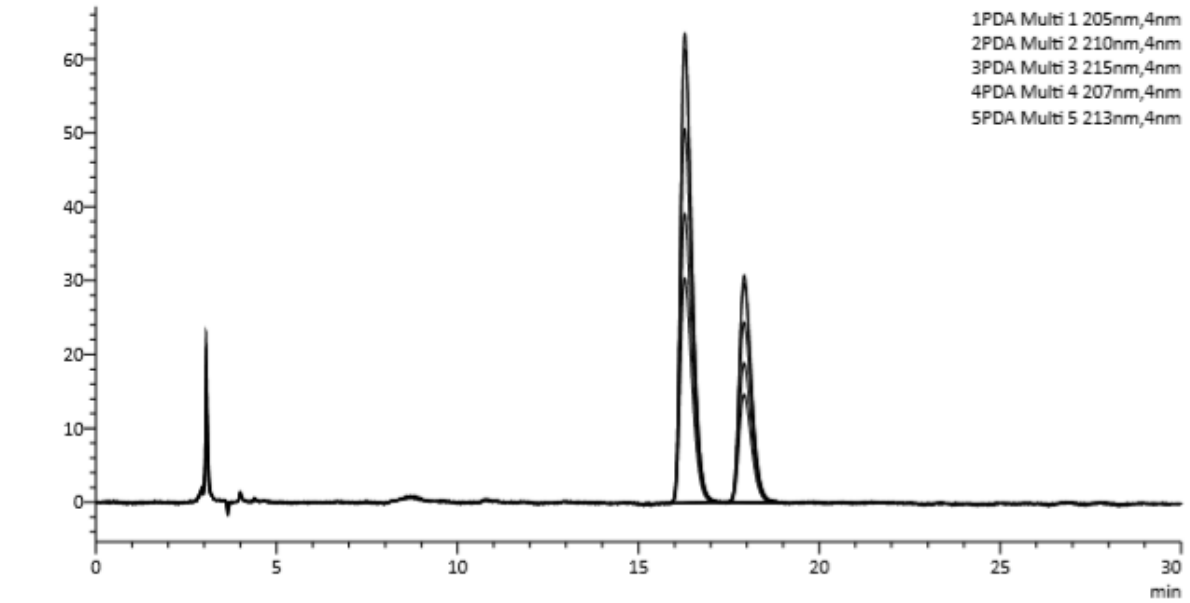
# Chiral HPLC Analysis

| | |
|---|---|
| Sample Name | : EPB-159B |
| Sample ID | : EPB-159B |
| Data File | : EPB-159B.lcd |
| Batch File | : BATCH021019.lcb |
| Vial# | : 17 |
| Injecti o Volume | : 5 |
| Method File | : Method_181214.lcm |
| Date Acquired | : 15/10/2019 21:06:23 |
| Date Processed | : 16/10/2019 08:15:51 |



*(R)*-**208**

Chromatogram
EPB-159B EPB-159B.lcd




Peak Table

PDA Ch1 205nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.287 | 1435128 | 65.764 | |
| | 2 | 17.927 | 747122 | 34.236 | |
| | Total | | 2182250 | 100.000 | |

PDA Ch2 210nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.287 | 1143803 | 65.899 | |
| | 2 | 17.927 | 591882 | 34.101 | |
| | Total | | 1735684 | 100.000 | |

PDA Ch3 215nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.288 | 686706 | 66.028 | |
| | 2 | 17.928 | 353314 | 33.972 | |
| | Total | | 1040020 | 100.000 | |

PDA Ch4 207nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.288 | 1385961 | 65.848 | |
| | 2 | 17.928 | 718830 | 34.152 | |
| | Total | | 2104791 | 100.000 | |

PDA Ch5 213nm

| Name | Peak# | Ret. Time | Area | Area% | Mark |
|---|---|---|---|---|---|
| | 1 | 16.288 | 884041 | 65.966 | |
| | 2 | 17.928 | 456100 | 34.034 | |
| | Total | | 1340141 | 100.000 | |

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