Chemospecific Cyclisations of Aryls and Heteroaryls with Sulfoxonium Ylides

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by:

Daniel James Clare

September 2019
Acknowledgements

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Finally, I would like to thank my parents for their unwavering support. This thesis would not have been possible without them.
Copyright Statement

The work presented in this thesis has been conducted at the University of Liverpool under the supervision of Dr Christophe Aïssa, between June 2016 and September 2019. Some of the work presented in chapter 2 was conducted at AstraZeneca’s Macclesfield Campus between October 2017 and December 2017 under the supervision of Dr Phillip Inglesby. Most of the second chapter has been published in a peer reviewed journal:


I confirm that the work presented herein was conducted by me, unless explicitly stated otherwise.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>Aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>BMS</td>
<td>Bristol Myers-Squibb</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
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<td>calcld</td>
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<tr>
<td>cap</td>
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<td>Cp*</td>
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<td>d</td>
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<td>DBU</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<table>
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<tr>
<td>dpa</td>
<td>diphenylacetate</td>
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<tr>
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<td>e.</td>
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<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
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<td>Equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionisation</td>
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<td>ethyl acetate</td>
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<td>ethanol</td>
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<td>FCC</td>
<td>flash column</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier-transform infrared spectroscopy</td>
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<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-hexafluoroisopropanol</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>iPrOH</td>
<td>isopropanol</td>
</tr>
<tr>
<td>J.</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>KOtBu</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>m.</td>
<td>(aromatic substitution): meta</td>
</tr>
<tr>
<td>m. (IR)</td>
<td>medium</td>
</tr>
<tr>
<td>m. (NMR)</td>
<td>multiplet</td>
</tr>
<tr>
<td>maj.</td>
<td>major</td>
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</tbody>
</table>
Experimental and Analysis Statement

Unless otherwise noted, all reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. THF was used after passage through Innovative Technology PureSolv MD system. All commercially available compounds were used as received. Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: Spectra were recorded on a Bruker DRX 500 or DPX 400 in CDCl$_3$; chemical shifts (δ) are given in ppm. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl$_3$: δC = 77.0 ppm; residual CHCl$_3$ in CDCl$_3$: δH = 7.26 ppm); apparent splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintuplet), m (multiplet), br (broad), and the appropriate combinations. In $^{13}$C NMR, an APT sequence was used to separate methylene groups and quaternary carbons (e, even) from methine and methyl groups (o, odd). IR: PerkinElmer Spectrum 100 FT-IR spectrometer, wavenumbers (ν) in cm$^{-1}$. HRMS determined at the University of Liverpool on micromass LCT mass spectrometer (ES+) and Trio-1000 or Agilent QTOF 7200 mass spectrometers (CI). Melting points: Griffin melting point apparatus (not corrected). Elemental analyses: Elementar Vario Micro Cube instrument at University of Liverpool. Compounds 366, 367, 369, 370, and 375 were synthesised and fully characterised by undergraduate students Pierre Palamini and Isobel Jobson, and so their characterisation data has not been included in this thesis. Compound 406 was synthesised and fully characterised by Sarah Livesley, and so its characterisation data has not been included in this thesis.
Abstract

α-Carbonyl sulfoxonium ylides have recently been gaining attention as alternative reagents to α-diazoketones, in part due to the supposed superior safety profile and stability of sulfoxonium ylides. However, functionalisation of aryls and heteroaryls using sulfoxonium ylides without the help of a directing group has so far remained a neglected area. Following on from previous work in the Aïssa group\(^1\), this thesis will discuss the development of two novel reactions for the functionalisation of aryls and heteroaryls. The first reaction allows the synthesis of 2-indanones and does not require a metal catalyst. It appears to proceed \textit{via} a five-centre, \(4\pi\) electron electrocyclisation, with C-S bond cleavage being encouraged by the strong hydrogen bond donating ability of the solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The second reaction allows the synthesis of pyrrolizinones and indolizinones from sulfoxonium ylides in the presence of an iridium catalyst. It appears to proceed \textit{via} nucleophilic attack by the aromatic ring on an iridium carbene, followed by 1,2-migration and re-aromatisation. Significantly, each reaction is chemospecific for a certain class of substrates: phenyl rings and benzofurans will cyclise under the HFIP-mediated electrocyclisation, but not in the presence of the iridium catalyst. Pyroles will cyclise in the presence of the iridium catalyst, but do not undergo the HFIP-mediated electrocyclisation. Indoles fall in between the two, depending on the nature of the substituent on nitrogen.

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Chapter 1
1.1 General Introduction to Sulfoxonium Ylides

1.1.1 Dimethylsulfoxonium methylide

The simplest sulfoxonium ylide is dimethylsulfoxonium methylide 1, which was first generated and used in 1962 by Corey and Chaykovski. This ylide could be generated by the deprotonation of trimethylsulfoxonium chloride 2 with sodium hydride, and subsequently, it could be used for the epoxidation of ketones (Scheme 1).

Scheme 1: Epoxidation of ketones with 1 reported by Corey and Chaykovski.

The method allowed access to numerous epoxides derived from aldehydes and ketones in moderate to excellent yields. However, α,β-unsaturated ketones tended to undergo cyclopropanation, rather than epoxidation. In 2008, the scope of this reaction was expanded by Shibasaki and co-workers to include access to chiral epoxides (Scheme 2). The reaction proceeded with a good level of enantioselectivity if both the chiral lanthanide catalyst and the phosphine oxide were present.

Scheme 2: Shibasaki’s enantioselective epoxidation of ketone 3 using chiral lanthanum catalyst 5

Although ylide 1 has been used in a variety of other reactions, including cyclopropanation, and ring expansion of epoxides and oxetanes and aziridines,
it has recently been more commonly used for the synthesis of more complex sulfoxonium ylides. This is largely accomplished by treatment of a suspension of 1 with an activated carboxylic acid or ester. For example, the process chemistry group at Bristol-Meyers Squibb (BMS) needed to synthesise chiral α-amino epoxides 6 (Scheme 3),9,10 which are intermediates in the synthesis of HIV protease inhibitors. These can be accessed via reduction and ring closure of the corresponding α-chloroketone 7. Traditionally, these have been made by hydrolysis of corresponding diazoketones 8, however due to safety concerns about large scale synthesis of such compounds, they decided to make the corresponding sulfoxonium ylides (e.g. 11) instead. These can be made from nitrophenyl esters such as 10, and 11 was synthesised in 99% yield and without loss of stereochemical integrity. The stereogenic centre was also maintained in the conversion of ylide 11 into α-chloroketone 12.

Scheme 3: The synthesis of α-chloroketone 12 through the acid hydrolysis of sulfoxonium ylides 11.

Other carboxylic acid derivatives, including acid chlorides11 and methyl esters9, and isocyanates12 have been used to synthesise sulfoxonium ylides by addition of the respective reagent to a suspension of 1 in THF at 0 °C (Scheme 4). Although in some instances, methyl and ethyl esters can be used to synthesise sulfoxonium ylides, 4-nitrophenyl esters remain the most reliable precursors.10 Moreover, cyclic sulfoxonium ylides such as 20 can be accessed via rhodium catalysed cyclisation of diazosulfoxides.13
Scheme 4: The use of acid chlorides, methyl esters, isocyanates and sulfoxides to synthesise sulfoxonium ylides.

Heteroaromatic rings that are prone to undergo nucleophilic aromatic substitution can also be used to generate bis-substituted sulfoxonium ylides.\(^\text{14}\) For example, 2-chloropyrimidine \(\text{20}\) underwent nucleophilic attack by \(\text{1}\) to make sulfoxonium ylide \(\text{21}\), which could then be further functionalised by treatment with other electrophiles such as phenyl isocyanate or acetyl chloride (Scheme 5). Other notable examples of the synthesis of bis-substituted sulfoxonium ylides include Burtoloso’s 2018 report on the coupling of sulfoxonium ylides with arynes,\(^\text{11}\) Aissa’s 2019 report on the palladium-catalysed cross coupling of sulfoxonium ylides with aryl bromides\(^\text{15}\) and Vaitla’s 2017 report on the synthesis of sulfoxonium ylides \(\text{via in situ}\) generated iodonium ylides\(^\text{16}\) (Scheme 6).

Scheme 5: Synthesis of sulfoxonium ylides \(\text{22}\) and \(\text{23}\) from 2-chloropyrimidine \(\text{21}\)
Scheme 6: Top: Burtoloso’s coupling of sulfoxonium ylides and arynes. Middle: Aissa’s palladium catalysed cross coupling between aryl bromides and sulfoxonium ylides. Bottom: Vaitla’s synthesis of sulfoxonium ylides via in situ generated iodonium ylides. MS = Molecular sieves

1.1.2 Applications of Complex Sulfoxonium Ylides
1.1.2.1 Metal Free Reactions
1.1.2.1.1 Hydrolysis
Complex sulfoxonium ylides have been used in various metal and non-metal catalysed reactions. Perhaps the simplest non-metal catalysed process is hydrolysis, and one example of this was described in the previous section (Scheme 3). In 1965, Metzger and Konig also used acid hydrolysis of sulfoxonium ylide 18 to generate α-chloro amide 32 in nearly quantitative yield (Scheme 7).
Scheme 7: Acid hydrolysis of 18 to give α-chloroamide 32

1.1.2.1.2 S-H Insertion

Metzger and Konig also showed that sulfoxonium ylides could undergo S-H insertion for the synthesis of β-keto thioethers. In 2016, Burtoloso and co-workers revisited this earlier work, and showed that sulfoxonium ylides such as 24 were able to undergo S-H insertion for the synthesis of β-keto thioethers 26 (Scheme 8). They found that a range of aromatic thiols were able to undergo the reaction smoothly, without any additional additive, or a metal catalyst. The reaction was also selective for the thiol group, as when the thiol contained other nucleophilic groups, such as -OH, -NH₂, or -CO₂H, only the thioether could be detected (Scheme 8, top). However, when an alkyl thiol was used, no reaction took place. The authors reasoned that this was because protonation of the ylide plays an important role in the mechanism of the reaction, with aromatic thiols (pKa ~10 in DMSO) being more acidic than alkyl thiols (pKa ~17 in DMSO). The addition of diphenyl phosphate 34 as an organocatalyst proved to be sufficient to protonate the ylide and allow the reaction to take place in good yield (Scheme 8, bottom).
Scheme 8: Top: Synthesis of β-keto thioethers 33 from sulfoxonium ylide 24 and aryl thiols. Bottom: Synthesis of β-keto thioethers 35 from 24 and alkyl thiols catalysed by phosphate 34.

Burtoloso’s group also showed that di-functionalisation of sulfoxonium ylides is possible,18 again building on the earlier work by Metzger and Konig. Simply by treating sulfoxonium ylides such as 24 with an alkyl halide, Burtoloso and co-workers were able to synthesise α-alkyl-α-haloketones in one step, avoiding enolate chemistry and the use of reactive reagents such as Br₂ or NBS (Scheme 9). The method also provided an easy way to access α,α-dihaloketones by replacing the alkyl iodide with an “X⁺” source (Selectfluor, NBS) and a “Y⁻” source (NaI, NaBr, TBAC), thus providing access to dihaloketones in one step in moderate to good yield (Scheme 9).

Scheme 9: Difunctionalisation of sulfoxonium ylide 24. NBS = N-bromosuccinimide. TBAC = Tetrabutylammonium bromide
1.1.2.2 Metal Catalysed Reactions

1.1.2.2.1 Carbon-Heteroatom Bond Formation

Sulfoxonium ylides have also been used in metal catalysed reactions. The first such report was by Baldwin in 1993, who reported the metal catalysed intramolecular N-H insertion of sulfoxonium ylide 38 for the synthesis of 3-oxopyrrolidine 39 (Scheme 10). They found that rhodium (II) trifluoroacetate was the best catalyst for this reaction, and although rhodium (II) acetate also promoted the reaction in reasonable yield, a variety of copper catalysts were completely inactive, or led to uncontrolled decomposition of the sulfoxonium ylide.

Scheme 10: Metal catalysed intramolecular N-H insertion of sulfoxonium ylide 38 to give 3-oxopyrrolidine 39.

This type of reactivity suggested the presence of a carbene intermediate, and later on, Mangion and co-workers at Merck re-visited this work and decided to develop a more general method for inter- and intramolecular X-H insertion reaction of sulfoxonium ylides (X = O, NH, NR, S, Scheme 11). A screening of possible catalysts showed that [Ir(cod)Cl]_2 was a better catalyst for this reaction than either of the rhodium (II) catalysts reported by Baldwin for the intramolecular N-H insertion (Scheme 11).
Scheme 11: Ir catalysed intermolecular X-H (X = O, N, S) insertion reaction of sulfoxonium ylide 40. a: At 70 °C in 1,2-DCE. b: Conducted at 35 °C with EtOH as solvent.

The iridium catalysed reaction worked well at room temperature for primary amines (Scheme 11, entry 1), however, when secondary amines were used, the temperature had to be increased to 70 °C and the solvent thus changed to 1,2-DCE (entry 2). O-H insertion could also be carried out if the alcohol was used as the solvent (entry 3), and S-H insertion was carried out in good yield (entry 4). Mangion also found that sulfoxonium ylides such as 41 could undergo intramolecular iridium catalysed N-H insertion, giving access to cyclic 3-oxo amines such as 42 (Scheme 12).

Scheme 12: Ir catalysed intramolecular N-H insertion of 41 to give cyclic 3-oxo amine 42

A year later, the same authors reported a gold (I) catalysed X-H insertion reaction of sulfoxonium ylides. In conducting further catalyst screening, the authors found that AuCl(SMe₂) provided a minor improvement in the yield as compared to the previously reported reaction with [Ir(cod)Cl]₂ (table 1, entry 1 vs entry 2). They also discovered that a variety of platinum (II) and gold (III) catalysts were able to efficiently carry out the reaction, though with a lower yield of product as compared to the gold (I) complex.
(table 1, entries 3 and 4 vs entry 1). A silver (I) salt was also examined, but it proved to be significantly less active than AuCl(SMe$_2$).

![Catalyst diagram]

<table>
<thead>
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<th>Entry</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>%Yield</th>
</tr>
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<tr>
<td>1</td>
<td>AuCl(SMe)$_2$</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>[Ir(cod)Cl]$_2$</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Pt(cod)Cl$_2$</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>AuC$_3$</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>AgCN</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>

**Table 1**

The gold (I) catalyst provided an improvement to the scope of the intermolecular X-H insertion reaction with respect to both sulfoxonium ylide and nucleophile, being efficient for the reaction of both bis-substituted sulfoxonium ylides such as 40 and carrying out the X-H insertion reaction of a variety of sulfoxonium ylides derived from protected amino acids such as 11, derived from Boc-protected phenylalanine (Scheme 13).

![Scheme 13: Gold (I) catalysed N-H insertion of aniline 44 into ylide 11.]

Sulfoxonium ylide 11 was synthesised following the method described by Nugent$^9$ without loss of stereochemical integrity, and were able to undergo N-H and O-H insertion, again without loss of stereochemical integrity, for example with electron deficient aniline 44. Interestingly, AuCl(SMe$_2$) proved to be far inferior than
[Ir(cod)Cl]₂ as a catalyst in the intramolecular N-H insertion (Scheme 14), perhaps because carbamates are much poorer nucleophiles than anilines or alcohols.

Scheme 14: Comparison between [Ir(cod)Cl]₂ and AuCl(SMe)₂ for the intramolecular N-H insertion of sulfoxonium ylide 41.

The previous two methods developed by Merck were able to be applied in the large-scale manufacture of two candidate drug molecules, MK7246 and MK7655. The synthesis of MK7246 (Scheme 15), a treatment for asthma, required the synthesis of ketone 48. They decided to make this compound from sulfoxonium ylide 47, which was synthesised by treating diester 46 with dimethylsulfoxonium methylide 1. An iridium catalysed intramolecular N-H insertion reaction then followed, which proceeded smoothly in 86% yield. Gratifyingly, this reaction proved to be significantly higher yielding than an alternative rhodium catalysed N-H insertion of diazoketone 49, which was used during earlier development of MK7246 (Scheme 15, bottom). Significantly, they were able to carry out the sulfoxonium ylide process on more than 100 kg of starting material. The sulfoxonium ylide process was therefore favoured over the N-H insertion reaction involving 49 due to the higher yield, and significant safety concerns over the large scale synthesis and storage of 49.
Scheme 15: Large scale synthesis of MK-7246 using an Ir catalysed intramolecular N-H insertion of sulfoxonium ylide 44

In 2018, Hopmann and co-workers published an iron catalysed reaction between vinyl sulfoxonium ylides such as 51 and substituted pyridines such as 52. This reaction uses the simple iron (II) salt, FeBr₂, and can be used for the synthesis of indolizines such as 53 (Scheme 16).

Scheme 16: Synthesis of indolizinone 53 from 51 and 52.

When vinyl sulfoxonium ylides such as 51 was treated with FeBr₂ in the presence of a pyridine, for example 52, indolizidine 53 was synthesised in 72% yield. In this case,
a sterically hindered 2-substituted pyridine was very well tolerated. The reaction was also able to tolerate electron deficient and electron rich aromatic rings well. In order to elucidate the mechanism of this reaction, DFT calculations suggested that the active catalyst is a complex between pyridine and FeBr₂, which attacks the sulfoxonium ylide to form complex 54, and enter the catalytic cycle. Intermediate 54 can easily lose DMSO (the activation barrier is 35.15 kJ mol⁻¹) to form iron carbene 55, which can then undergo intermolecular attack by another molecule of pyridine to form 56. Although the activation barrier for this step is high, 56 is predicted to be much lower in energy than 55 (56 is -53.56 kJ mol⁻¹ more stable than 55), making the conversion of 55 into 56 irreversible. Intermediate 56 can then undergo very fast C-C bond formation (barrier 10.46 kJ mol⁻¹) to release 57. Intermediate 57 can then undergo re-aromatisation to form the indolizine products such as 53. Attack of another molecule each of pyridine and sulfoxonium ylide 51 on 56 regenerates complex 54 which can then re-enter the catalytic cycle.

Scheme 17: Proposed mechanism of FeBr₂ catalysed formation of indolizidines from vinyl sulfoxonium ylides 51 and pyridines. Pyr = 2-benzylpyridine
1.1.2.2 Carbon-Carbon Bond Formation Without a Directing Group

In 2012, a patent was published in which the iridium (I) catalysed cyclisation of sulfoxonium ylide 58 was disclosed. Substituted pyrrole 58, with an alkyl chain bearing the sulfoxonium ylide moiety, undergoes cyclisation in moderate yield when treated with with 10 mol% [Ir(cod)Cl]₂ in 1,2-DCE to give the seven membered ring 59 (Scheme 18).

Scheme 18: Iridium catalysed intramolecular cyclisation of sulfoxonium ylide 58

In 2017, the group of Hopmann published an iridium catalysed reaction between β-enamino esters and sulfoxonium ylides for the synthesis of 3,5-substituted pyrroles (Scheme 19).

Scheme 19: Selected scope of the iridium catalysed C-H insertion reaction between β-enamino esters and sulfoxonium ylides.

The reaction afforded highly substituted N-alkylated and N-H pyrroles, and halides were tolerated in the reaction, for example with sulfoxonium ylide 61, which underwent reaction with 60 to afford p-methoxybenzyl (PMB) protected pyrrole 62 in 64% yield. The reaction could also be extended to bis-substituted sulfoxonium ylides, and was applied to the synthesis of the important statin atorvastatin/Lipitor. The mechanism of the reaction is shown in Scheme 20. Insertion of the sulfoxonium ylide
into [Ir(cod)Cl]$_2$ produces iridium carbene 63. This undergoes attack by the β-enamino esters to form complex 64, which then undergoes protonolysis to release enamine 65. It is noteworthy that these β-enamino esters selectively undergo formal C-H, rather than N-H insertion. This is most likely due to the highly nucleophilic nature of the substrate. Intermediate 65 can then undergo acid catalysed cyclisation to give the observed pyrrole products such as 62.

![Scheme 20: Proposed mechanism for the formation of pyrroles from sulfoxonium ylides and β-enamino esters.](image)

1.1.2.2.3 Carbon-Carbon Bond Formation with a Directing Group

Later on in 2017, further reports of metal catalysed C-H activation for carbon-carbon bond formation were published by the groups of Aïssa$^{28}$ and Li.$^{29}$ Li’s group reported a rhodium (III) catalysed C-H activation reaction between 1-(pyrimidin-2-yl)-1H-indole 66 and α-ketosulfoxonium ylide 24 to give ketone 67 in 96% yield. (Scheme 21).
Scheme 21: Li’s reported Rh (III) catalysed C-H activation reaction between 66 and 24 to give 67.

Aissa and co-workers disclosed a similar rhodium (III) catalysed directed C-H insertion reaction between 2-phenylpyridine 68 and sulfoxonium ylide 69, in the presence of the solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, Scheme 22).

Scheme 22: Reaction reported by Aissa and co-workers between 2-phenylpyridine 68 and sulfoxonium ylide 69 to give ketone 70.

Through extensive optimisation of the conditions, a crucial factor to the success of this reaction was the choice of solvent, HFIP, as all attempts to use other protic or aprotic solvents failed. Mechanistically, the reactions reported by Aissa and Li are similar (Scheme 23). Cyclometallation of the active catalyst species with 66 or 68 occurs to give complex 74. Coordination of sulfoxonium ylide 24 or 69 with 74 gives rhodium (III) alkyl species 75. Complex 75 undergoes α-elimination of DMSO to give rhodium carbene species 76. Migratory insertion of the rhodium-aryl bond into the carbene generates rhodium (III) alkyl species 77, which undergoes protonolysis by a molecule of HX to release products 67 or 70 and regenerate the active catalyst. In the reaction described by Aissa, HFIP is promoting protonolysis of complex 77, whereas for Li’s reaction, it is pivalic acid. However, the authors could not rule out the possibility of an Sn2-type displacement of DMSO by the aryl group of complex 75.
Scheme 23: Proposed catalytic cycle for the reactions reported by Li and Aïssa. HX = HFIP or PivOH.

Since the publication of these two reactions, many more metal catalysed C-H activation reactions have been disclosed, notably for the synthesis of heterocycles, such as Wu’s report on the synthesis of 2-sustituted indoles, Cheng’s reported synthesis of 5-arylimidazo[2,1-\alpha]isoquinolines and Fan’s synthesis of carbazoles (Scheme 24).

During efforts to expand the scope of the rhodium (III) catalysed reaction reported by Aissa\textsuperscript{28} and co-workers, sulfoxonium ylide \textit{85} was synthesised and subjected to the optimised reaction conditions (Scheme 25).

Scheme 25: Unexpected synthesis of indanone \textit{87} from sulfoxonium ylide \textit{85} under the optimised reaction conditions

The major product of this reaction was in fact 2-indanone \textit{87}, which was isolated in 57\% yield. Sulfoxonium ylide \textit{85} thus appears to have undergone an intramolecular, Friedel-Crafts type reaction, rather than the desired intermolecular C-H activation reaction. To the best of our knowledge, the synthesis of 2-indanones in this manner
has not been reported from sulfoxonium ylides. However, it is a well-studied reaction of other ylides, most notably α-diazoketones, but also iodonium ylides, and gold carbenes formed in situ from alkynes, which we will briefly review in the next section.

1.2 Friedel Crafts Reactions of Ylides

1.2.1 Friedel Crafts Reactions of α-Diazoketones

1.2.1.1 Metal Catalysed Reactions of α-Diazoketones

1.2.1.1.1 C-C Bond Formation on Phenyl Rings

The first example of a metal-catalysed Friedel-Crafts reaction of α-diazoketones was reported by Taylor and Davies in 1986\(^3\). They reported the rhodium (II) catalysed conversion of diazoketone 88 into naphthol 89 (Scheme 26) which proceeded in 99% yield.

![Scheme 26](image)

**Scheme 26**: Taylor and Davies’ report on the Rh (II) catalysed reaction of diazoketone 85

The following year, Saba reported\(^3\) the copper catalysed synthesis of benzopyranone 91 from α-diazoketone 90. The catalyst in this case is copper (II) hexafluoroacetylacetonate (catalyst A). Using these conditions, 91 could be isolated in 86% yield (Scheme 27).
Scheme 27: The synthesis of benzopyranones reported by Saba

Also in 1990, McKervey and co-workers reported the synthesis of 2-tetralone 94 from diazoketone 92 (Scheme 28). This reaction is an intramolecular Buchner reaction, and proceeds via the intermediate azulenone 93, which can be isolated. However, the group discovered that, on prolonged exposure to silica gel, 93 would be converted to the 2-tetralone 94. Further investigation of this reactivity led to the one pot procedure shown whereby treatment of 92 with catalytic amounts of rhodium (II) acetate followed by 1 drop of TFA leads exclusively to the 2-tetralone 94.

Scheme 28: Synthesis of 2-tetralone 94 from diazoketone 92 via azulenone 93.

The regioselectivity of the reaction was affected by substituents in the ortho and para positions (Schemes 29 and 30). Diazoketone 95 (Scheme 29), with an ortho-methyl group, afforded 2-tetralone 97, indicating that cyclisation had occurred away from the substituent, likely to minimize steric hindrance. However, diazketone 98, with an ortho-OMe group afforded 2-tetralone 100, indicating that the cyclisation occurred in the proximity of the substituent. The authors speculate that this could be explained by co-ordination of the carbenoid intermediate to the oxygen atom of the methoxy group, which would direct the cyclisation.
Scheme 29: The reaction of ortho-substituted diazoketones 95 and 98.

Having at least one substituent in the meta position of the diazoketone again changed the regioselectivity (Scheme 30). When diazoketone 101 was subject to the rhodium (II) catalysed conditions, tetralone 102 was isolated without the addition of TFA, and none of the corresponding azulenone could be detected. Diazoketone 103 also bypassed the azulenone intermediate and gave an 80:20 mixture of regioisomeric tetralones 104 and 105 in 96% overall yield.

Scheme 30: The reaction of diazoketones 101 and 103.

Related to this work, in 1997, Sudrik and co-workers published a synthesis of 2-tetralones and 2-benzosuberones as part of their total synthesis of (+)-arthimachalene 106 (Scheme 31), an important terpenoid natural product. This work demonstrated that seven membered rings could be synthesised by this method, as...
diazoketone 107 underwent rhodium-catalysed Buchner reaction to give azulenone 108, which was converted to the 2-benzosuberone 109 by addition of the Lewis acid BF$_3$•OEt$_2$ in 94% yield from 107. This reaction allowed the authors to synthesise 106 in 3 steps from diazoketone 107.

Scheme 31: Reaction of diazoketone 107 via azulenone 108.

In 1990, Nakatani further developed this rhodium catalysed reaction when he investigated the competition between aromatic C-H insertion for the synthesis of 2-indanones, secondary aliphatic C-H insertion for the synthesis of cyclopentanones, and intramolecular cyclopropanation of alkene C=C bonds\(^{37}\) (Scheme 32). When diazoketone 110 underwent rhodium catalysed decomposition, 2-indanone 111 was the major product, but cyclopentanone 112 was also isolated in 18% yield. This product comes from insertion of the rhodium carbenoid into the secondary aliphatic C-H bond of the \(n\)-propyl group. In the case of diazoketone 113, aromatic C-H insertion was only the minor product, 2-indanone 114 being isolated in 26% yield. The major product in this case was cyclopropane 115, which derives from reaction of the carbenoid with the C=C double bond of the allyl group. No trace of insertion of the carbenoid into the secondary aliphatic C-H bond was observed. From these results, it appears that cyclopropanation is the most favoured process, followed by aromatic C-H insertion, then secondary aliphatic C-H insertion, at least with Rh$_2$(OAc)$_4$ as the catalyst.
The effect of changing the carboxylate ligand has also been investigated extensively by Moody and Padwa.\textsuperscript{38,39,40} They have discovered that using fluorinated carboxylate ligands on the rhodium (II) centre, such as in rhodium (II) perfluorobutyrate (Rh\textsubscript{2}(pfb)\textsubscript{4}) or rhodium (II) trifluoroacetate (Rh\textsubscript{2}(tfa)\textsubscript{4}), or using amidate ligands such as in rhodium (II) caprolactamate (Rh\textsubscript{2}(cap)\textsubscript{4}), tends to favour aromatic C-H insertion, even when other pathways are possible. For example, in 1993, Padwa reported\textsuperscript{39} the rhodium (II) catalysed reaction of diazoketone 113 (Scheme 33).

Using Rh\textsubscript{2}(OAc)\textsubscript{4} as the catalyst, overall isolated yield of indanone 114 and cyclopropane 115 was 99%, but the selectivity was poor. Using Rh\textsubscript{2}(pfb)\textsubscript{4} “switched off” the cyclopropanation pathway, and indanone 114 was isolated in 95% yield as the sole product. In contrast, Rh\textsubscript{2}(cap)\textsubscript{4} produced the opposite selectivity, and 115 was isolated in 72% yield as the sole product. Similar results were reported in competition reactions between aliphatic C-H insertion and cyclopropanation (not shown in Scheme).
Scheme 33: Reaction of diazoketone 113 with different rhodium (II) carboxylates.

The authors rationalised this by speculating that the change from a highly electrophilic metal centre in Rh₂(pfb)₄ to a weakly electrophilic metal centre (Rh₂(cap)₄) accounts for the selectivity, as the less stable (and therefore more reactive) carbenoid arising from Rh₂(pfb)₄ would prefer to use the less entropically demanding pathway, i.e., aromatic substitution. The following year, Moody and Padwa reported³⁸ their investigations into the rhodium catalysed reactions of diazoamides for the synthesis of oxindoles (Scheme 34). They discovered that the reaction of diazoamide 116 is controlled by the choice of ligand on the rhodium, in a similar manner to that described above. Rhodium (II) perfluorocarboxylates such as Rh₂(pfb)₄ or Rh₂(tfa)₄ produced exclusively oxindole 117 (i.e. the rhodium carbenoid underwent aromatic C-H insertion as opposed to aliphatic C-H insertion), but with impractical reaction times (entries 2 and 3 respectively). Switching to trifluoroacetamide or perfluorobutyramide ligands led to a dramatic decrease in the reaction time, but with no loss in selectivity, with 117 being the only detectable product (entries 4 and 5). Once again, this remarkable selectivity is attributed to the strongly electrophilic metal centre in carbenoids derived from rhodium (II) perfluorocarboxylates or perfluoroamidates.

Scheme 34: Selectivity of different rhodium (II) catalysts for aliphatic or aromatic C-H insertion.

Another study of the effect of ligands on the selectivity of the rhodium (II) catalysed reaction was published in 1992 by Ikegami and co-workers⁴¹ (Scheme 35). They
looked at the competition between aliphatic and aromatic C-H insertion in diazoketone 119 to give either cyclopentanone 120 or indanone 121. Like Moody and Padwa, they found that using Rh₂(OAc)₄ gave them a high yield (86%) but poor selectivity (Scheme 35, entry 1). However, by switching the catalyst to rhodium (II) diphenylacetate (Rh₂(dpa)₄, entry 2), they were able to maintain the high yield, but increase selectivity for indanone 121 dramatically, and rhodium (II) triphenylacetate (Rh₂(tpa)₄, entry 3), improved on this again, giving a 92% overall yield and a 4:96 ratio of 120/121. This suggests that using ligands with steric bulk also switches the selectivity of the reaction towards aromatic C-H insertion.

![Scheme 35](image)

**Scheme 35**: Reaction of diazoketone 119 with different Rh (II) carboxylates.

Rh₂(dpa)₄: Rhodium (II) diphenylacetate. Rh₂(tpa)₄: Rhodium (II) triphenylacetate.

Despite many reports of the metal catalysed Friedel-Crafts cyclisation of diazo compounds, there was no definitive mechanistic study until 2009, when Jung and co-workers reported the synthesis of isoquinolinone derivatives such as 123 from phenylsulfonyl substituted diazoketones such as 122 (Scheme 36), using Rh₂(pfb)₄ as the catalyst. They showed that this reaction is not a simple C-H insertion (a σ-bond metathesis) as the case of aliphatic C-H bonds, but is more like electrophilic aromatic substitution (SₐEAr). They examined the effects of the substituent on the aromatic ring on the regioselectivity of the reaction (Scheme 36), and found that substituent effects match well with what would be expected from an SₐEAr reaction. For example, a methoxy group in the meta (R²) position as in 122 yielded isoquinolinone 123 in 96% yield in only 2 hours. However, with a trifluoromethyl group instead of a methoxy, as in 124, isoquinolinone 125 was isolated in only 27% yield after 48 hours.
Scheme 36: Substituent effects in the intramolecular Rh (II) catalysed reaction of diazoketones 122 and 124. Rh$_2$(pfb)$_4$: Rhodium (II) perfluorobutyrate.

With substituent effects established, the team then decided to investigate deuterium kinetic isotope effects (Scheme 37). They synthesised mono-deuterated diazoketone 126 and subjected it to the standard conditions to obtain 127 and 128 in 46.1% and 53.9% yield respectively. This gave them $k_H/k_D = 0.855$, thus implying that there is no primary kinetic isotope effect and thus direct C-H activation could be ruled out. The observation of the inverse secondary deuterium kinetic isotope effect is consistent with an sp$^2$ to sp$^3$ hybridisation change during the addition of a rhodium carbenoid to the aromatic ring to form a σ-complex as the rate determining step. This unambiguously warrants an S$_E$Ar mechanism rather than direct C-H activation. The final proposed mechanism is shown in the bottom half of Scheme 35. Addition of the catalyst to the diazoketone and extrusion of nitrogen gas forms the rhodium carbenoid 130 irreversibly. Attack of the aromatic ring onto 130 generates Wheland intermediate 131. Intermediate 131 can then be re-aromatised by hydrogen transfer from the ring to the former carbenoid carbon.
1.2.1.1.2 C-C Bond Formation on Pyrroles

In addition to the intramolecular C-C bond forming reactions on phenyl rings described in the previous section, there are also reports of intramolecular C-C bond formation reactions using metal catalysed reactions of diazoketones on heterocyclic rings. These include pyrroles, furans and thiophenes.

In 1986, Jefford and co-workers needed to synthesise dihydroindolizinone 137 as part of their total synthesis of ipalbidine (Scheme 38)\(^4\). To accomplish this, they decided to synthesise diazoketone 132, and use an intramolecular rhodium (II) catalysed cyclisation. In this reaction, two products, dihydroindolizinone 137 and indanone 142 are possible. The major product was 137, giving a 36:1 ratio of indolzinone/indanone, and an 89% overall yield. They decided to test the selectivity of the reaction by varying the electronics of the phenyl ring, and so diazoketones 133-136 were synthesised (Scheme 38). As expected, the pyrrole ring proved more reactive in all cases, even when the phenyl ring carried an electron donating group (134 and 135). An electon poor ring as in 136 \((R = \text{NO}_2)\) led to almost complete selectivity for the indolizinone, with no indanone detected. Using acetoxy-
substituted dihydroindolizinone 132, the authors were able to synthesise (±)-ipalbidine in 4 steps from 132.

![Image of (±)-Ipalbidine](image)

**Scheme 38**: Intramolecular reaction of diazoketones 132-136.

1.2.1.1.3 C-C Bond Formation on Furans

Furanyl diazoketones have also been reported to undergo metal-catalysed decomposition. However, unlike phenyl or pyrrole rings, the furan rings prefer to undergo cyclopropanation followed by electrocyclic ring opening to an unsaturated aldehyde. The first report of this reaction was by Nwaji and Onyiriuka, when they reported\(^4^1\) the reaction of diazoketone 147 to give cyclic unsaturated aldehyde 149 (Scheme 39), catalysed by copper (II) sulfate. The reaction was presumed to proceed via cyclopropane intermediate 148, followed by electrocyclic ring opening to give the observed aldehyde. Intermediate 148 could not be detected or isolated, even on early quenching of the reaction.
Scheme 39: Intramolecular Cu (II) catalysed reaction of furanyl diazoketone 147.

This reaction has been re-visited several times over the years, most notably by the groups of Padwa and Wenkert. A change of catalyst to Rh\(_2\)(OAc)\(_4\) allowed Padwa and co-workers to confirm the identity of the product, and confirm that the geometry of the exocyclic double bond as Z, rather than E as initially reported by Onyiriuka (Scheme 40). They were also able to isolate cyclopropane 153 under identical reaction conditions, thus confirming, in the authors’ eyes at least, the mechanism of the reaction. Cyclopropane 153 was able to undergo acid catalysed ring opening to give dihydrobenzofuranone 154 in 85% yield, showing that it is possible to obtain formal C-H insertion products from furanyl diazoketones.

![Scheme 39](image)

Scheme 40: Rh (II) catalysed reactions of diazoketones 150 and 152, and acid-catalysed ring opening of 153 to give 154.

Although Wenkert and co-workers were further able to expand the scope (Scheme 41), for example with the synthesis of tran fused unsaturated aldehyde 156, synthesised from diazoketone 155, they were unable to detect or isolate any cyclopropane intermediates.

![Scheme 40](image)
Scheme 41: The reaction of diazoketone 155.

1.2.1.1.4 C-C Bond Formation on Thiophenes
Intramolecular reaction of thienyl diazoketone 157 was reported by Capretta and co-workers\textsuperscript{49} to give tetrahydrobenzothiophenone 159 (Scheme 42), and, like the analogous furanyl diazoketones described above, the reaction is assumed to proceed \textit{via} cyclopropane intermediate 158. Unlike the reaction of the furanyl derivatives, 158 undergoes ring opening to give 159, leaving the thiophene ring intact. The difference in reactivity of the two cyclopropane intermediates has been attributed to the formation of a stronger C=O bond in the opening of the furan ring.

Scheme 42: Contrasting reactions of furanyl and thienyl diazoketones

1.2.1.2 Acid Catalysed Reactions of α-Diazoketones
Friedel-Crafts alkylation of phenyl rings with diazoketones has also been accomplished in the absence of a transition metal catalyst. In these cases, Lewis and Brnsted acids are the catalysts. The first report of an acid catalysed Friedel-Crafts alkylation came in 1945, when Cook and Schoental reported\textsuperscript{50} the synthesis of 2-chrysenol 161 from the diazoketone 160 (Scheme 43) using a 10% solution of concentrated sulfuric acid in acetic acid.

Scheme 43: Acid catalysed reaction of diazoketone 160.
Then, in 1960, Wilds reported the synthesis of indanone 163 from diazoketone 162, this time using a Lewis acid, BF$_3$•OEt$_2$ (Scheme 44), although more forcing conditions were required in this case.

Scheme 44: BF$_3$•OEt$_2$ catalysed reaction of diazoketone 163.

Mander and co-workers then published a series of papers which investigated the reactions of a series of phenolic and methoxy-substituted phenyl diazoketones. For instance, diazoketone 164 (Scheme 45) undergoes TFA-mediated cyclisation to give dienone 165. The reaction is thought to proceed via formation of cyclobutanone 167, which results from the attack of the diazoketone at the para position to the methoxy group. Intermediate 167 can then undergo rearrangement to 165 via cyclobutanone ring opening and demethylation.

Scheme 45: Acid promoted cyclisation of diazoketone 164.
This methodology has been applied to the total synthesis of natural products, for example by Mander in his synthesis of \((\pm)\)-gibberellin A, and by Chatterjee and Pandit in their synthesis of deserpidine\(^{57}\). The methodology has also been extended to the intermolecular Friedel-Crafts alkylation of diazoketones for the synthesis of substituted oxindoles\(^{58}\).

### 1.2.2 Friedel-Crafts Reactions of Iodonium Ylides

In contrast with the many examples of Friedel-Crafts type reactions of diazoketones, only one example has been described for iodonium ylides\(^{59}\). The advantage of using iodonium ylides over diazoketones is that iodonium ylides are much less hazardous and do not require reagents such as diazomethane for their synthesis. In 1997, Moriarty and co-workers reported the synthesis of 2-tetralones \(175-176\) and \(179\) from \(\beta\)-dicarbonyl iodonium ylides \(169-170\) and \(177\) (Schemes 46 and 47), mediated by stoichiometric amounts of copper (I) chloride. Like the reactions of the diazoketones reported by McKervey\(^{35}\) and diazoketone \(107\) reported by Sudrik\(^{36}\), the reactions of \(o\)- and \(p\)-OMe substituted iodonium ylides \(169\) and \(170\) (Scheme 46) appear to proceed via cyclopropanation, to give intermediates \(171\) and \(172\). These appeared to be in equilibrium with azulenones \(173\) and \(174\), as these could both be detected by both \(^1\)H NMR and TLC. After column chromatography though, the only products isolated were tetralones \(175\) and \(176\), in 75% and 85% yield respectively.

![Scheme 46: Reaction of iodonium ylides 169 and 170.](image)

In contrast to \(169\) and \(170\), \(meta\)-methoxy iodonium ylide \(177\) appeared to undergo direct Friedel-Crafts alkylation with participation of the methoxy group (Scheme 47) to give Wheland intermediate \(178\), which would then rearomatize to give \(179\) in 90% yield. Direct alkylation is suspected in this case as no azulenone intermediate such as \(171\) or \(172\) could be detected by either \(^1\)H NMR or TLC.
Scheme 47: Reaction of iodonium ylide 177 via direct alkylation

The authors also attempted to extend this methodology to the synthesis of indanones from iodonium ylides (Scheme 48). However, only meta-methoxy substituted ylide 180 proceeded to give indanone 181 in 65% yield. Iodonium ylides 182 and 183, o- and p-methoxy substituted respectively, only produced dimers 184 and 185. Presumably this is because if intramolecular cyclopropanation were to occur, the result would be a highly strained tricyclic butanone, whereas for m-methoxy iodonium ylide 180, direct alkylation with participation of the methoxy group is possible. Curiously, the role of CuCl is unknown in this reaction, and the formation of a copper carbene was not suspected.

Scheme 48: Reactions of iodonium ylides 180, 182 and 183.
1.2.3 Alkynes as Diazo Surrogates

1.2.3.1 Reactions with an Internal Oxidant

There are also numerous reports of alkynes and an oxidant being used as diazo surrogates to access gold or platinum carbenes. These could then undergo Friedel-Crafts type cyclisation if aryl alkynes are used. Like the use of iodonium ylides, this is an attractive method for accessing metal carbenoids without the drawbacks of diazoketones. For example, in 2007, the groups of Toste and Zhang reported the synthesis of benzothiazepinones such as 188 and 190 from alkynyl sulfoxides 186 and 189 (Scheme 49) using gold (III) and gold (I) catalysts.

![Scheme 49: Cyclisation of alkynes 186 and 189.](image)

In these cases, no external oxidant is required as the sulfoxide oxygen can attack the alkyne as it is complexed to the metal, forming intermediate 192 (Scheme 50). In this case, Zhang showed that an α-oxo gold carbene is not involved in the reaction. Instead, intermediate 192 can undergo a [3,3] sigmatropic rearrangement to form intermediate 193. Re-aromatisation and protodeauration then gives the product 188.
Scheme 50: Proposed mechanism for gold catalysed cyclisation of alkynes 186 and 189.

Since then, numerous examples of the intramolecular cyclisation of aryl alkynes using an internal oxidant have been reported,\(^6\) extending the scope to include five and six membered rings, and using nitrones rather than sulfoxides as the internal oxidant.

1.2.3.2 Reactions with an External Oxidant

Numerous examples have also been reported of the in-situ generation of gold carbenes from alkynes using an external oxidant, mostly pyridine N-oxides. For example, in 2013, Gagosz and co-workers reported\(^6\) the synthesis of 2-indanones from propargyl arenes catalysed by a bisarylphosphonite gold (I) complex, and later on in the same year, Li reported\(^6\) the synthesis of oxindoles via the gold catalysed oxidative cyclisation of N-arylamides (Scheme 51).
Scheme 51: Gold catalysed oxidative cyclisation of N-arylnamides with pyridine-N-oxide as the external oxidant

Gold (I) catalyst Ph$_3$PAuCl was chosen as the optimum catalyst for this reaction, and yields were generally reasonably poor, however, halogens, electron rich and electron poor aryl groups were tolerated in the reaction. For example, ynamide 194 gave oxindole 195 in 42% yield. Meta-substituted ynamide 196 gave a mixture of regioisomers 197 and 198 in 55% yield and a 1:0.7 ratio. The mechanism of this reaction does seem to involve the formation of a gold carbene (Scheme 52).

Scheme 52: Proposed mechanism of the gold catalysed oxidative cyclisation of ynamides with pyridine N-oxide as the external oxidant.

Deuterium kinetic isotope effect experiments indicated that C-H cleavage was unlikely to be involved in the rate determining step, thus an electrophilic aromatic substitution
mechanism was proposed. This is thought to involve attack of pyridine N-oxide on the alkyne as it co-ordinates to the catalyst to generate intermediate 199. Electrophilic aromatic substitution can then occur to form Wheland intermediate 200, which can then re-aromatise to give intermediate 201. Intermediate 201 can then undergo protodeauration to release the final products. Many more such examples have been published using a gold (I) or (III) catalyst with an external oxidant, such as Yang’s synthesis of 1H-pyrrolo[1,2-a]indol-2(3-H)-ones,68 Ye’s synthesis of isoquinolines and β-carbolines69 and Hashmi’s synthesis of benz[a]fluorenones using a combination of oxidative gold catalysis and photochemistry.70

1.2.2.3 Reactions without a metal catalyst

Interestingly, it is also possible to carry out this reaction without a metal catalyst: in 1975, Utawanit and Katzellenbogen reported71 the synthesis of indanone 205 from alkyne 202, simply by heating 202 to 90 °C either neat, or in CCl₄ solution (Scheme 53).

Scheme 53: Metal free cyclisation of alkyne 202 to indanone 203.

The reaction appears to proceed via a Claisen-type rearrangement from 203 to form ketene 204, which can rapidly cyclise and rearomatize to form 205.

References


(11) Talero, A. G.; Martins, B. S.; Burtoloso, A. C. B. Coupling of Sulfoxonium


(68) Li, T.; Yang, P. Au(I)-Catalyzed Access to 1H-Pyrrolo[1,2-a]Indol-2(3-H)-


Chapter 2
2.1 Aims

As described in the previous section, in 2017 the group published\(^1\) a paper describing the functionalisation of aromatic C-H bonds (Scheme 54) with α-ketosulfoxonium ylides. While the scope of the reaction was broad, sulfoxonium ylide 85 did not react in the expected manner, producing ketone 86 in only 10% yield. Instead, the major product was 2-indanone 87. As previously described, one of the major methods to synthesise 2-indanones is to start from the parent α-diazoketone.

**Scheme 54**: Top: previous work within the Aïssa group on Rh (II) catalysed C-H insertion reaction of sulfoxonium ylides. Bottom: Unpublished result with sulfoxonium ylide 85, in which the major product was indanone 87.

Further investigation of the reaction described in Scheme 54 (bottom) found that the yield of 87 improved from 57% to 77% in the absence of [Cp*RhCl\(_2\)]\(_2\), AgSbF\(_6\) and phenylpyridine. The initial aims of this thesis were therefore:

i) to optimise the reaction with respect to the base and the solvent
ii) to expand the scope of the reaction to heterocycles
iii) to study the mechanism of the reaction.

Furthermore, one motivation for exploring the chemistry of sulfoxonium ylides is to provide an alternative reagent to α-diazoketones, which are often considered to be highly unstable and explosive compounds. However, barring a few relatively limited examples\(^2\)–\(^5\), quantitative data on the thermal stability of diazoketones is not widely available. For sulfoxonium ylides, only one example of the thermal stability of a
sulfoxonium ylide has been described\(^6\). Therefore, one additional aim of the project was to collect some quantitative data on the thermal stability of sulfoxonium ylide \(85\), and compare it with the equivalent diazoketone.

Diazketone \(208\) was synthesised (Scheme 55), and differential scanning calorimetry (DSC) data was collected on both it and sulfoxonium ylide \(85\). A DSC experiment would reveal at exactly what temperature decomposition of each compound occurred, whether decomposition was endothermic or exothermic, and the magnitude of any endotherms or exotherms.

\[
\text{Scheme 55: Synthesis of diazoketone } 208 \text{ from carboxylic acid } 206.
\]

Compound \(206\) was treated with SOCl\(_2\) and DMF to synthesise the acid chloride \(207\), and then, after the DCM and excess SOCl\(_2\) had been removed, the acid chloride was dissolved in dry diethyl ether and treated with a solution of trimethylsilyl diazomethane in hexane to afford the diazoketone \(208\) in 38% yield as a bright orange solid. Compound \(208\) was then shipped to AstraZeneca’s Macclesfield Campus, and subject to the DSC experiment (chart 1). The DSC experiments were carried out by Benjamin Dobson.
10.4 mg of 208 was weighed out and sealed in a crucible, then heated slowly from room temperature to 500 °C. Firstly, there is an endotherm (chart 1, blue peak) beginning at around 34 °C and peaking 60 °C. The size of this endotherm is -73 J·g⁻¹, and is likely to be related to the melting of 208. Then, there is a large exotherm (red peak) beginning at 73 °C, and continuing up to 244 °C, releasing a total of 866 J·g⁻¹. According to United Nations guidelines⁷, a substance cannot be explosive if the decomposition energy released between 0 and 500 °C is less than 800 J·g⁻¹. With a decomposition energy of 866 J·g⁻¹, 208 is squarely above this limit, and thus must be considered an explosive. Also likely to be of concern is the relatively low temperature (~73 °C) that this exotherm begins at, as this could be close to the temperature a reaction is being conducted at, thereby increasing the risk of an incident. Chart 1 can be contrasted with the DSC data of sulfoxonium ylide 85 (chart 2).
This experiment was conducted according to the same procedure as for 208, using 5.7 mg of 85. This compound also has a small endotherm (-15 J•g⁻¹) beginning at 134 °C, and then there is an exotherm beginning at 145 °C, and continuing up to 172 °C. The decomposition energy released during this event is 264 J•g⁻¹, which is well below the limit set by the United Nations guidelines, thus, 85 cannot be considered as an explosive material. Furthermore, this exotherm has a much smaller range than 208 (27 °C for 85, vs 171 °C for 208), and it occurs at a much higher temperature. There are then two smaller exotherms, beginning at 179 °C and 412 °C, which are likely to be related to the decomposition of DMSO. Taking these into account, the total exotherm released is 650 J•g⁻¹, still well below the United Nations limit for a compound to be considered explosive.

2.2 Optimisation of the Reaction

2.2.1 Variation of the solvent

As it had already been established that the reaction proceeds in the absence of phenylpyridine, [Cp*RhCl₂]₂ and AgSbF₆, it was decided to next vary the solvent. A variety of solvents were tested, both protic and aprotic, and spanning a range of polarities (table 2).
Simply changing the solvent from HFIP to TFE (2,2,2-trifluoroethanol) (entry 1 vs entry 2) led to no reaction, and the starting material was recovered unchanged. Moving away from fluorinated alcohols, 1,2-DCE did not promote the reaction at all (entry 3), not even upon the addition of additives with a similar pKa to that of HFIP (entries 4 and 5; HFIP pKa: 9.2, A pKa $\sim$10.99; B pKa $\sim$10.28). Isopropanol, tert-butanol or ethanol did not promote the reaction either (entries 6-8). It is worth noting that in entries 2, 5 and 6-8, the starting material was recovered intact, with no traces of any O-H or N-H insertion products. Aprotic solvents such as THF (entry 9), toluene (entry 10) and ethyl acetate (entry 11) did nothing to promote the reaction. However, upon the use of HFIP as a co-solvent, the reactivity was recovered (entries 12-14), and the yields were virtually unchanged from the initial conditions in entry 1. These results, particularly entries 2, 4-5 and 6-8, suggest that the role of HFIP must be more than to simply act as a proton source, and the implications of this will be discussed.
further in a later section. Given the results in table 2, it was decided to use HFIP as the solvent for the rest of the screening reactions.

### 2.2.2 Variation of the base

Next, it was decided to vary the base to see if what, if any, effect this would have on the reaction (table 3).

![Chemical structure](image)

**Table 3**: Variation of the base. Conditions: 85 (50 mg, 0.17 mmol), base (1 equiv), dissolved in HFIP (0.9 mL, 0.2 M) and heated at 60 °C for 16 h. a: Isolated yield of 87. b: With 2 equiv base. c: Reaction conducted using 200 mg 85.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>%Yield^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOAc</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>KOPOiv</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc(^b)</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>KOPOiv(^c)</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>K(_2)CO(_3)</td>
<td>80 (^9)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>K(_3)PO(_4)</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>NaHCO(_3)</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>NaH(^-)</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>Et(_3)N</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>DIPEA</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>DBU</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>DABCO</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>Pyridine</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>DMAP</td>
<td>42</td>
</tr>
<tr>
<td>15</td>
<td>Li(_2)CO(_3)</td>
<td>8(^1)</td>
</tr>
<tr>
<td>16</td>
<td>Na(_2)CO(_3)</td>
<td>74</td>
</tr>
<tr>
<td>17</td>
<td>Cs(_2)CO(_3)</td>
<td>83</td>
</tr>
<tr>
<td>18</td>
<td>None</td>
<td>51</td>
</tr>
</tbody>
</table>

Changing the base to KOPOiv did not result in a significant increase in the yield (entry 1 vs entry 2), and neither did using 2 equivalents of base (entries 3 and 4 vs entries 1 and 2). Neither K\(_2\)CO\(_3\) nor K\(_3\)PO\(_4\) caused any significant increase in the yield of 87 (entries 5 and 6). NaHCO\(_3\) and NaH both caused significant drops in yield (entries 7 and 8), perhaps surprisingly given their different pKa values. Next, a series of amine bases were attempted (entries 9-14). Triethylamine, DIPEA and DABCO did not cause a significant increase in yield of 87 (entries 9, 10 and 12 respectively), however, DBU, pyridine and DMAP caused significant drops in the yield of 87 (entries 11, 13 and 14).
respectively). Next, the rest of the alkali metal carbonates were tried (entries 15-17), which all resulted in similar yields of 87. However, it is also noteworthy that the reaction worked to some extent in the complete absence of base (entry 18), albeit with a lower yield. Since potassium carbonate is cheap and abundant, it was decided to use it in all subsequent reactions to expand the scope of the reaction, particularly after the reaction was scaled up from initial 50 mg scale to 200 mg (entry 5, 91% isolated yield).

2.3 Synthesis of Sulfoxonium Ylides

As there are many literature reports of sulfoxonium ylides being synthesised from methyl or ethyl esters, the synthesis of sulfoxonium ylide 85 was first attempted from methyl ester 209 and 1 derived from trimethylsulfoxonium iodide 210 and KO\textsubscript{t}Bu (Scheme 56), proved to be problematic.

![Scheme 56](image)

**Scheme 56**: The synthesis of sulfoxonium ylide 85 from ester 209.

Compound 210 was suspended in dry THF, KO\textsubscript{t}Bu was added and the mixture was heated at reflux in the dark for 2 hours, before being cooled to room temperature. Neat 209 was then added in one portion, and the reaction was heated to reflux for 16 h. The conversion of ester 209 by this procedure was low, as was the yield of 85 (31%). The purity of the isolated material also proved to be poor, as observed by \textsuperscript{1}H NMR, even after chromatography. Perhaps more seriously, the results were not reproducible and further attempts to synthesise 85 from methyl ester 209 were unsuccessful. Given Nugent’s reports\textsuperscript{8,9} of the synthesis of sulfoxonium ylides from 4-nitrophenyl esters in high yield, and the reported synthesis of sulfoxonium ylides from acid chlorides, these methods were next investigated (Scheme 57).
Scheme 57: Top: Synthesis of sulfoxonium ylide 85 from 4-nitrophenyl ester 212. Bottom: synthesis of 85 via acid chloride 207.

Firstly, 4-nitrophenyl ester 212 was synthesised from commercially available acid 206 and 4-nitrophenol 211 in 91% isolated yield after column chromatography. Compound 212 was then used to synthesise 85. For this reaction, the experimental procedure was modified: compound 210 and KOtBu were refluxed for 2 hours in the dark in THF as before, however, the suspension was then cooled to 0 °C. A solution of ester 212 in THF was added dropwise, then the mixture was stirred at room temperature. This procedure led to full conversion of 212 in 30 mins. Compound 85 could be isolated in 48% yield after column chromatography and re-crystallisation from ethyl acetate, and in satisfactory purity. Importantly, this proved to be reproducible, with a further batch of 85 being synthesised in 50% yield from 212. An attempt to synthesise 85 from acid chloride 207 was made in an attempt to further improve the yield. The acid chloride 207 was synthesised from the acid 206 and SOCl₂, however, no attempt was made to isolate or characterise it. DCM and excess SOCl₂ were evaporated on the Schlenck line, and a THF solution of acid chloride 207 was added dropwise at 0 °C. Full conversion was achieved in just 15 minutes, and 85 was isolated in 62% yield after re-crystallisation of the crude material from ethyl acetate. Importantly, this also proved to be reproducible, with a further batch of 85 being synthesised via acid chloride 207 in 58% yield over two steps from acid 206. Because of the higher yield, and the shorter reaction time from acid 206, all further batches of 85 were synthesised via the acid chloride. However, it is noteworthy that, although the acid chloride method proved to
be the best way of synthesising some sulfoxonium ylides in this chapter (Scheme 58),
the more reliable method for most was found to be the nitrophenyl ester (Scheme 60).
This variability was attributed to the presence of small amounts of SOCl₂ and HCl,
even after evaporation on the Schlenck line for several hours.

![Scheme 58](image)

**Scheme 58:** Sulfoxonium ylides discussed in this chapter which were synthesised via
the acid chloride

Compound 213 was synthesised in 67% yield, whereas a series of 4-substituted
sulfoxonium ylides 214-218 were synthesised from the corresponding carboxylic
acids in 40-62% yield. In the case of 214, the corresponding carboxylic acid is
ibuprofen, the common non-steroidal anti-inflammatory drug (NSAID), and therefore
commercially available. However, corresponding carboxylic acids for 215-218 were
synthesised by deprotonation of commercially available methyl esters with LDA,
followed by addition of MeI. Subsequent saponification of the resulting ester resulted
in the carboxylic acids. **Gem**-dimethyl sulfoxonium ylide 219 was synthesised in 94%
yield from the commercially available carboxylic acid. Allyl, benzyl and cyclohexyl
substituted sulfoxonium ylides 220, 221 and 222 were synthesised in 58%, 25% and 36% yields respectively. Carboxylic acids for 220 and 221 were synthesised by a similar method described for 215-218, except that the enolate was quenched with allyl bromide and benzyl bromide respectively. The carboxylic acid leading to 222 was commercially available. As discussed, severe reductions in yield could be due to the presence of small amounts of HCl or SOCl₂ present, even after evaporation under high vacuum. Compound 223 was synthesised in 37% yield. In this case, the carboxylic acid was not commercially available, and so was synthesised via the palladium catalysed cross coupling of bromobenzene 224 with an enolate derived from ester 225 (Scheme 59).

![Scheme 59: Palladium catalysed cross coupling of bromobenzene 224 with ester 225.](image)

Compound 226 could be isolated in 62% yield after column chromatography, and saponification of 226 with NaOH led to the carboxylic acid. The majority of sulfoxonium ylides were synthesised from the corresponding 4-nitrophenyl esters, for example 227 and 228 (Scheme 60).

![Scheme 60: Sulfoxonium ylides synthesised from the corresponding 4-nitrophenyl esters.](image)

In the case of both 227 and 228, the corresponding carboxylic acids were purchased from Sigma Aldrich and Fluorochem respectively and used as received. Compound
was isolated in 81% yield from the corresponding 4-nitrophenyl ester, whereas 
was isolated in 64% yield from the corresponding nitrophenyl ester. The synthesis
and structures of further sulfoxonium ylides will be discussed at the beginning of the
relevant sections.

2.4 Scope of the HFIP-mediated reaction

2.4.1 Variation of the substituents on the phenyl ring

With both the optimum synthesis of sulfoxonium ylides, and the optimum conditions
for the HFIP mediated reaction established, attention was next turned to expanding the
scope. Firstly, variation of the substituent in the \( \text{para} \) position of the phenyl ring was
attempted (Scheme 61). Variation in this position was attempted first as a single
regioisomer of product would be formed, thus simplifying analysis and purification.

Scheme 61: Reaction of sulfoxonium ylides 213-218. Conditions: Sulfoxonium ylide
(0.66 mmol), \( \text{K}_2\text{CO}_3 \) (0.66 mmol) in HFIP (3.3 mL, 0.2 M) at 60 °C for 16 h. a: At 80
°C in the microwave for 2 h. b: At 90 °C

Compound 213 (\( R^1 = \text{H} \)) was subjected to the optimised reaction conditions, and
indanone 229 was isolated in 46% yield, with the remainder of the mass balance
consisting of unreacted starting material. Compound 214 (\( R^1 = \text{iBu} \)) led to indanone
230 in 77% yield, whereas compound 215, with an aromatic ring bearing a strongly electron-donating group, led to only 65% yield of indanone 231, with the remainder of the mass balance consisting of solvolysis product 232, which was isolated in 25% yield. Halogen substituents were well tolerated, with compound 216 (R1 = Cl) leading to 51% yield of 233 under the optimised conditions. This yield could be increased to 81% by heating the reaction at 80 °C in the microwave for 2 h. Compound 217 (R1 = Br) led to 34% yield of indanone 234 under the optimised conditions, however this yield could also be increased, this time by simply increasing the temperature to 90 °C. Compound 218, with an aromatic ring bearing a strong electron-withdrawing group, also needed the temperature to be increased to 90 °C, and these conditions led to 61% yield of indanone 235. Attention was then turned to sulfoxonium ylides 227 and 228, desmethyl analogues of 212 and 215 respectively (Scheme 62).

Scheme 62: Reaction of compounds 227 and 228 under the HFIP mediated conditions.

In the case of 227, indanone 236 could not be detected. Instead, the product of the reaction was ketone 237, which was isolated in 54% yield. This is compared to compound 212, where the indanone 228 was the major product (65% yield), and ketone 229 was only isolated in 25% yield. In the case of 228, indanone 241 also could not be detected, and the only product of the reaction was HFIP ester 239. These results led us to consider that substitution at the benzylic carbon was important, and that the Thorpe-Ingold effect was therefore playing an important role in governing the
reactivity of each sulfoxonium ylide towards cyclisation. Attention was then turned to gem-dimethyl substituted sulfoxonium ylide 219 (Scheme 63).

![Scheme 63: Reaction of sulfoxonium ylide 219 under the HFIP mediated conditions.](image)

According to the Thorpe-Ingold effect, a gem-dimethyl group ought to have made 219 very reactive towards cyclisation, however, indanone 240 could not be detected, and 219 was recovered unchanged. This result meant that the Thorpe-Ingold effect could be discounted when considering the difference in reactivity between 215 and 227, and between 218 and 228. Attention was next turned to proposing a mechanism for the reaction to account for these observations, as well as the fact that HFIP appears to play a crucial role in facilitating the reaction.

### 2.4.2 Proposed Mechanism

#### 2.4.2.1 Properties of HFIP

HFIP has several unique properties which might explain its role in the reaction (table 4), and which TFE and iPrOH do not share to the same extent\(^1\).

<table>
<thead>
<tr>
<th>Property</th>
<th>HFIP</th>
<th>TFE</th>
<th>iPrOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>1.605</td>
<td>1.383</td>
<td>0.781</td>
</tr>
<tr>
<td>Boiling point/°C</td>
<td>58.6</td>
<td>73.5</td>
<td>82.5</td>
</tr>
<tr>
<td>Dipole Moment/D</td>
<td>2.05</td>
<td>2.03</td>
<td>1.68</td>
</tr>
<tr>
<td>Viscosity/CP</td>
<td>1.62</td>
<td>1.78</td>
<td>2.08</td>
</tr>
<tr>
<td>pK₃ in water</td>
<td>9.30</td>
<td>12.37</td>
<td>17</td>
</tr>
<tr>
<td>Entropy of vaporisation</td>
<td>26.2</td>
<td>28.0</td>
<td>28.3</td>
</tr>
</tbody>
</table>

Table 4: Properties of HFIP, TFE and iPrOH.
When compared with TFE and iPrOH, HFIP has a lower viscosity, lower boiling point and lower entropy of vaporisation, which indicates that the degree of intermolecular hydrogen bonding in neat HFIP is lower than in TFE or iPrOH. This is because HFIP is a poor hydrogen bond acceptor, but as a hydrogen bond donor, it is uniquely strong (table 5).

<table>
<thead>
<tr>
<th>Acceptor</th>
<th>HFIP</th>
<th>TFE</th>
<th>EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>36.4</td>
<td>23.4</td>
<td>NA</td>
</tr>
<tr>
<td>Acetone</td>
<td>28.0</td>
<td>15.5</td>
<td>10.5</td>
</tr>
<tr>
<td>THF</td>
<td>26.4</td>
<td>21.3</td>
<td>NA</td>
</tr>
<tr>
<td>Diethyl sulfide</td>
<td>21.3</td>
<td>NA</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Table 5: Strengths (-ΔH/kJ mol⁻¹) of hydrogen bonds between HFIP, TFE and EtOH, and selected hydrogen bond acceptors. Measured in CCl₄, NA = not available.

According to table 5,¹⁰,¹¹ the strength of the hydrogen bond between HFIP and a hydrogen bond acceptor is much stronger than the bond between TFE or EtOH and an acceptor. Most relevantly for the reaction of sulfoxonium ylides, the hydrogen bond between HFIP and DMSO is much stronger (ΔH = -36.4 kJ mol⁻¹) than the hydrogen bond between TFE and DMSO (ΔH = -23.4 kJ mol⁻¹). This is significant, as it could mean that hydrogen bonding between the sulfoxonium moiety of the ylide and HFIP could increase the ability of DMSO to act as a leaving group. Indeed, there is ample literature precedent where the hydrogen bond donating ability of HFIP is used to activate a leaving group, for example Paquin and co-worker’s report of a Friedel-Crafts reaction of benzyl fluorides¹² (Scheme 64).
Benzyl fluoride 241 was reported to undergo a Friedel-Crafts arylation reaction in the presence of 5 equivalents of \( p \)-xylene 242 in HFIP/DCM (1:9), to give diarylmethane 243 in 90% yield. Given that the reaction would not proceed in the absence of HFIP, the presence of a base, or the presence of the methyl ether of HFIP instead of HFIP, a mechanism was proposed whereby the benzyl fluoride would form a hydrogen bond with HFIP to form complex 244. Cleavage of the C-F bond would then take place, via TS1, to form carbocation 245 and a fluoride ion hydrogen bonded to HFIP. Cation 245 can then undergo electrophilic aromatic substitution with \( Ar^+ \)H to generate the diarylmethane and a proton, which would combine with fluoride to generate HF. Since HF is itself a very strong hydrogen bond donor, it could then enter the reaction as the active catalyst, turning over more benzyl fluoride and generating more HF. The overall driving force of the reaction is proposed to be the generation of strong hydrogen bonds along the reaction pathway. Other reported examples of HFIP allowing a reaction to take place by forming hydrogen bonds with a leaving group include Moran’s report of Friedel-Crafts reactions of highly electronically deactivated benzyl alcohols,\(^{13}\) Aubé’s reports on the inter- and intramolecular Friedel-Crafts acylation of arenes,\(^{14,15}\) Zhu’s report of the use of HFIP in combination with LiCl for Friedel-Crafts reactions,\(^{16}\) and Adrio’s report on the dramatic acceleration in rate of olefin epoxidation in HFIP.\(^ {17}\)
Another possible explanation of the crucial role HFIP plays in promoting the cyclisation reaction is its ability to stabilise carbocations. For instance, HFIP has been reported to arrest certain electrophilic aromatic substitutions, increasing the half-life of radical cations enough to allow their study by EPR spectroscopy\textsuperscript{10}. Moreover, the use of fluorinated alcohols such as HFIP and TFE has been reported to generate oxy- or hydroxyallyl cations from a variety of ketones with leaving groups in $\alpha$-position. For instance, Tang and co-workers reported\textsuperscript{18} the reaction between 2-chlorocyclohexanone \textbf{246} and 2-naphthol \textbf{247} to give \textbf{249} (Scheme 65).

\begin{equation*}
\begin{align*}
\text{246} & \quad 1 \text{ equiv} \\
\text{247} & \quad 1 \text{ equiv} \\
\text{HFIP (0.5 M)} & \quad \text{Na}_2\text{CO}_3 (1.2 \text{ equiv}) \\
\text{rt. 10 h} & \\
\text{248} & \quad \text{96\%}
\end{align*}
\end{equation*}

\textbf{Scheme 65}: Reaction between \textbf{246} and \textbf{247} in the presence of HFIP and a base. a: Yield determined by $^1$H NMR.

The reaction was proposed to proceed via oxyallyl cation \textbf{248}, which is trapped by naphthol \textbf{246}. The absolute requirement for the presence of HFIP or TFE is demonstrated by all attempts to conduct the reaction in alternative solvents. DMF, DMSO, toluene, DCM and acetonitrile all failed to promote the reaction, with only traces of product being detected by $^1$H NMR. This concept is also illustrated by MacMillan’s reported\textsuperscript{19} generation of oxyallyl cations from $\alpha$-tosyloxyketones in the presence of fluorinated alcohols. Thanks to these observations, an initial mechanism was proposed where an oxyallyl cation was formed from the sulfoxonium ylide, which would then be attacked by the aromatic ring via an S\textsubscript{E}Ar mechanism. Attention was then turned to gathering experimental evidence for this mechanism.
2.4.2.2 Proposed Mechanism

The reaction of compound 85 under the standard conditions was followed by $^1$H NMR, and the concentration of starting material was plotted as a function of time (chart 3). $^1$H NMR data was collected at AstraZeneca by David Whittaker.

![Chart 3: Plot of ln ([SM]) vs time](image)

The graph of ln([SM]) vs time is linear, with a good correlation ($R^2 = 0.99$). This suggests that the reaction is first order with respect to 85, and should allow the natural logarithm to be used when calculating $k_{obs}$ for the Hammett plot. After ~5.5 hours, the concentration of starting material had dropped to below 5%, and thus calculations of concentration became unreliable. Therefore, these points have been excluded from chart 3.

2.4.2.3 Hammett Plots

As sulfoxonium ylides 214-218 contain para-substituted aryl rings and ylide 213 contains an unsubstituted ring, it was reasoned that it should be possible to analyse each reaction using the Hammett equation, and thus obtain the reaction constant, $\rho$. Generation of an oxyallyl cation followed by Friedel-Crafts attack of the aromatic ring would be expected generate a strongly negative ($\leq -2.5$) $^20$-$^22$ $\rho$ value, as electron density would be leaving the aromatic ring during the rate determining step.
Experiments were conducted on 213-218 in order to measure the initial rate constant, $k_{\text{obs}}$. Each reaction was stopped after 15 mins, and the temperature was increased to 90 °C in order to have sufficient conversion into product.

Table 6: Conversions of ylides 213-218. [SM] = concentration of starting material after 15 mins. a: Conversions determined by $^1$H NMR spectroscopy.

Using 213 (R = H, entry 1) led to 28% conversion. 214 had 32% conversion after 15 mins, whereas the more electron rich 215 (entry 3, R = OMe) led only to slightly increased conversion (35%). 216 (entry 4, R = Cl) led to 19% conversion after 15 mins, and 218 led to 18% conversion. Conversions established, equation 1 was then used to obtain $k_{\text{obs}}$ for each sulfoxonium ylide (table 7).

$$k_{\text{obs}} = \frac{\ln([\text{SM}]_0 - [\text{SM}]_t)}{t}$$

where $[\text{SM}]_0$ = initial concentration of starting material
$[\text{SM}]_t$ = concentration of starting material at time $t$ (15 mins).

Table 7: Initial rate constants ($k_{\text{obs}}$) of sulfoxonium ylides 213-218. a: The $\sigma_p$ value for a methyl group was used.
Initial rate constants in hand, the Hammett plot could now be obtained (chart 4). The Hammett $\sigma_p$ constants were used, and were plotted against $\log((k_{obs}(X))/(k_{obs}(H)))$, where $k_{obs}(X)$ is the initial rate constant for 214-216, and $k_{obs}(H)$ is the initial rate constant for 213.

$$\log\left(\frac{k_{obs}(X)}{k_{obs}(H)}\right)$$ \hspace{1cm} (2)

Chart 4: Plot of log ($k_{obs}(X)/k_{obs}(H)$) vs Hammett $\sigma_p$ constants.

Taking the gradient of chart 3 gives a $\rho$ value of -0.6 ($R^2 = 0.97$). This does not support a mechanism where positive charge is put onto the aromatic ring during the rate determining step, however, it does suggest a mechanism where electron density is leaving the aromatic ring. An identical plot using the Hammett $\sigma^+$ values led to a $\rho$ value of -0.3, but with a poorer correlation ($R^2 = 0.70$, chart 5).
Chart 5: Plot of log (kX/kH) vs Hammett σ⁺ values.

A ρ value of -0.6 is in fact consistent with ρ values reported for a 5-centre, 4π electron antarafacial electrocyclisation reaction to form the indanone ring.²³⁻²⁵ For instance, in 2012, Antonchick and co-workers reported²⁴ a synthesis of carbazoles 251 from acetanilides 250, mediated by hypervalent iodine in HFIP (Scheme 66, top).

Scheme 66: Synthesis of carbazoles 251 and 252 from acetanilides 250.
A series of para substituted acetanilides 250 were synthesised, subject to the optimised reaction conditions, and the product ratios were correlated with Hammett $\sigma_p$ values. Using this method, Antonchick and co-workers were able to obtain a $\rho$ value of -0.501, with a good correlation ($R^2 = 0.99$). Having obtained a negative $\rho$ value, they concluded that electron density was flowing away from the aromatic ring in the rate determining step. Using this, and experiments to determine the primary kinetic isotope effect, they were able to propose a mechanism for the reaction (Scheme 66, bottom). Oxidation of 250 with hypervalent iodine leads to intermediate 253, which leads to the formation of 254. Intermediate 254 can then undergo a 5-centre, antarafacial, $4\pi$ electron electrocyclic ring closure to form intermediate 255, which re-aromatises to give products 251.

Having obtained a plausible mechanism for the key C-C bond forming step, one further observation was important in enabling a full mechanism to be proposed. During the characterisation of all sulfoxonium ylides utilised in this chapter, it was noted that the carbonyl C=O stretch in the infrared spectra was not where it was expected, around 1750 cm$^{-1}$. Instead, in all cases it was observed at ~1560 cm$^{-1}$, e.g., for 85, it was at 1559 cm$^{-1}$ (Scheme 67). This suggests that the predominant resonance form of the sulfoxonium ylide is not as a ketone, but as an enolate 256 (Scheme 67).

Scheme 67: C=O stretch in the infrared spectrum of 85.

Using these data, a full mechanism for the reaction has been proposed (Scheme 68).
Scheme 68: Proposed mechanism of formation of indanones from sulfoxonium ylides under the HFIP mediated conditions.

Starting from the enolate resonance form of the sulfoxonium ylides, protonation by HFIP leads to intermediate 257 (the keto resonance form). Base promoted formation of intermediate 258, followed by C-S bond cleavage and loss of DMSO would lead to key intermediate 259. The formation of 259 from 258 is thought to be the step in which HFIP is indispensable, as its strong hydrogen bond donating abilities would allow it to form a hydrogen bonding network with DMSO, promoting C-S bond cleavage. Intermediate 259 could then under a 5-centre, 4π electron antarafacial electrocyclisation to give intermediate 260, which could then undergo a facile re-aromatisation to give the indanone products. This mechanism, particularly the formation of intermediate 259, can also explain the formation of solvolysis products 229 and 237 and Favorskii rearrangement product 239 (Scheme 69).
If R\(^1\) = OMe, then an equilibrium between 259 and 261 led to attack by HFIP on 262, a resonance form of 261, to give the solvolysis products 229 and 237. If R\(^2\) = H, then nucleophilic attack of HFIP is unhindered, and presumably proceeded faster than the electrocyclisation. However, if R\(^2\) is a more sterically bulky Me group, then the carbon atom is more hindered, and nucleophilic attack is slower. That would allow the base to convert 261 back to 259 and the electrocyclisation to take place. Conversely, if R\(^1\) = CF\(_3\) and R\(^2\) = H, then 259 can undergo the Favorskii rearrangement to form intermediate 263, which can then undergo ring opening by attack of HFIP on the cyclopropananone to form 239. With a satisfactory mechanism proposed, attention then turned to further expanding the scope of the reaction.

### 2.4.3 α-Carbon Substitution

The next thing that was explored was substitution at the α-carbon atom (Scheme 70). This was conducted in order to challenge the system with more sterically demanding substituents (e.g. cyclohexyl), and to test the regioselectivity of the reaction.
Scheme 70: Variation of the substituent at the α-carbon. a: Reaction conducted at 90 °C.

Compound 220 (R = allyl) reacted smoothly to give indanone 114 in 88% yield, whereas compound 221 (R = benzyl) reacted to give indanone 264 in 67% yield, although this required the temperature to be increased to 90 °C. It is noteworthy that compound 264 was the sole product of this reaction, with no trace of cyclisation with the benzyl group. A more sterically hindered cyclohexyl group in compound 222 led to a correspondingly reduced yield, with 265 being isolated in just 8% yield. Next, attention was turned to sulfoxonium ylides that would further challenge the regioselectivity of the reaction.

2.4.4 Regioselectivity

Sulfoxonium ylide 223 was synthesised via the acid chloride, and subject to the optimised reaction conditions. Compound 223 was a desirable compound as it contain two aryl rings which have the potential for cyclisation to occur, with one being more electron rich than the other (Scheme 71).
Scheme 71: Reaction of sulfoxonium ylide 223 under the HFIP mediated electrocyclisation.

Compound 220 gave a mixture of regioisomers 263 and 264 in 74% yield and in a 6:1 ratio. As expected, the major regioisomer resulted from cyclisation occurring on the more electron rich ring. Unfortunately, the two regioisomers could not be separated by column chromatography. To further test the regioselectivity of the reaction, sulfoxonium ylides 268-271 were synthesised (Scheme 72).

Scheme 72: Synthesis of sulfoxonium ylides 268-271 via the 4-nitrophenyl esters

Compound 268 was isolated in quantitative yield from the corresponding 4-nitrophenyl ester. Compounds 269-271 are derived from the NSAIDs naproxen, carprofen and zaltoprofen respectively, so the carboxylic acids were commercially available. In the case of naproxen and zaltoprofen, the acids were used as received in
the DCC mediated coupling, whereas carprofen had to first undergo N-methylation by
deprotonation with excess NaH followed by quenching with MeI. The resulting acid
was then used in the DCC mediated coupling. Compound 269 was isolated in 85%
yield, compound 270 in 77% yield and compound 271 in 45% yield. The results of
compounds 268-271 under the HFIP mediated electrocyclisation reaction are shown
in Scheme 73.

Scheme 73: Reaction of 268-271 in the HFIP mediated electrocyclisation. a: After 48
h at 60 °C.

Compound 268 gave indanone 272 in 85% yield as a single regioisomer. The
regioselectivity can be explained by a desire to avoid steric clash with the methoxy
groups, as would happen it the other regioisomer was formed. Compound 269 gave
compound 273 in 91% yield, again as a single regioisomer, although it required an
extended reaction time to achieve this yield. Compound 270 gave compound 277 in
68% yield, again as a single regioisomer, and again requiring an extended reaction
time. However, compound 271 gave 1:1 ratio of both regioisomers 278 and 276 in
51% yield. Unfortunately, the regioisomers could not be separated by column
chromatography. To further expand the scope of the reaction, compounds 277 and 278 were synthesised (Scheme 74).

**Scheme 74: Synthesis of sulfoxonium ylides 277 and 278**

In both cases, the sulfoxonium ylides were synthesised from the 4-nitrophenyl esters. In this case, the carboxylic acids were not commercially available, and required multi-step syntheses. For instance, in the case of 277, the first step was the palladium catalysed cross-coupling between 4-bromoindole 279 and tert-butyl acetate to give ester 286 (Scheme 75). Enolate formation and subsequent quenching with MeI led to ester 287, followed by trimethylsilyliodide mediated hydrolysis to give acid 285. This was a common intermediate in the synthesis of 277 and 278. For 277, it could be used directly in the synthesis of the 4-nitrophenyl ester. For 278, tosyl deprotection with refluxing KOH, followed by N-methylation gave the relevant carboxylic acid, which was then used in the synthesis of the nitrophenyl ester. For full details on the synthesis of all intermediates and sulfoxonium ylides, see chapter 3.
Scheme 75: Synthesis of carboxylic acid 285.

With 277 and 278 in hand, both were subjected to the HFIP mediated electrocyclisation reaction (Scheme 76). Tosyl was chosen as the protecting group due to literature precedent suggesting that carbamates, particularly tert-butoxycarbonyl (Boc) groups can be deprotected using HFIP.26

Scheme 76: Reaction of 277 and 278 in the HFIP mediated electrocyclisation.

Compound 277 reacted smoothly to produce indanone 286 in 65% yield, with the Ts group remaining intact throughout the reaction. Compound 278 also reacted smoothly to produce indanone 287 in 64% yield. The electronic nature of the nitrogen substituents in 277 and 278 is very different, yet the yield remained virtually unchanged for both. Therefore, it was assumed that the electronic nature of the nitrogen substituent had not had any effect on the reactivity of either 277 or 278. Encouraged by these results, further expansion of the scope was conducted with the synthesis of sulfoxonium ylides 285-290 (Scheme 77). These were synthesised in
order to challenge the system further, as an alternative reaction with the pyrrole rings is also theoretically possible.

Scheme 77: Synthesis of sulfoxonium ylides 285-287.

Sulfoxonium ylides 285-287 were synthesised via the 4-nitrophenyl esters in moderate yields. However, since the carboxylic acids were not commercially available, they also required multi-step syntheses. For instance, carboxylic acid 290, leading to 285, was synthesised in 2 steps (Scheme 78), by first treating ester 288 with K$_2$CO$_3$ and paraformaldehyde to synthesise acrylate 289 in 16% yield. Tandem Michael addition/saponification led to acid 290, which could be used directly in the synthesis of the nitrophenyl ester.
In the case of 286 and 287, synthesis of the carboxylic acids was accomplished by deprotonation of 288 and methyl phenylacetate respectively with LDA in a similar manner to that described for 277 and 278 (Scheme 75), followed by addition of the relevant alkylating agent. Saponification of the resulting methyl ester led to the carboxylic acids. Alkyl iodide 292 and alkyl bromide 295 (Scheme 79) were found to be the best alkylating agents for the synthesis of 286 and 287 respectively, and they were synthesised using the methods outlined in Scheme 79. For full details of the synthesis of intermediate carboxylic acids, see chapter 3.

 Scheme 79: Synthesis of 292 and 295.

With sulfoxonium ylides 285-287 in hand, each was subjected to the HFIP mediated electrocyclisation reaction (Scheme 80).
Contrary to expectations, compounds 285 and 287 proved to be unreactive. Neither indanones 296 and 298, nor 6- and 8-membered rings 297 or 299 were detected, and the starting materials were recovered unchanged. In contrast, compound 286 proved to be very reactive indeed, as tetracycle 300 was isolated in 85% yield, with azepinone 301 being isolated in 15% yield. The formation of 300 is presumed to proceed via the 4π electron electrocyclisation to give the indanone 302, which then undergoes intramolecular nucleophilic attack by the pyrrole (Scheme 81, top) to give tertiary alcohol 303. Base mediated E2 elimination would then take place to form 300. Compound 301 is likely formed by an S_{E}Ar-type mechanism involving nucleophilic attack of the pyrrole on the protonated ylide (Scheme 81, bottom). All attempts to prevent intramolecular nucleophilic attack of the pyrrole, including addition of 1-10 equivalents of water or DMSO, and lowering the reaction time or temperature to prevent the elimination, simply resulted in lower yields of 300 and 301.

To check whether compound 301 was an intermediate in the conversion of 286 into 300 or indanone 302, it was subjected to the standard reaction conditions (Scheme 85). However, no reaction was observed and compound 301 was recovered unchanged.

Scheme 85: Attempted conversion of 301 into indanone 302 or tetracycle 300.

2.4.5 Heterocycles

Encouraged by the isolation of azepinone 301, which proved that under some circumstances, pyrrole could undergo cyclisation under the HFIP mediated conditions, attention was next turned to the synthesis of sulfoxonium ylides 306-311 (Scheme 86).
Scheme 86: Synthesis of sulfoxonium ylides 306-311.

Sulfoxonium ylides 306-311 were synthesised via the corresponding 4-nitrophenyl esters in moderate to excellent yields. Again, carboxylic acids were not commercially available, so were synthesised in house. For instance, carboxylic acids leading to 307 and 309-311 were synthesised in one step from alanine, phenylglycine, phenylalanine and homophenylalanine respectively, using a similar method to that shown for alkyl bromide 295 (Scheme 79, bottom). Full details on the synthesis of all intermediates is available in chapter 3. With sulfoxonium ylides in hand, 306-308 were first subjected to the HFIP mediated electrocyclisation (Scheme 90).

Scheme 90: Reaction of 306-308 under the HFIP mediated electrocyclisation conditions.
Unlike compound 286, compounds 306-308 did not appear to undergo cyclisation, as solvolysis products 312-314, were the only detectable products. Yields were uniformly poor, with the remainder of the mass balance being unreacted starting material. Compounds 309 and 310 were next subject to the HFIP mediated electrocyclisation reaction (Scheme 85).

Scheme 85: Reaction of 309 and 310 under the HFIP mediated electrocyclisation conditions.

In the case of 309, solvolysis product 315 was isolated in 56% yield. In contrast, 310 proved to be unreactive, with no traces of solvolysis product 316 detected, and the starting material was recovered unchanged. To account for these observations, a mechanism was proposed (Scheme 86) which involved the formation of intermediate 319, where the carbocation could be stabilised by its proximity to the electron rich pyrrole ring. Intermediate 319 could then be attacked by HFIP to form 320, protonation of which would form the observed products 312-315.
Undeterred, it was next decided to synthesise sulfoxonium ylides 321-325, to see if heterocycles other than pyrrole would react under the HFIP mediated electrocyclisation conditions (Scheme 90).

Scheme 90: Synthesis of 321-325.

Compounds 321-325 were synthesised from the 4-nitrophenyl esters in moderate yields. Carboxylic acids again required multi-step syntheses. For example, 321 and 322 required Wittig reactions between 2- and 3-coumaranones 326 and 329 and commercially available phosphonium ylide 327 (Scheme 88) to give esters 328 and
Saponification of 328 and 330 led to the carboxylic acids which could then be used directly in the synthesis of the 4-nitrophenoxy esters.

Scheme 88: Synthesis of esters 329 and 331.

Compound 324 was synthesised from ester 331 by treating it with 10 equivalents of NaOH and 10 equivalents of TsCl in DCM at -20 °C (Scheme 89) which gave tosyl protected ester 332. Methylation of 332 with LDA/MeI using methods described previously followed by saponification led to the carboxylic acid. For full details, see chapter 3.

Scheme 89: Synthesis of 332, an intermediate in the synthesis of 323.

Sulfoxonium ylides in hand, compounds 321 and 322 were first subjected to the HFIP mediated electrocyclisation (Scheme 90).
Compound 321 reacted smoothly produce indanone 333 in 87% yield, and compound 322 also underwent clean conversion to indanone 334 and isomer 335 in 13% and 75% yield respectively. In neither case could any solvolysis product be detected. Interestingly, 335 proved to be an intermediate in the reaction, as 28% conversion to 334 by $^1$H NMR was observed when 335 was subjected to the standard conditions. This perhaps suggests that reaction of 322 is slower than 321. Compounds 323 and 324 were then subjected to the electrocyclisation conditions (Scheme 91).

**Scheme 90**: Reaction of 321 and 322.

**Scheme 91**: Reaction of compounds 323 and 324.
Compound 323 proved to be less reactive than either compound 321 or 322, with indanone 336 being isolated in only 30% yield, with 8% yield of methyl ketone 337. Ketone 337 and indanone 336 could not be separated by column chromatography. Compound 337 is likely to be formed by protonation of reaction intermediates such as 259. Interestingly, compound 324 proved to be much more reactive, with indanone 338 being isolated in 50% yield, alongside compound 339 in 31% yield. Compounds 338 and 339 were easily separable by column chromatography, and, like compound 335, compound 339 proved to be an intermediate in the reaction, as evidenced by its conversion into indanone 338 when placed under the standard conditions. Next, compound 325 was subjected to the electrocyclisation reaction (Scheme 92).

![Scheme 92: Reaction of 325.](image)

Compounds 340 was not detected, and compound 325 was recovered unchanged. Attention was then turned back to compounds 305 and 306 as well as 325, and attempts were made to carry out cyclisation of these compounds.

2.5 Iridium Catalysed Cyclisation of Heteroaryl Sulfoxonium Ylides

2.5.1 Introduction

Exploration of the intramolecular metal catalysed cyclisation of sulfoxonium ylides was begun in order to achieve cyclisation on heteroaromatic rings such as pyrroles 305 and 306, or indole 322, none of which underwent HFIP mediated electocyclisation. Inspired by the apparent intramolecular C-H functionalisation on a pyrrole using [Ir(cod)Cl]$_2$\textsuperscript{27}, and Hopmann’s 2017 report on the synthesis of pyrroles by C-H functionalisation of β-enamino esters\textsuperscript{28}, cyclisation of 305 into 340 and 306 into 342 was accomplished using 10 mol% [Ir(codCl)$_2$ (Scheme 93).
### 2.5.2 Optimisation of Conditions

![Scheme 93: Iridium catalysed cyclisations of 305 and 306.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>R</th>
<th>Catalyst</th>
<th>X</th>
<th>t</th>
<th>Product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>306</td>
<td>Me</td>
<td>[Ir(cod)Cl]₂</td>
<td>10</td>
<td>10 min</td>
<td>342</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>306</td>
<td>Me</td>
<td>[Ir(cod)Cl]₂</td>
<td>10</td>
<td>16 h</td>
<td>342</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>306</td>
<td>Me</td>
<td>[Ir(cod)Cl]₂</td>
<td>1</td>
<td>2 h</td>
<td>342</td>
<td>64⁴</td>
</tr>
<tr>
<td>4</td>
<td>305</td>
<td>H</td>
<td>[Ir(cod)Cl]₂</td>
<td>10</td>
<td>10 min</td>
<td>341</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>305</td>
<td>H</td>
<td>[Rh(cod)Cl]₂</td>
<td>10</td>
<td>10 min</td>
<td>341</td>
<td>0</td>
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<tr>
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<td>305</td>
<td>H</td>
<td>Cp*IrCl₂</td>
<td>10</td>
<td>10 min</td>
<td>341</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>305</td>
<td>H</td>
<td>Cp*RhCl₂</td>
<td>10</td>
<td>10 min</td>
<td>341</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>306</td>
<td>Me</td>
<td>Rh₂(OAc)₄</td>
<td>10</td>
<td>10 min</td>
<td>342</td>
<td>0²</td>
</tr>
<tr>
<td>9</td>
<td>306</td>
<td>Me</td>
<td>Rh₂(OAc)₄</td>
<td>10</td>
<td>2 h</td>
<td>342</td>
<td>0²</td>
</tr>
<tr>
<td>10</td>
<td>306</td>
<td>Me</td>
<td>Rh₂(OAc)₄</td>
<td>10</td>
<td>16 h</td>
<td>342</td>
<td>63</td>
</tr>
<tr>
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<td>306</td>
<td>Me</td>
<td>Rh₂(tfa)</td>
<td>5</td>
<td>16 h</td>
<td>342</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>306</td>
<td>Me</td>
<td>FeBr₂</td>
<td>5</td>
<td>16 h</td>
<td>342</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>306</td>
<td>Me</td>
<td>AuCl(tht)</td>
<td>5</td>
<td>16 h</td>
<td>342</td>
<td>0</td>
</tr>
</tbody>
</table>

**Scheme 94: Optimisation of the catalyst.** a: Microwave heating used. tfa: Trifluoroacetate. tht: Tetrahydrothiophene

Firstly, attempts were made at changing the catalyst. Treating 306 with 10 mol% [Ir(cod)Cl]₂ in 1,2-DCE at 80 °C for 10 mins resulted in only 18% yield of 342 (entry 1). Increasing the reaction time to 16 h led to 60% yield of 342 (entry 2), and the catalyst loading and reaction time could both be lowered by switching to microwave heating.
heating (entry 3), which resulted in a 64% yield of 342. Switching to 305 (R = H) with 10 mol% [Ir(cod)Cl]2 for 10 mins resulted in 74% yield of 341 (entry 4). Switching to 10 mol% [Rh(cod)Cl]2 resulted in no reaction under identical conditions (entry 5), and the starting material was recovered unchanged. Using 10 mol% [Cp*IrCl2]2 (entry 6) resulted in 65% yield of 341, whereas [Cp*RhCl2]2 also resulted in no reaction (entry 7). Since rhodium (II) carboxylates are used for the intramolecular cyclisation of α-diazoketones (chapter 1), it was decided to test Rh2(OAc)4 and Rh2(tfa)4 (tfa = trifluoroacetate) for the intramolecular cyclisation of 306 (entries 6-8). When 10 mol% Rh2(OAc)4 was used, after 10 mins there was no reaction (entry 8). Even when microwave heating was used, no reaction was observed (entry 3 vs entry 9). Only when the reaction time was extended to 16 h (entry 10) did the yield of 342 increase to a comparable level to that obtained using [Ir(cod)Cl]2 (entry 10 vs entries 2 and 3), however, using 5 mol% of Rh2(tfa)4 resulted in no reaction (entry 11). Simple iron (II) salt FeBr2 was reported by Hopmann’s group29 for the synthesis of indolizines from vinyl sulfoxonium ylides and pyridines, so it was decided to try this salt for the intramolecular cyclisation of 306. However, using 5 mol% FeBr2 resulted in no reaction (entry 12). Gold (I) catalysts have been reported by Merck30 for the X-H insertion of sulfoxonium ylides, however, gold (I) complex AuCl(tht) (tht = tetrahydrothiophene) showed no reactivity towards the intramolecular cyclisation of 306 (entry 13). Since no catalyst had shown improvement over [Ir(cod)Cl]2, it was chosen to examine the reaction of compound 325 under metal catalysis (Scheme 95).

Scheme 95: Reaction of 325 under iridium catalysis.

To our delight, compound 325 underwent smooth cyclisation into 340 with 10 mol% [Ir(cod)Cl]2 in 58% yield after 10 mins. Noting that, in the case of compound 305, microwave irradiation had allowed reduction of the catalyst loading to 1 mol% whilst maintaining the yield of 341 (Scheme 94, entry 3), it was decided to examine the effect of microwave irradiation much more closely (Scheme 96).
Scheme 96: Effect of microwave irradiation and catalyst loading on reaction time and yield. MW = microwave.

With 10 mol% [Ir(cod)Cl]₂, after 10 minutes in the microwave, the reaction had gone to completion and 89% yield of 340 was obtained (entry 1). Lowering the catalyst loading to 5 mol% lowered the yield to 66% (entry 2). Therefore, when the catalyst loading was lowered to 1 mol% (entry 3), the reaction time was increased to 1 h, and this resulted in 80% yield of 340. Increasing the reaction time to 2 h (entry 4) increased the yield to 85%. Optimised conditions in hand (Scheme 95, entry 4), attention was next turned to the expansion of the scope of the reaction.

2.5.3 Scope

2.5.3.1 Regioselectivity

Firstly, the reaction of compounds 308-310 under iridium catalysis was examined (Scheme 97). Compounds 308-310 would challenge the system as all three contain alternative aromatic rings or C-H bonds that have been reported to undergo rhodium (II) catalysed reaction with α-diazoketones (chapter 1).
Compound 308 contains an alternative aromatic C-H bond that could be functionalised to synthesise indanone 343. However, 343 was not detected, and pyrrolizinone 344 was isolated in 90% yield. Compound 309 could undergo a Buchner reaction to synthesise azulenone 345. However, 345 was not detected, and pyrrolizinone 346 was isolated in 95% yield. Compound 310 could undergo either secondary aliphatic C-H insertion to give cyclopentanone 347, or heteroaromatic C-H insertion to give compound 348. However, compound 347 was not detected, and pyrrolizinone 348 was isolated in 79% yield, albeit with an increased catalyst loading. Next, compounds 285-287 were subjected to iridium catalysis, to further examine the regioselectivity of the reaction (Scheme 98).
Compound 285 underwent smooth reaction to give indolizinone 297 in 94% yield, with no trace of indanone 296. Similarly, 286 underwent smooth reaction to give azepinone 301 in 90% yield, with no trace of indanone 302. This is a much higher yield and greater selectivity compared with the HFIP mediated electrocyclisation of compound 286, which gave tetracycle 300 in 85% yield, with 15% yield of 301. Compound 287 underwent smooth reaction to give azocinone 299 in 56% yield, again with no trace of indanone 298, although this reaction required higher catalyst loading and temperature, and longer reaction time. In each case, reaction has occurred on the more nucleophilic aromatic ring, even though it is the less entropically favoured pathway.

2.5.3.2 Substituted Pyrrole

In order to test the impact of an electron withdrawing substituent on the pyrrole, compound 351 was synthesised (Scheme 99). A piperazine amide was chosen as saturated heterocycles and amide groups are common motifs in biologically active molecules.
Scheme 99: Synthesis of compound 351.

Compound 351 was synthesised from acid 349 via 4-nitrophenyl ester 350 in 78% yield. Acid 349 was synthesised in 3 steps (Scheme 100) from commercially available 1-Boc-piperazine 352 and acid 353, utilising an amide coupling with PyBOP as the coupling agent to give compound 354. Compound 354 was then deprotonated using NaH, then quenched with ethyl bromoacetate. The resulting ester underwent saponification to give compound 349.

Scheme 100: Synthesis of acid 346.

With compound 351 in hand, it was subjected to iridium catalysis to synthesise compound 355 (Scheme 101).
With 1 mol% [Ir(cod)Cl]$_2$ at 80 °C for 2 h, only 26% yield of 355 was observed (entry 1). When the reaction time was increased from 2 h to 3 h (entry 2), the yield improved to 42%. When the catalyst loading was increased to 5 mol% (entry 3), the yield improved still further to 61%, and when the temperature was increased to 100 °C (entry 4), the yield was a moderate 53% with 2.5 mol% catalyst. The reduced reactivity of 351 is presumably due to the electron withdrawing nature of the amide group, thus making the pyrrole less nucleophilic.

### 2.5.3.3 Indoles

In order to further expand the scope of the reaction, compound 358 was synthesised (Scheme 102).

Compound 358 was synthesised via the corresponding 4-nitrophenyl ester, and was isolated in moderate yields. Compound 358 was derived from L-tryptophan, which
underwent N-methylation to synthesise acid 356. It is worth noting that the stereocentre survived the ylide formation without significant degradation, as reported by Nugent and co-workers for the synthesis of sulfoxonium ylides derived from chiral amino acids. With compound 358 in hand, it, along with compounds 323-324 were subjected to iridium catalysis (Schemes 103 and 104).

Scheme 103: Reaction of compound 358. MW = microwave.

Compound 358, underwent smooth cyclisation to afford compound 359 in 85% yield, but with significant erosion of stereochemical integrity, with the e.e. dropping from 92% to 57%. The origin of this loss of e.e. is unknown. Compounds 323 and 324 were then subjected to iridium catalysis (Scheme 104).

Scheme 104: Reaction of 323 and 324 under iridium catalysis.

Compound 323 underwent smooth cyclisation to afford compound 336 in 80% yield, which was isolated cleanly by column chromatography. Compound 337, produced in 8% yield during the HFIP mediated electrocyclisation reaction, was not detected. On
the other hand, compound 324 produced a complex mixture of products, from which, compound 339 could be isolated in 5% yield. No other product could be isolated or identified, and it appears that compound 324 underwent uncontrolled decomposition under the iridium catalysed conditions. Compounds 277 and 278 were next subjected to iridium catalysis (Scheme 105).

![Scheme 105: Reaction of compounds 277 and 278 under iridium catalysis.](image)

Compounds 277 and 278 did not undergo cyclisation. In both cases, a complex mixture of products was obtained, from which neither indanones 283 or 284, nor compounds 360 or 361 could be detected. It appeared that, like compound 324, compounds 277 and 278 also underwent uncontrolled decomposition under the iridium catalysed conditions.

### 2.5.3.4 Benzofurans

Compounds 321 and 322 were next subjected to iridium catalysis, to further broaden the scope of the reaction to include other heterocycles (Scheme 106).

![Scheme 106: Reaction of compounds 321 and 322 under iridium catalysis.](image)
Compound 321 did not cyclise smoothly, and a complex mixture of products was obtained, in which compound 333 could not be detected. Similarly, compound 322 did not undergo cyclisation, and neither compound 334 nor compound 335 could be detected in the complex mixture of products that was obtained.

2.5.3.5 Amides

In order to further broaden the scope of the reaction, amide sulfoxonium ylides 367 and 368 were synthesised (Scheme 107). Synthesis and full characterisation of compound 365-368 was carried out by undergraduate students Pierre Palamini and Isobel Jobson.

![Scheme 107: Synthesis of compounds 366 and 367. Synthesis carried out by Pierre Palamini and Isobel Jobson. CDI: carbonyldiimidazole.](image)

A THF solution of N-methyl anilines 362 and 363 was added slowly to a refluxing solution of carbonyldiimidazole (CDI) to afford imidazole 1-carboxamides 364 and 365. Compounds 364 and 365 were converted into 366 and 367 by treatment with dimethylsulfoxonium methyldi 1 at 0 °C. With compound 366 and 367 in hand, both were subjected to iridium catalysis for the synthesis of oxindoles. Oxindoles have previously been synthesised from diazoketones (Scheme 108), and are structural motifs found in many natural products and biologically active compounds.

![Scheme 108: Synthesis of oxindoles from diazoacetamides](image)
Various transition metal catalysts have been used for the Friedel-Crafts type cyclisation of the aromatic ring onto the corresponding metal carbenoids, including rhodium (II) carboxylates$^{31-33}$, copper (II) salts$^{34-36}$, and palladium (0)$^{37}$. These reactions were generally high yielding, and by careful choice of ligand, selectivity for aromatic C-H insertion over competing secondary aliphatic C-H insertion or N-H insertion could be achieved. This transformation has also been achieved through non-metal catalysed reactions, including with the Bronsted-acidic resin Nafion-H$^{32,38}$, $N$-halosuccinimides$^{39,40}$, and the electrophilic fluorine source NFSI$^{41}$. However, this transformation has not been achieved using an iridium (I) catalyst, nor has it been reported for sulfoxonium ylides. Thus, 366 and 367 were synthesised and subjected to the optimised reaction conditions (Scheme 109). Reaction of 367 was carried out by Isobel Jobson.

![Scheme 109](image)

**Scheme 109**: Reaction of compounds 366 and 367 under iridium catalysis.

Compound 366 reacted smoothly with 2.5 mol% [Ir(cod)Cl]$_2$ at 80 °C for 2 h, giving oxindole 368 in 51% isolated yield. However, when 367 was subjected to the iridium catalysis, oxindole 370 was isolated in only 21% yield, with 16% yield of dimer 369. The remainder of the mass balance in this case was unreacted 367. The lower reactivity and presence of dimer 369 can be explained by the low solubility of 367 in 1,2-DCE, forcing molecules of 367 into close proximity, thus promoting dimerisation. In order to suppress dimerisation, the use of DMF as a co-solvent was investigated (Scheme 110).
Scheme 110: O’Shea’s reported synthesis of 48 from 47 using [Ir(cod)Cl]₂ in toluene/DMF as part of the synthesis of MK-7246. Bottom: Use of DMF as a co-solvent in the iridium catalysed reaction of 368. This reaction was carried out by me.

The choice of DMF as a co-solvent was inspired by O’Shea’s report of the large-scale synthesis of MK-7246⁴², in which 48 was synthesised from 47 using [Ir(cod)Cl]₂ in a toluene/DMF mixture. This was necessary due to the low solubility of 47 in toluene. Thus, when 367 was treated with 2.5 mol% [Ir(cod)Cl]₂ in an 8.5:1 mixture of 1,2-DCE and DMF, compound 369 could not be detected, and oxindole 370 was isolated in 41% yield, with the remainder of the mass balance being unreacted 367. This reaction was carried out by me. The solubility of 367 appeared to be increased in the DCE/DMF mixture, and the absence of dimer 369 suggests that low solubility was indeed the reason for its formation in 1,2-DCE alone. Investigation of other polar aprotic solvents such as NMP or DMSO, either as co-solvents with DCE, or alone, was not investigated, but would be useful in order to increase the yield of 370, and to further increase the scope of oxindoles accessible from sulfoxonium ylides such as 367.

2.5.4 Cyclopropanation vs Formal Aromatic C-H Insertion

α-Diazoketones have been reported to undergo cyclopropanation catalysed by rhodium (II) carboxylates (chapter 1). Good selectivity could be achieved for aromatic
C-H insertion over cyclopropanation by changing to very electron withdrawing carboxylate ligand, e.g. perfluorobutyrate (Rh\(_2\)(pfb)_4). This was rationalised by considering that the more electrophilic metal centre in Rh\(_2\)(pfb)_4 preferred to undergo the least entropically demanding pathway i.e. C-H insertion. In order to compare these results with the iridium catalysed reaction of sulfoxonium ylide, compounds 220 and 308 were subjected to iridium catalysis (Scheme 111).

![Reaction Scheme](image)

**Scheme 111**: Reaction of compounds 220 and 308 under iridium catalysis.

When 220 was subjected to the optimised reaction conditions, 100% selectivity was achieved for cyclopropanation, and 115 was isolated in 85% yield. None of the indanone 114 could be detected. The presence of 115 when starting from compound 220 is strong evidence that an iridium carbene is indeed present in this reaction. The selectivity of the iridium catalysed reaction is comparable to the reaction of diazoketone 113 with Rh\(_2\)(cap)_4, so it could be inferred that the iridium carbene generated from 220 and the rhodium carbene generated from 113 and Rh\(_2\)(cap)_4 have similar electrophilicity. The iridium catalysed reaction and HFIP mediated electrocyclisation of 220 are therefore regiodivergent: the HFIP mediated electrocyclisation results in indanone 114 in 88% yield, whereas the iridium catalysed reaction results in exclusively cyclopropane 115 in 85% yield. Improvement of the diastereoselectivity of the reaction by addition of a chiral ligand was not attempted, but would be useful way to develop this reaction further. In contrast, the selectivity of the iridium catalysed reaction with 308 is poor, with pyrrolizinone 371 being the major product, and cyclopropane 372 being isolated in only 39% yield, but with a similar
The poorer selectivity could be due to the more nucleophilic nature of the pyrrole ring compared with the phenyl ring of 220: the more nucleophilic pyrrole could favour the less entropically demanding reaction pathway (i.e. formal C-H insertion), whereas the less nucleophilic phenyl ring allows the more entropically demanding cyclopropanation reaction to take place. Next, compound 376 was synthesised (Scheme 112). Synthesis and full characterisation of compound 374-375 was carried out by Isobel Jobson.

**Scheme 112: Synthesis of compound 375.**

Compound 374 was synthesised from N-allylaniline 373 using the same route described for compounds 365 and 366. Compound 375 in hand, it was subjected to iridium catalysis (Scheme 115). This reaction was carried out by Isobel Jobson.

**Scheme 113: Reaction of compound 375 under iridium catalysis.**

Compound 375 reacted smoothly to give oxindole 376 in 26% yield and cyclopropane 377 in 74% yield. In this case, the selectivity is the reverse of that seen for compound 308. This result could be explained in the context of 220 and 308 by considering the relative nucleophilicity of each aromatic ring. The very electron rich pyrrole in 308 favours formal C-H insertion, and thus 371 is the major product. A slightly less electron rich aromatic system in 375 means that although both possible products are formed, cyclopropane 377 is the major one. An even less electron aromatic system in 220 means that formal aromatic C-H insertion does not occur, and cyclopropane 115...
is the only product. The trend of less electron rich aromatic rings favouring cyclopropanation suggests that the reaction does not proceed via formal insertion of the carbene into the aromatic C-H bond.

2.5.5 Mechanistic Study

Attention was next turned to the elution of a potential mechanism for the reaction. Compounds 381 and d-381 (Scheme 114) were synthesised in order to study the deuterium kinetic isotope effect to see if C-H cleavage was likely to be involved in the rate determining step.

Scheme 114: Top: synthesis of compound 386 and d-386.

Compound 381 and d-381 were synthesised from carboxylic acids 379 and d-379 respectively, via the 4-nitrophenyl esters 380 and d-380 in 70% and 62% yield. Compound 379 was synthesised in two steps from indole 385 (Scheme 115). Compound 385 was deprotonated with NaH, and the resulting anion was quenched with methyl bromoacetate to afford ester 386, which was saponified with NaOH to afford acid 379 (Scheme 115, top). Acid d-379 was synthesised from deuterated indole d-385. Compound d-385 was synthesised from 385 (Scheme 115, bottom), first by protection with benzenesulfonyl chloride to afford compound 390, then by directed ortho-lithiation with "BuLi followed by quenching with D2O to give compound d-390. Removal of the benzenesulfonyl group with NaOH gave d-385. Compound d-385 was then subject to the same sequence of reactions as 385 to afford compound d-381. For full details, see chapter 3.

With compound 381 and d-381 in hand, both were subjected to iridium catalysis (Scheme 116).

Scheme 115: Reaction of 386 and d-386. MW = microwave

Compound 381 reacted smoothly to afford compound 385 in 85% yield. A catalyst loading of 2.5 mol% was required in order to achieve this yield, and attempts to lower the catalyst loading to 1 mol% resulted in both lower conversion of 381 and lower
isolated yield of 385. Compound d-381, which was found to be 100% deuterated using $^1$H and deuterium NMR, was then subjected to identical conditions, which led to a 78% isolated yield of 385. However, $^1$H and deuterium NMR of 385 isolated after column chromatography showed that no deuterium incorporation had occurred, despite d-381 being 100% deuterated. The reaction with d-381 was therefore repeated, and $^1$H and deuterium NMR were recorded on the crude product (Scheme 117).

Scheme 117: Reaction of d-381 and deuterium incorporation into the product

After 30 mins at 100 °C, crude $^1$H NMR showed that there was full conversion of d-381 into 385, and deuterium NMR confirmed that 385 had been 60% deuterated at 3-position of the indole, with smaller levels of deuteration either side of the ketone. It was assumed that the deuterium had been lost during column chromatography. Parallel reactions of 381 and d-381 were then carried out, with the conversion being measured by $^1$H NMR of the crude residue after evaporation of the solvent. To allow measurement of the initial rate, the catalyst loading was reduced to 1 mol% and the temperature was lowered to 80 °C (Scheme 118).
Reaction of compound \(381\) under these conditions resulted in 30.02\% conversion to \(385\), whereas compound \(d\)-\(381\) resulted in 30.00\% conversion to \(d\)-\(385\), giving a deuterium kinetic isotope effect \(k_H/k_D = 1.00\). This result means that there is no deuterium kinetic isotope effect, therefore C-H cleavage is not involved in the rate determining step. The proposed mechanism that explains the observed deuterium labelling and lack of kinetic isotope effect is shown in Scheme 119.
Scheme 119: Proposed mechanism of the iridium catalysed cyclisation.

Iridium carbene 386 would be formed from 381 or d-381, and this would undergo a nucleophilic attack by the aromatic ring to give intermediate 390. Intermediate 390 could then undergo a 1,2-migration to give intermediate 388. Elimination of the iridium from 388 would give 389, which could undergo a facile re-aromatisation to give 385 and d-385. Alternatively, intermediate 386 could undergo cyclopropanation to give intermediate 390. Collapse of 390 would give intermediate 391, which is also capable of undergoing a 1,2-migration to give intermediate 389. This mechanism would explain the observed deuterium labelling, as deuterium would be transferred to the 3-position during the 1,2-migration.
2.5.6 Chemospecificity

During the optimisation of the HFIP-mediated electrocyclisation, a variety of metal catalysts were tested in the reaction (Scheme 120). This work was carried out to check if any metal catalyst could give a comparable yield to the metal free, HFIP-mediated electrocyclisation.

Scheme 120: Reactivity of 85 towards different metal catalysts.

However, 85 proved to be unreactive towards iridium (I), rhodium (I), iridium (III), rhodium (III) and copper (II) catalysts, both in the presence and absence of 2 equivalents of AgBF$_4$ as an additive. This was the case even when 10 mol\% [Ir(cod)Cl]$_2$ was used in conjunction with microwave heating (entry 2), with 85 being recovered unchanged. This contrasts with 305 and 306, which both reacted smoothly under microwave irradiation. Since rhodium (II) carboxylates have been reported to undergo aromatic C-H insertion with aryl \(\alpha\)-diazoketones, it was decided to test Rh$_2$(OAc)$_4$ and Rh$_2$(tfa)$_4$, alongside FeBr$_2$ and AuCl(tht) (Scheme 121).
Scheme 121: Reaction of 85 with rhodium (II), gold (I) and iron (II) catalysts

Using 10 mol% of Rh$_2$(OAc)$_4$ (entry 1) resulted in no reaction, and even under microwave irradiation, there was no reaction with this catalyst (entry 2). Rh$_2$(tfa)$_4$ also proved to be unreactive (entry 3), as did AuCl(tht) and FeBr$_2$ (entries 4 and 5). Finally, a selection of sulfoxonium ylides that had shown reactivity under the HFIP mediated conditions (Scheme 122).

Scheme 122: Examples of sulfoxonium ylides which did not undergo the iridium catalysed reaction

Compound 270, which had cyclised smoothly to give indanone 271 under the HFIP mediated electrocyclisation, showed no reactivity under the iridium catalysed conditions. Compound 227 was similarly unreactive, as no indanone could be detected, and 227 was recovered unchanged. Compound 216, which under the HFIP mediated conditions gave 233 in 81% yield with microwave irradiation was unreactive under the iridium catalysed conditions, with no 233 being detected. Compound 269, which had produced 273 in 91% yield under the HFIP mediated electrocyclisation, also did not react under the iridium catalysed conditions, with neither 273 nor its regioisomer being detected.
2.6 Future Work

2.6.1 HFIP Mediated Electrocyclisation

2.6.1.1 Further Investigation of the Regioselectivity

Although the regioselectivity of the reaction has already been examined somewhat, examination of 3-substituted aromatic rings was desired in order to test the effect of steric on the reaction. To that end, a preliminary investigation using sulfoxonium ylide 394 was synthesised, (Scheme 123), and preliminary investigations were carried out (Scheme 124).

![Scheme 122: Synthesis of ylide 394.](image)

Compound 394 was synthesised in 27% yield via 4-nitrophenyl ester 393. Since this compound was synthesised for preliminary results only, it was characterised by $^1$H NMR only. Compound 392 was synthesised in 2 steps from 2-phenylpyridine and methyl 2-bromopropanate (Scheme 123).

![Scheme 123: Synthesis of acid 392.](image)

A ruthenium (II) catalysed alkylation of 2-phenylpyridine with methyl 2-bromopropanoate gave ester 395 in 68% yield. Saponification of 395 led to acid 392. With compound 394 in hand, it was subjected to the HFIP mediated electrocyclisation (Scheme 124).
Scheme 124: Reaction of sulfoxonium ylide 394.

If 394 undergoes cyclisation, two regioisomers are possible, 396 if H\(^1\) is lost, and 397 if H\(^2\) is lost. Since H\(^1\) is much more sterically hindered than H\(^2\), it might be expected that 397 would be the dominant isomer. A total yield of 52% was observed for this reaction, with a 1:2.7 regioisomeric ratio. It is notable in this case that the two regioisomers were separable by flash column chromatography, and it was assumed that 397 was the dominant regioisomer for the steric reasons outlined previously. With these preliminary results in hand, it would be desirable to synthesise a range of 3-phenyl, 3-methyl and 3-isopropyl phenyl sulfoxonium ylides, and test the effect on the regioselectivity of the HFIP-mediated electrocyclisation (Scheme 125).

Scheme 125: Potential future work testing the steric effects of substituents in the 3-position.

Furthermore, the rhodium (III) catalysed reaction disclosed previously by the Aïssa group was also carried out on compound 394 (Scheme 126).
Scheme 126: Rhodium (III) catalysed reaction of compound 394.

In this case, it may be expected that compound 396 would be the dominant regioisomer. However, both isomers were isolated in 31% total yield in a 1:1 ratio. Further investigation of the reasons for this, and attempts to modify the reaction conditions to improve the yield and regioselectivity, would be worthwhile.

2.6.1.2 Application to a Biologically Active Molecule

It may also be desirable to show that a reaction works on multi-gram scale, and to show its application in the synthesis of biologically active molecules. In 2012, Abbott disclosed 398 (Scheme 127) as a potent inhibitor of GlyT1 for the treatment of neurological and psychiatric disorders, and this compound offers the opportunity to demonstrate both scale up, and application of the HFIP-mediated electrocyclisation.

A functional group interconversion of the amine to the ketone reveals indanone 399. Disconnection of the C-O bond and formation of a methyl ether gives 400, which can then be disconnected back to sulfoxonium ylide 401. For the forward synthesis, a multi-gram scale HFIP mediated cyclisation of 401 would give 400, and a reductive amination with azetidine would give amine 402. Demethylation of the methyl ether with BBr$_3$ would give phenol 403, and alkylation of this with 404 would give the final product in 4 steps from the sulfoxonium ylide.

2.6.1.3 Intermolecular Reactions

Given the postulated mechanism outlined in Scheme 68, it would be desirable to see if intermediate 259 can trapped with nucleophiles other than HFIP. To that end, sulfoxonium ylide 227 was reacted with aniline 405 in HFIP, both in the presence of
K₂CO₃, and in its absence (Scheme 128). This reaction was carried out by Sarah Livesley.

Scheme 128: Intermolecular reaction of sulfoxonium ylide 227 with aniline 405 to give 406.

Methyl ketone 406 was isolated in 34% yield under the optimised reaction conditions for intramolecular cyclisation. These preliminary results suggest that intermolecular trapping of intermediate 256 is possible, and it would be desirable to optimise the reaction further and build a scope with a variety of C-, N-, O-, and S-based nucleophiles for the synthesis of substituted methyl ketones.

2.6.2 Iridium Catalysed Cyclisation

To further investigate the regioselectivity of the iridium catalysed cyclisation, compound 412 was next synthesised (Scheme 129) via the nitrophenyl ester. This compound was synthesised via 4-nitrophenyl ester 411. The carboxylic acid was synthesised from 2-vinylpyridine 407 and TOSMIC to give pyrrole 408. Alkylation of the pyrrole with methyl bromoacetate gave ester 409, and saponification of 409 gave the acid 410.
Scheme 129: Synthesis of sulfoxonium ylide 412.

With compound 412 in hand, it was subjected to the iridium catalysed reaction (Scheme 130). In this case, it might be expected that compound 413 would be the dominant regioisomer, as the pyridine would co-ordinate to the iridium during the course of the reaction.

Scheme 130: Reaction of ylide 412 under the iridium catalysed conditions.

Regioisomers 413 and 414 were both produced in this reaction, in low overall yield, and poor regioselectivity (1.5:1 ratio). Once again, 413 and 414 were separable by column chromatography. It would be desirable to try to increase both the yield and regioisomeric ratio of this reaction, and to synthesise sulfoxonium ylides with a phenyl ring in the 3-position, to compare yields and selectivities (Scheme 131).
Scheme 131: Future development of the reaction in Scheme 130.

2.7 Conclusion

In conclusion, we have developed a chemospecific cyclisation reaction of sulfoxonium ylides on aryl and heteroaryl rings. Firstly, quantitative suggestions of the superior safety of sulfoxonium ylides have been obtained through the collection of differential scanning calorimetry (DSC) data, with sulfoxonium ylide 85 giving a much lower exotherm than its equivalent diazoketone.

Secondly, the synthesis of keto sulfoxonium ylides from \( p \)-nitrophenyl esters and acid chlorides has been accomplished, although the former was preferred in most cases due to the difficulty in removing excess \( \text{SOCl}_2 \) and \( \text{HCl} \) from synthesised acid chlorides. Thirdly, the HFIP mediated electrocyclisation was optimised and the crucial role of HFIP in the cyclisation was established, with no other solvent promoting the reaction to any degree. HFIP could be used as a co-solvent with toluene or 1,2-DCE, but its presence was always required. Fourthly, the scope of the HFIP mediated electrocyclisation reaction was established, with 15 different indanones being successfully synthesised in yields ranging from 42%-92%. It was also established that particularly electron rich (hetero)aromatic rings e.g. pyrroles produced solvolysis products, as either the sole product, or as a minor side product with cyclisation being the major reaction pathway. Electron poor rings could undergo a Favorskii rearrangement to obtain an HFIP ester. Through the observation of first-order kinetics with respect to the sulfoxonium ylide, and the construction of a Hammett plot, it was determined that the reaction proceeded via a 5-centre, 4π electron antarafacial electrocyclisation of key intermediate 259. The presence of key intermediate 259 could also explain the formation of solvolysis and Favorskii side products.
The iridium catalysed cyclisation of heteroaromatic rings was also developed in tandem. The catalyst loading was lowered to 1 mol% and the reaction time decreased through the introduction of microwave heating. The scope of the reaction was developed for the synthesis of pyrrolizinones, indolizinones, azepinones and acocinones. 2- and 3-substituted indoles were also able to undergo cyclisation, and the method was also applied to the synthesis of oxindoles and cyclopropanes.

Finally, the striking chemospecificity of the reaction was demonstrated, as aryl sulfoxonium ylides \textbf{85, 216, 227, 269} and \textbf{270} and benzofuranyl sulfoxonium ylides \textbf{321} and \textbf{322} were unreactive under the iridium catalysed conditions, whereas pyrrole sulfoxonium ylides \textbf{305-310} did not cyclise in the HFIP mediated electrocyclisation. This chemospecificity has not previously been observed for \(\alpha\)-diazoketones or other ylides.

**References for Chapter 2**


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Chapter 3
Chapter 3: Experimental Section

3.1 Synthesis of Compound 205

In a flame dried 2-neck RB flask under N₂, compound 206 (1 g, 4.71 mmol, 1.0 equiv) was dissolved in dry DCM (3 mL, 1.4 M) and cooled to 0 °C using an ice/water bath. SOCl₂ (0.5 mL, 7.07 mmol, 1.5 equiv) was added dropwise, followed by dry DMF (1 drop). The reaction was stirred at room temperature for 30 mins, after which a small aliquot was taken and quenched carefully with MeOH. TLC showed full conversion of 206, and so all volatiles were evaporated using Schlenck techniques. The residue was re-dissolved in dry diethyl ether (17 mL, 0.28 M) and TMS-diazomethane (2 M in hexanes, 5 mL, 9.89 mmol, 2.1 equiv) was added carefully. The reaction was stirred at room temperature overnight, then quenched with water, and extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ solution, then brine, then dried (MgSO₄), filtered and concentrated in vacuo.

The residue was purified by FCC (9:1 petroleum ether:ethyl acetate) to afford compound 205 as a bright orange gum (0.42 g, 1.78 mmol, 38%)/

**Compound 208.** ¹H NMR (500 MHz, CDCl₃): δ 7.32 (m, 10H), 5.25 (s, 1H), 4.93 (s, 1H), in agreement with previously reported data¹.
### 3.2 Synthesis of Compounds 82 and 210-220

**Representative Procedure A:** In a flame dried 2-neck RB flask under N₂, compound 206 (10 g, 47.12 mmol, 1.0 equiv) was dissolved in DCM (34 mL, 1.4 M), and the solution was cooled to 0 °C. SOCl₂ (5.2 mL, 70.67 mmol, 1.5 equiv) was added dropwise, followed by dry DMF (1 drop). The reaction was stirred for 30 mins at rt, and a small aliquot was taken and quenched with MeOH. If this showed full conversion of the acid, then all volatiles were evaporated using Schlenck techniques. The acid chloride was then re-dissolved in dry THF (94 mL). Meanwhile, in a flame dried, 3-neck 500 mL RB flask under N₂, trimethylsulfoxonium iodide (21 g, 94.24 mmol, 3 equiv) was suspended in THF (168 mL) and KO'Bu (11 g, 94.24 mmol, 3 equiv) was added in one portion. The suspension was protected from light using aluminium foil and heated at reflux for 2 h, before being cooled to 0 °C using an ice/water bath. The THF solution of acid chloride was added dropwise, and then the reaction was allowed to warm up to rt over 30 mins. The reaction mixture was then filtered through Celite, the Celite pad was washed thoroughly with DCM, and the filtrate was concentrated *in vacuo*. The residue was recrystallised from EtOAc to afford compound 82 as a white powder (7.73 g, 27.01 mmol, 57%).

**Compound 85.** m.p.: 123–126 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.29 (m, 8H), 7.23-7.20 (m, 2H), 4.85 (s, 1H), 4.38 (s, 1H), 3.38 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 188.9 (e), 141.0 (e, 2C), 129.0 (o, 4C), 128.3 (o, 4C), 126.5 (o, 2C), 71.2 (o), 62.2 (o), 42.0 (e, 2C); IR (neat): ν ~ 3098 (w), 3083 (w), 3053 (w), 3005 (w), 2972 (w), 2918 (w), 1596 (w), 1559 (s), 1493 (m), 1458 (w), 1448 (w), 1431 (w), 1374 (s), 1322 (w), 1291 (w), 1257 (w), 1231 (w), 1167 (s), 1119 (s), 1071 (w), 1030 (s), 989 (w), 948 (w), 929 (w), 909 (w), 861 (s), 818 (w), 789 (w), 758 (w), 743 (s), 724 (s), 695 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₇H₁₈O₂S+H⁺: 287.1100 [M+H]⁺; found 287.1103.
Representative Procedure B: To a flame dried 2-neck RB flask under N\textsubscript{2} was added \textsuperscript{i}Pr\textsubscript{2}NH (2.5 mL, 17.98 mmol, 1.8 equiv) followed by THF (14 mL). The reaction was cooled to -10 °C using an ice/brine bath, and \textsuperscript{n}BuLi (2.5 M in hexanes, 6 mL, 15.98 mmol, 1.6 equiv) was added dropwise. The reaction was stirred at -10 °C for 15 min, before a solution of methyl phenylacetate (1.4 mL, 9.99 mmol, 1.0 equiv) in THF (28 mL) was added dropwise. The reaction was then stirred at -10 °C for 30 mins, before a solution of methyl iodide (1.2 mL, 19.98 mmol, 2.0 equiv) in THF (14 mL) was added slowly. The reaction was allowed to warm up to rt over 1 h, then quenched with H\textsubscript{2}O. The layers were separated and the aqueous washed with EtOAc (x3), and the combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo} to afford a brown oil which was used in the next step without further purification (1.8 g, 10.96 mmol, quant).

**Compound 415.** \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.35-7.28 (m, 4H), 7.27-7.22 (m, 1H), 3.72 (q, \(J = 7.5\) Hz, 1H), 3.66 (s, 3H), 1.50 (d, \(J = 7.2\) Hz, 3H), in agreement with previously reported data\textsuperscript{2}.

Representative Procedure C: Compound 415 (1.80 g, 10.96 mmol, 1.0 equiv) was dissolved in THF/H\textsubscript{2}O (1:1, 44 mL, 0.25 M) and powdered NaOH (2.2 g, 54.81 mmol, 5.0 equiv) was added. The reaction was heated at reflux for 4 h, then cooled to rt and carefully acidified to pH 1 with concentrated HCl, then extracted three times with...
DCM. The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuum to afford a sticky brown gum that was used without further purification (0.96 g, 6.39 mmol, 58%).

**Compound 416.** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.31 (m, 4H), 7.29-7.25 (m, 1H), 3.74 (q, $J$ = 7.2 Hz, 1H), 1.52 (d, $J$ = 7.2 Hz, 3H), in agreement with previously reported data.$^3$

**Compound 213**: Synthesised according to representative procedure A, except that crude compound was purified by FCC (9:1 EtOAc:MeOH), from acid 416 (0.96 g, 6.39 mmol) to afford compound 213 as a cream powder (0.96 g, 4.29 mmol, 67%). m.p. = 68-70 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.30-7.29 (m, 4H), 7.24-7.19 (m, 1H), 4.27 (s, 1H), 3.53 (q, $J$ = 7.2 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 1.45 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 191.8 (e), 143.3 (e), 128.3 (o, 2C), 127.6 (o, 2C), 126.4 (o), 68.7 (o), 50.4 (o), 42.2 (o), 42.1 (o), 18.3 (o, 2C); IR (neat): $\tilde{\nu}$ = 3076 (w), 3012 (w), 2998 (w), 2980 (w), 2959 (w), 2923 (w), 2867 (w), 1601 (w), 1556 (s), 1490 (w), 1453 (m), 1429 (w), 1376 (s), 1362 (s), 1328 (m), 1304 (m), 1291 (m), 1267 (w), 1247 (w), 1184 (s), 1161 (s), 1127 (s), 1089 (w), 1052 (w), 1030 (s), 993 (m), 946 (m), 916 (w), 889 (w), 854 (s), 802 (w), 771 (s), 754 (m), 724 (s), 703 (s), 673 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{12}$H$_{16}$O$_2$S+H [M+H]$^+$ 225.0944; found 225.0947.

**Compound 214.** Synthesised according to representative procedure A, except that crude compound was purified by FCC (93:7 DCM:MeOH) followed by trituration in Et$_2$O, from 2-(4-isobutylphenyl)propanoic acid (Ibuprofen, 1.09 g, 4.85 mmol) to afford compound 214 as white plates (766 mg, 2.73 mmol, 56%). m.p. = 105-108 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.18 (d, $J$ = 8.1 Hz, 2H), 7.06 (d, $J$ = 8.2 Hz, 2H), 4.27 (s, 1H), 3.49 (q, $J$ = 7.2 Hz, 1H), 3.33 (d, $J$ = 18.7 Hz, 6H), 2.43 (d, $J$ = 7.2 Hz, 2H), 1.84 (sept, $J$ = 7.0 Hz, 1H); 0.89 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 192.2 (e), 140.3 (e), 139.6 (e), 129.0 (o, 2C), 127.2 (o, 2C), 68.9 (o), 49.9 (o), 44.9 (e), 42.0 (o), 41.9 (o), 30.1 (o), 22.3 (o), 18.3 (o, 2C); IR (neat): $\tilde{\nu}$ = 3119 (w), 3081 (w), 3013 (w), 2958 (w), 2923 (w), 2867 (w), 2844 (w), 1562 (s), 1508 (w), 1463 (w), 1384 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{12}$H$_{16}$O$_2$S+H [M+H]$^+$ 225.0944; found 225.0947.
Compound 417. Synthesised according to representative procedure B from methyl (4-methoxyphenyl)acetate (1.5 g, 8.32 mmol) to afford compound 417 as a pale brown oil that was used without further purification (1.84 g, 9.47 mmol, quant). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.22 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 3.68 (q, $J = 7.1$ Hz, 1H), 3.65 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H), in agreement with previously reported data$^4$.

Compound 215. Compound 417 (1.84 g, 9.47 mmol) was used in representative procedure C to afford acid 418 (1.49 g, 8.27 mmol, 87%), whose identity was verified by $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.24 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 3.69 (q, $J = 7.3$ Hz, 1H), 1.49 (d, $J = 7.2$ Hz, 3H), in agreement with previously reported data$^5$. Acid 418 was then used according to representative procedure A, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by recrystallisation from EtOAc, to afford compound 215 as a white powder (1.08 g, 4.25 mmol, 51%). m.p. = 90-92 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.24 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 4.28 (s, 1H), 3.81 (s, 3H), 3.50 (q, $J = 7.2$ Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 1.45 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.4 (e), 158.2 (e), 135.5 (e), 128.6 (o, 2C), 113.8 (o, 2C), 68.6 (o), 55.2 (o), 49.6 (o), 42.3 (o), 42.2 (o), 18.5 (o); IR (neat): $\tilde{\nu}$ = 3068 (w), 3016 (w), 2968 (w), 2927 (w), 2834 (w), 1611 (w), 1563 (s), 1509 (s), 1462 (m), 1443 (w), 1428 (w), 1414 (w), 1374 (s), 1334 (m), 1303 (m), 1263 (m), 1247 (s), 1169 (s), 1158 (s), 1132 (s), 1113 (m), 1073 (w), 1060 (w), 1027 (s), 994 (m), 951 (w), 891 (w), 854 (s), 838 (m), 824 (w), 812 (m), 761 (s), 758 (w), 729 (m), 694 (w), 671 (w) cm$^{-1}$; HRMS (ESI): m/z calcld for C$_{13}$H$_{18}$O$_3$S+H$^+$ [M+H]$^+$ 255.1049; found 255.1055.
Compound 419. Methyl (4-chlorophenyl)acetate (1.5 g, 8.12 mmol) was used according to representative procedure B to give 1.46 g of a brown oil which was used according to representative procedure C to give compound 419 as a sticky brown gum (1.13 g, 6.12 mmol, 75%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.30 (dt, J = 8.6, 2.0 Hz, 2H), 7.25 (dt, J = 8.6, 2.2 Hz, 2H), 3.72 (q, J = 7.2 Hz, 1H), 1.50 (d, J = 7.1 Hz, 3H), in agreement with previously reported data. \(^6\)

Compound 216. Synthesised according to representative procedure A, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by recrystallisation from EtOAc, from 419 (1.81 g, 9.83 mmol) to afford compound 216 as a white powder (1.30 g, 5.04 mmol, 51%). m.p. = 106-110 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.29-7.22 (m, 4H), 4.27 (s, 1H), 3.50 (q, J = 7.1 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): δ 191.1 (e), 141.7 (e), 132.1 (e), 129.0 (o, 2C), 128.4 (o, 2C), 68.9 (o), 49.6 (o), 42.2 (o), 42.0 (o), 18.3 (o); IR (neat): \(\tilde{\nu}\) = 3068 (w); 3016 (w); 2968 (w); 2834 (w); 1611 (w); 1563 (s); 1509 (s); 1462 (m); 1443 (w); 1428 (w); 1414 (w); 1374 (s); 1334 (m); 1303 (m); 1263 (m); 1247 (s); 1169 (s); 1158 (s); 1113 (m); 1073 (w); 1060 (w); 1027 (s); 994 (m); 951 (w); 891 (w); 854 (s); 838 (m); 824 (w); 812 (m); 758 (w); 729 (m); 694 (w); 671 (w) cm\(^{-1}\); HRMS (ESI): m/z calcd for C\(_{12}\)H\(_{15}\)ClO\(_2\)S\(^+\)Na\(^+\): 281.0379; found: 281.0370; elemental analysis calcd (%) for C\(_{12}\)H\(_{15}\)ClO\(_2\)S: C 55.70, H 5.84, S 12.39; found: C 55.89, H 5.92, S 12.35.

Compound 217. Synthesised according to representative procedure A, except that crude compound was purified by FCC (98:2 DCM:MeOH), from 2-(4-bromophenyl)propanoic acid (3.49 g, 9.97 mmol) to afford compound 217 as white powder (1.21 g, 3.39 mmol, 40%). m.p.: 133-135 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.41 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 4.27 (s, 1H), 3.49 (q, J = 7.2 Hz, 1H), 3.36 (s, 3H), 3.31 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): δ 191.0 (e), 142.2 (e), 131.4 (o, 2C), 129.4 (o, 2C), 120.2 (e), 68.9 (o), 49.7 (o), 42.2 (o), 42.1 (o), 18.3 (o); IR (neat): \(\tilde{\nu}\) = 3072 (w); 3016 (w); 2968 (w); 2872 (w); 1564 (s), 1486 (m), 1460 (m), 1449 (w), 1421 (w), 1408 (m), 1376 (s), 1359 (s), 1337...
Compound 420. Methyl (4-trifluoromethyl)phenylacetate (2.7 g, 11.63 mmol) was used according to representative procedure B to afford a brown oil (3.82 g), which was used according to representative procedure C to afford compound 420 as a sticky brown gum (2.19 g, 10.04 mmol, 81%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.60 (d, $J$ = 8.1 Hz, 2H), 7.44 (d, $J$ = 8.2 Hz, 2H), 3.82 (q, $J$ = 7.3 Hz, 1H), 1.55 (d, $J$ = 7.3 Hz, 3H), in agreement with previously reported data.$^7$

Compound 218. Synthesised according to representative procedure A, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by trituration in Et$_2$O, from compound 420 (2.19 g, 10.04 mmol) to afford compound 218 as an off-white powder (837 mg, 2.86 mmol, 29%) m.p. = 73-76 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J$ = 8.1 Hz, 2H), 7.42 (d, $J$ = 8.2 Hz, 2H), 4.31 (s, 1H), 3.59 (q, $J$ = 7.2 Hz, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 1.46 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.4 (e), 147.2 (e), 128.6 (e, q, $J$ = 32.4 Hz), 127.9 (o, 2C), 126.6 (e), 125.2 (o, q, $J$ = 3.6 Hz, 2C), 124.9 (e, q, $J$ = 273 Hz), 69.2 (o), 50.1 (o), 42.1 (o), 42.0 (o), 18.3 (o); $^{19}$F NMR (376.5 MHz, CDCl$_3$): $\delta$ -62.33 (s, 3F); IR (neat): $\tilde{\nu}$ = 3069 (w), 2991 (w), 2928 (w), 1617 (w), 1566 (s), 1463 (w), 1418 (w), 1376 (s), 1362 (m), 1322 (s), 1256 (w), 1161 (s), 1106 (s), 1069 (s), 1031 (s), 1017 (s), 988 (m), 953 (m), 857 (s), 846 (s), 804 (m), 777 (w), 760 (w), 747 (w), 715 (w), 695 (w), 675 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{13}$H$_{15}$F$_3$O$_2$S+$\text{H}^+$: 293.0823 [M+H]$^+$; found: 293.0822; elemental analysis calcd (%) for C$_{13}$H$_{15}$F$_3$O$_2$S: C 53.42, H 5.17; found: C 53.57, H 5.18.
**Compound 219.** Synthesised according to representative procedure A, except that crude compound was purified by FCC (98:2 DCM:MeOH), from commercially available 2-methyl-2-phenylpropanoic acid (1.11 g, 6.08 mmol) to afford compound 219 as fine white flakes (1.37 g, 5.75 mmol, 94%). m.p. = 92-93 °C; 1H NMR (500 MHz, CDCl₃): δ 7.37-7.35 (m, 2H), 7.31-7.28 (m, 2H), 7.22-7.18 (m, 1H), 4.12 (s, 1H), 3.33 (s, 6H), 1.50 (s, 6H); 13C NMR (100 MHz, CDCl₃): δ 195.6 (e), 147.1 (e), 128.0 (o, 2C), 126.2 (o, 2C), 125.9 (o), 63.4 (o), 48.8 (o), 41.9 (o, 2C), 26.8 (o, 2C); IR (neat): ν = 3094 (w), 3059 (w), 3001 (w), 2974 (w), 2968 (w), 2926 (w), 2909 (w), 1572 (m), 1498 (m), 1472 (m), 1435 (w), 1380 (m), 1351 (m), 1324 (m), 1306 (m), 1237 (w), 1191 (w), 1149 (s), 1115 (s), 1096 (s), 1071 (m), 1031 (s), 1004 (m), 982 (m), 946 (m), 912 (w), 875 (m), 857 (m), 847 (m), 779 (m), 765 (m), 748 (m), 730 (m), 696 (s), 679 (m) cm⁻¹; HRMS (ESI): m/z calcd for C₁₃H₁₉O₂S ([M+H]+) 239.1100; found: 239.1101.

**Compound 421:** To a flame dried 2-neck RB flask under N₂ was added iPr₂NH (5 mL, 35.96 mmol, 1.8 equiv) followed by THF (28 mL). The reaction was cooled to -10 °C using an ice/brine bath, and nBuLi (2.5 M in hexanes, 13 mL, 31.97 mmol, 1.6 equiv) was added dropwise. The reaction was stirred at -10 °C for 15 min, before a solution of methyl phenylacetate (2.8 mL, 19.98 mmol, 1.0 equiv) in THF (55 mL) was added dropwise. The reaction was then stirred at -10 °C for 30 mins, before a solution of allyl bromide (3.5 mL, 39.96 mmol, 2.0 equiv) in THF (28 mL) was added slowly. The reaction was allowed to warm up to rt over 1 h, then quenched with H₂O. The layers were separated and the aqueous washed with EtOAc (x3), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified by FCC.
(95:5 PE:EtOAc) to afford compound 421 as pale brown oil (2.37 g, 12.46 mmol, 62%). This batch was combined with another batch of 2.21 g prepared in the same manner for use in the next step. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34-7.29 (m, 4H), 7.28-7.23 (m, 1H), 5.78-5.67 (m, 1H), 5.07 (dq, $J = 17.0$, 1.5 Hz, 1H), 5.00 (dq, $J = 10.1$, 1.2 Hz, 1H), 3.67-3.64 (m, 4H), 2.88-2.78 (m, 1H), 2.56-2.47 (m, 1H), in agreement with previously reported data.$^8$

**Compound 220.** Compound 421 (2.37 g, 12.46 mmol) was used according to representative procedure C to afford a sticky brown residue (2.70 g). This was immediately used according to representative procedure A, except that crude compound was purified by FCC (97:3 EtOAc:MeOH), to afford compound 220 as an off-white solid (2.24 g, 8.95 mmol, 58%). m.p. = 88-90°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31-7.27 (m, 4H), 7.23-7.19 (m, 1H), 5.77-5.68 (m, 1H), 5.03 (dq, $J = 1.4$, 17.1, 1.4 Hz, 1H), 4.94-4.92 (m, 1H), 4.32 (s, 1H), 3.43 (t, $J = 7.5$ Hz, 1H), 3.35 (s, 3H), 3.29 (s, 3H), 2.86-2.80 (m, 1H), 2.51-2.45 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.0, 141.2, 136.7, 128.3 (2C), 228.0 (2C), 126.5, 115.8, 69.3, 56.2, 42.2, 42.1; IR (neat): $\tilde{\nu} = 3069$ (m); 3007 (m); 2920 (m); 2855 (m); 1642 (w); 1601 (w); 1566 (s); 1497 (w); 1455 (w); 1426 (w); 1375 (s); 1303 (m); 1248 (w); 1167 (s); 1125 (m); 1105 (m); 1025 (s); 1001 (m); 985 (m); 945 (m); 912 (m); 884 (w); 853 (s); 774 (s); 750 (m); 724 (m); 700 (s); 675 (m) cm$^{-1}$; HRMS (Cl(NH$_3$)): m/z calcd for C$_{14}$H$_{18}$O$_2$S+H$: 251.1106 [M+H]$^+$; found: 251.1096.
**Compound 423:** To a flame dried 2-neck RB flask under N$_2$ was added iPr$_2$NH (3.4 mL, 23.97 mmol, 1.8 equiv) followed by THF (18 mL). The reaction was cooled to -10 °C using an ice/brine bath, and nBuLi (2.5 M in hexanes, 8.5 mL, 21.31 mmol, 1.6 equiv) was added dropwise. The reaction was stirred at -10 °C for 15 min, before a solution of methyl phenylacetate (1.9 mL, 13.32 mmol, 1.0 equiv) in THF (37 mL) was added dropwise. The reaction was then stirred at -10 °C for 30 mins, before benzyl bromide (3.2 mL, 26.64 mmol, 2.0 equiv) was added slowly. The reaction was allowed to warm up to rt over 1 h, then quenched with H$_2$O. The layers were separated and the aqueous washed with EtOAc (x3), and the combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified by FCC (petroleum ether/EtOAc = 95:5) to afford compound 423 as colourless oil (2.40 g, 7.05 mmol, 75%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.33-7.29 (m, 4H), 7.28-7.21 (m, 3H), 7.19-7.15 (m, 1H), 7.14-7.09 (m, 2H), 3.85 (dd, J = 6.8, 8.9 Hz, 1H), 3.60 (s, 3H), 3.42 (dd, J = 8.8, 13.7 Hz, 1H), 3.02 (dd, J = 6.7, 13.6 Hz, 1H); in agreement with previously reported data$^9$.

**Compound 221.** Compound 423 (2.40 g, 7.05 mmol) was used according to representative procedure C to afford a sticky brown residue (2.86 g, 12.63 mmol). This was then used immediately according to representative procedure A, except that crude compound was purified by FCC (DCM/MeOH = 98:2), to afford compound 221 as a cream powder (0.96 g, 3.19 mmol, 25%). m. p. 74-76 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.33-7.26 (m, 4H), 7.22-7.18 (m, 3H), 7.15-7.12 (m, 3H), 4.24 (s, 1H), 3.64 (t, J= 7.7 Hz, 1H), 3.44 (dd, J= 8.4, 13.3 Hz, 1H), 2.99-2.94 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 189.5 (e), 141.3 (e), 140.4 (e), 129.1 (o, 2C), 128.3 (o, 2C), 128.02 (o, 2C), 127.97 (o, 2C), 126.5 (o), 125.8 (o), 69.7 (o), 58.2 (o), 42.1 (o, 2C), 39.4 (e); IR (neat): $\tilde{\nu}$ = 3065 (w), 3026 (w), 3007 (w), 2992 (w), 2941 (w), 2915 (w), 2855 (w), 1963 (w), 1732 (w), 1600 (w), 1568 (m), 1539 (s), 1493 (m), 1452 (m), 1377 (s), 1305 (m), 1242 (m), 1185 (s), 1171 (s), 1108 (m), 1071 (m), 1031 (s), 1003 (w), 991 (w), 963 (w), 945 (m), 895 (m), 861 (m), 831 (w), 801 (m), 770 (w), 760 (w), 745 (m), 733 (s); HRMS (ESI): m/z calcd for C$_{18}$H$_{20}$O$_2$S$^+$[M+Na]$^+$ 323.1082; found 323.1079.
**Compound 222.** Synthesised according to representative procedure A, except that crude compound was purified by FCC (DCM to 9:1 DCM:MeOH) followed by recrystallisation from EtOAc, from commercially available 2-cyclohexyl-2-phenylacetic acid (1 g, 4.58 mmol) to afford compound **222** as an off-white powder (486 mg, 1.66 mmol, 36%). M.p. = 162-164 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.33-7.29 (m, 2H), 7.28-7.24 (m, 2H), 7.19 (tt, J = 6.5, 1.4 Hz, 1H), 4.41 (s, 1H), 3.37 (s, 3H), 3.26 (s, 3H), 2.99 (d, J = 10.7 Hz, 1H), 2.06 (qq, J = 11.4, 3.5 Hz, 1H), 1.97-1.88 (m 1H), 1.75-1.67 (m, 1H), 1.65-1.55 (m, 2H), 1.38-1.24 (m, 2H), 1.20-1.07 (m, 2H), 1.05-0.95 (m, 1H), 0.71 (qd, J = 12.6, 3.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.5 (e), 140.8 (e), 128.4 (o, 2C), 128.1 (o, 2C), 126.2 (o), 69.7 (o), 63.7 (o), 42.2 (o), 42.0 (o), 40.2 (o), 32.1 (e), 31.0 (e), 26.5 (e), 26.2 (e, 2C); IR (neat): $\tilde{\nu} = 3093$ (w), 3058 (w), 2998 (w), 2939 (w), 2914 (w), 2841 (w), 1595 (w), 1557 (s), 1492 (w), 1446 (w), 1430 (w), 1376 (s), 1342 (w), 1323 (w), 1301 (w), 1254 (w), 1208 (w), 1174 (s), 1134 (w), 1104 (m), 1065 (w), 1033 (s), 991 (w), 946 (w), 930 (w), 911 (w), 903 (w), 895 (w), 886 (w), 860 (m), 848 (m), 830 (w), 800 (w), 786 (w), 780 (w), 758 (w), 726 (w), 719 (w), 695 (s), 682 (w); HRMS (ESI): m/z calcd for C$_{17}$H$_{24}$O$_2$S+H [M+H]$^+$ 293.1570; found 293.1570.

![Chemical Structure](image)

**224** 1 equiv

**225** 2.3 equiv

**226** 62%

**424** 80%

**223** 37%

**210** (3 equiv)

**Ligand C:**

![Chemical Structure](image)
**Compound 226**: To a flame dried, 2-neck RB flask was added Pd(OAc)$_2$ (43 mg, 0.19 mmol, 3 mol%), ligand C (160 mg, 0.40 mmol, 6.3 mol%) and solid LiHMDS (2.66 g, 15.92 mmol, 2.5 equiv). The flask was evacuated and backfilled with N$_2$ three times before dry toluene (25 mL, 0.25 M) was added and the reaction was stirred at rt for 10 mins, then cooled to -10 °C using an ice/brine bath. Methyl (4-methoxyphenyl)acetate (2.3 mL, 14.65 mmol, 2.3 equiv) was added dropwise, and the reaction was stirred at -10 °C for a further 10 mins. Bromobenzene (0.7 mL, 6.37 mmol, 1.0 equiv) was added dropwise, and the reaction was heated at 80 °C for 30 mins. The reaction was then filtered through a short plug of silica gel, eluting with toluene, and the filtrate was concentrated in vacuo. The crude residue was purified by FCC (9:1 PE:EtOAc) to afford compound 226 as a pale yellow liquid (791 mg, 3.09 mmol, 48%), which was combined with an earlier batch of 101 mg for use in the next step. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.34-7.27 (m, 4H), 7.27-7.25 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.98 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H); in agreement with previously reported data$^{10}$. 

**Compound 223.** Compound 226 (892 mg, 3.47 mmol, 1.0 equiv) was used according to representative procedure C to afford a sticky brown solid (414 mg, 1.71 mmol). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.34-7.27 (m, 4H), 7.27-7.25 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.98 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H); in agreement with previously reported data$^{11}$. This was then used immediately according to representative procedure A, except that crude compound was purified by FCC (95:5 DCM:MeOH) followed by recrystallisation in EtOAc, to afford compound 223 as a white powder (133 mg, 0.42 mmol, 25%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.28 (m, 4H), 7.20 (m, 3H), 6.83 (d, J= 8.6 Hz, 2H), 4.79 (s, 1H), 4.37 (s, 1H), 3.78 (s, 3H), 3.38 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 189.3 (e), 158.2 (e), 141.4 (e), 133.2 (e), 129.9 (o, 2C), 128.9 (o, 2C), 128.3 (o, 2C), 126.4 (o), 113.7 (o, 2C), 71.0 (o), 61.3 (o), 55.2 (o), 42.1 (o, 2C); IR (neat): $\tilde{\nu}$ = 3065 (w), 3011 (w), 2920 (w), 2836 (w), 2051 (w), 1610 (w), 1567 (s), 1509 (s), 1492 (m), 1465 (w), 1455 (w), 1443 (w), 1425 (w), 1373 (s), 1300 (m), 1248 (s), 1167 (s), 1110 (m), 1026 (s), 982 (w), 939 (w), 923 (w), 883 (w), 868 (m), 844 (m), 834 (m), 805 (w), 784 (m), 770 (w), 753 (w), 739 (m), 728 (m), 701 (m), 672 (m) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{18}$H$_{20}$O$_3$S+Na$^+$ [M+Na]$^+$ 339.1031; found 339.1025.

**Representative Procedure D:** Under air, 4-methoxyphenylacetic acid (2 g, 12.03 mmol, 1.0 equiv) and 4-nitrophenol (2.19 g, 15.64 mmol, 1.3 equiv) were dissolved in THF, and DCC (3.23 g, 15.64 mmol, 1.3 equiv) was added. The reaction was stirred at rt for 18 h, then filtered through Celite. The Celite pad was washed with DCM, and the filtrate was concentrated in vacuo. The residue was purified by FCC (4:1 PE:EtOAc) to afford compound 425 as an amorphous yellow solid (2.50 g, 8.71 mmol, 72%).

**Compound 425.** $^1$H NMR (500 MHz, DMSO-d6): $\delta$ 8.30 (d, $J = 9.1$ Hz, 2H), 7.43 (d, $J = 9.1$ Hz, 2H), 7.31 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 3.95 (s, 2H), 3.75 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d6): $\delta$ 172.9 (e), 158.4 (e), 155.4 (e), 135.8 (e), 130.6 (o, 2C), 130.3 (o, 2C), 127.0 (e), 126.2 (o, 2C), 114.0 (o, 2C), 55.0 (o), 40.0 (e); IR (neat): $\tilde{\nu} =$ 3121 (w), 3086 (w), 3016 (w), 2934 (w), 2913 (w), 2839 (w), 2117 (w), 2040 (w), 1927 (w), 1757 (s), 1611 (s), 1587 (m), 1531 (w), 1514 (s), 1488 (s), 1464 (m), 1455 (m), 1442 (w), 1402 (w), 1345 (s), 1335 (s), 1302 (m), 1243 (s), 1213 (s), 1201 (s), 1177 (s), 1165 (m), 1101 (s), 1025 (s), 1011 (s), 970 (w), 951 (w), 916 (m), 871 (s), 855 (s), 826 (s), 820 (s), 805 (m), 767 (m), 750 (s), 727 (w), 701 (m), 675 (m), 685 (w), 642 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{15}$H$_{13}$NO$_5$+Na$^+$ [M+Na]$^+$: 310.0691; found 310.0690.

**Representative Procedure E:** To a flame dried, 2-neck RB flask under N$_2$ was added compound 210 (5.51 g, 25.05 mmol, 3.0 equiv) and KOtBu (2.81 g, 25.05 mmol, 3.0 equiv), and the flask was evacuated and backfilled with N$_2$ three times. THF (30 mL)
was added and the suspension protected from light and heated at reflux for 2 h. The reaction was then cooled to 0 °C, and a solution of compound 425 (2.4 g, 8.35 mmol, 1.0 equiv) in THF (17 mL) was added dropwise. The reaction was stirred at rt for 15 min, then filtered through Celite. The Celite pad was washed with DCM, and the filtrate was concentrated in vacuo and purified by FCC (9:1 DCM:MeOH) to afford compound 227 as a yellow powder (1.62 g, 6.76 mmol, 81%).

**Compound 227.** m.p. = 1H NMR (500 MHz, CDCl₃): δ 7.15 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.23 (s, 1H), 3.78 (s, 3H), 3.40 (s, 2H), 3.34 (s, 6H); 13C NMR (100 MHz, CDCl₃): δ 189.0 (e), 158.2 (e), 130.3 (o, 2C), 129.2 (e), 113.8 (o, 2C), 69.5 (o), 55.2 (o), 47.1 (e), 42.1 (o, 2C); IR (neat): ν = 3069 (w), 3016 (w), 2964 (w), 2927 (w), 2840 (w), 1610 (w), 1583 (w), 1562 (s), 1509 (s), 1469 (w), 1459 (w), 1443 (w), 1431 (w), 1375 (s), 1329 (w), 1274 (w), 1246 (s), 1186 (w), 1168 (s), 1155 (s), 1117 (m), 1087 (m), 1022 (s), 995 (m), 957 (w), 935 (m), 857 (w), 846 (m), 832 (m), 813 (m), 789 (s), 758 (w), 719 (m), 698 (w), 687 (m) cm⁻¹; HRMS (ESI) m/z calcd for C₁₂H₁₆O₃S⁺Na⁺: 263.0718 [M+Na⁺]; found: 263.0727; elemental analysis calcd for C₁₂H₁₆O₃S: C 59.98, H 6.71, S 13.34; found: C 59.99, H 6.73, S 13.41.

**Compound 426.** Synthesised according to representative procedure D from 4-trifluoromethylphenylacetic acid (2 g, 9.80 mmol) to afford compound 426 as a pale green amorphous solid (1.45 g, 4.46 mmol, 46%). 1H NMR (500 MHz, CDCl₃): δ 8.26 (d, J = 9.3 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 9.4 Hz, 2H), 3.97 (s, 2H); 13C NMR (100 MHz, CDCl₃): δ 168.3 (e), 155.1 (e), 145.5 (e), 136.5 (e), 130.1 (e, q, J = 32.5 Hz), 129.8 (o, 2C), 125.8 (o, q, J = 4.1 Hz, 2C), 125.2 (o, 2C), 124.0 (e, q, J = 272.0 Hz), 122.3 (o, 2C), 40.9 (e); IR (neat): ν = 3120 (w), 3088 (w), 1759 (w), 1666 (w), 1593 (m), 1519 (s), 1490 (m), 1453 (w), 1421 (w), 1412 (w), 1349 (m), 1337 (s), 1322 (s), 1219 (s), 1207 (m), 1161 (m), 1111 (s), 1063 (s), 1020 (s), 968 (w), 928 (w), 876 (s), 865 (m), 854 (s), 825 (s), 770 (m), 753 (w), 738 (s), 704 (s), 679 (m), 665 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₅H₁₀F₃NO₄⁺Na⁺ [M+Na⁺]: 348.0460; found 348.0459.
Compound 228: Synthesised according to representative procedure E, except that crude material was purified by FCC (97:3 DCM:MeOH) followed by trituration in Et₂O, from compound 426 (1.32 g, 4.06 mmol) to afford compound 228 as a white powder (727 mg, 2.61 mmol, 64%). m.p. = 80-82 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.28 (s, 1H), 3.52 (s, 2H), 3.36 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 186.9 (e), 141.1 (e), 129.6 (o, 2C), 128.6 (q, J = 32.6 Hz), 125.2 (o, q, J = 3.6 Hz, 2C), 124.3 (e, q, J = 272.1 Hz), 70.0 (o), 47.5 (e), 42.1 (o, 2C); IR (neat): ν = 3088 (w), 3014 (w), 2926 (w), 1614 (w), 1562 (s), 1482 (w), 1417 (m), 1403 (m), 1375 (s), 1315 (s), 1288 (m), 1252 (w), 1205 (w), 1187 (m), 1157 (s), 1113 (s), 1092 (s), 1061 (s), 1026 (s), 1017 (s), 988 (m), 959 (m), 951 (m), 935 (m), 912 (w), 870 (s), 845 (m), 821 (s), 779 (m), 758 (m), 741 (w), 721 (w), 710 (m), 692 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₂H₁₃F₃O₂S+H⁺: 279.0661 [M+H]⁺; found: 279.0657; elemental analysis calcd (%) for C₁₂H₁₃F₃O₂S: C 51.79, H 4.71; found: C 51.63, H 4.69.

Compound 427. Synthesised according to representative procedure D, from 2-(3,4-dimethoxyphenyl)propanoic acid (1.24 g, 5.90 mmol, 1.0 equiv), to afford compound 427 as an amorphous yellow solid (3.49 g, 9.69 mmol, 62%). ¹H NMR (500 MHz, CDCl₃): δ 8.23 (d, J = 9.3 Hz, 2H), 7.18 (d, J = 9.3 Hz, 2H), 6.94 (dd, J = 8.1, 2.0 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 3.93 (q, J = 7.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.62 (d, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.3 (e), 155.5 (e), 149.2 (e), 148.5 (e), 141.6 (e), 131.7 (e), 125.1 (o, 2C), 122.2 (o, 2C), 119.6 (o), 111.4 (o), 110.5 (o), 55.91 (o), 55.87 (o), 45.1 (o), 18.3 (o); IR (neat): ν = 3081 (w), 2936 (w), 2836 (w), 2019 (w), 1755 (s), 1614 (w), 1591 (w), 1516 (s), 1489 (s), 1454 (m), 1419 (w), 1345 (s), 1253 (m), 1235 (m), 1205 (s), 1143 (s), 1070 (s), 1026 (s), 918 (w), 891 (w), 863 (m), 810 (w), 782 (w), 765 (w), 751 (w), 718 (w), 682 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₇H₁₇NO₆+Na⁺: 354.0948 [M+Na]⁺; found: 354.0956.
**Compound 268.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (98:2 DCM:MeOH), from compound 427 (1.24 g, 3.74 mmol) to afford compound 268 as a pale green amorphous gum (1.08 g, 3.79 mmol, quant).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.86-6.77 (m, 3H), 4.28 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.47 (q, J = 7.5 Hz, 1H), 3.36 (s, 3H); 3.32 (s, 3H), 1.43 (d, J = 7.2 Hz, 3H);$^{13}$C NMR (100 MHz, CDCl$_3$): δ 192.1 (e), 148.9 (e), 147.5 (e), 135.9 (e), 119.5 (o), 111.0 (o), 110.9 (o), 68.7 (o), 55.8 (o), 55.8 (o), 49.9 (o), 42.1 (o), 42.0 (o), 18.4 (o); IR (neat): $\tilde{\nu}$ = 3431 (w), 3007 (w), 2964 (w), 2926 (w), 2835 (w), 2251 (w), 1567 (s), 1513 (s), 1453 (m), 1416 (m), 1375 (s), 1300 (w), 1260 (s), 1232 (s), 1174 (s), 1141 (s), 1077 (w), 1057 (w), 1025 (w), 944 (w), 916 (w), 856 (m), 812 (w), 778 (w), 762 (w), 730 (w), 676 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{14}$H$_{21}$O$_4$S+H$^+$ [M+H]$^+$ 285.1155; found 285.1154.

**Compound 428.** Synthesised according to representative procedure D from racemic naproxen (1 g, 4.34 mmol) to afford compound 428 as white solid (1.21 g, 3.39 mmol, 40%). m.p.: 133–135 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 8.21 (d, J = 9.2 Hz, 2H), 7.79-7.72 (m, 3H), 7.47 (d, J = 8.5, 2.0 Hz, 1H), 7.20-7.14 (m, 4H), 4.12 (q, J = 7.0 Hz, 1H), 3.93 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 172.2 (e), 157.8 (e), 155.5 (e), 145.2 (e), 134.3 (e), 133.9 (e), 129.2 (o), 128.9 (e), 127.5 (o), 126.1 (o), 125.8 (o), 125.0 (o), 122.2 (o), 119.2 (o), 105.6 (o), 55.2 (o), 45.5 (o), 18.2 (o); IR (neat): $\tilde{\nu}$ = 3116 (w), 3080 (w), 2988 (w), 2937 (w), 2459 (w), 2117 (w), 1924 (w), 1754 (s), 1632 (w), 1616 (w), 1603 (m), 1592 (m), 1533 (m), 1523 (s), 1505 (m), 1489 (m), 1463 (w), 1452 (w), 1417 (w), 1390 (w), 1377 (w), 1345 (s), 1325 (m), 1290 (w), 1264 (m), 1227 (m), 1205 (s), 1161 (s), 1127 (s), 1083 (w), 1067 (s), 1030 (m), 1012 (m), 1012 (w), 994 (w), 958 (w), 927 (w), 899 (m), 853 (s), 814 (m), 789 (m), 754 (w), 740 (m), 700 (m), 675 (w), 657 (w) cm$^{-1}$; HRMS (Cl(CH$_4$)): m/z calcd for C$_{20}$H$_{17}$NO$_5$H$^+$: 352.1185 [M+H]$^+$; found: 352.1183.
**Compound 269.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH 98 :2), from compound 428 (1.20 g, 3.41 mmol) to afford compound 269 as an off-white solid (855 mg, 2.81 mmol, 82%). m.p.: 118–119 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.70-7.65 (m, 3H), 7.41 (dd, \( J = 8.5, 2.0 \) Hz, 1H), 7.13-7.10 (m, 2H), 4.30 (s, 1H), 3.91 (s, 3H), 3.66 (q, \( J = 7.1 \) Hz, 1H), 3.36 (s, 3H), 3.30 (s, 3H), 1.52 (d, \( J = 7.1 \) Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 192.0 (e), 157.3 (e), 138.5 (e), 133.3 (e), 129.2 (o), 129.0 (e), 126.79 (o), 126.76 (o), 125.7 (o), 118.6 (o), 105.5 (o), 69.1 (o), 55.2 (o), 50.3 (o), 42.1 (o), 42.0 (o), 18.2 (o); IR (neat): \( \tilde{\nu} = 3008 \) (w), 2977 (w), 2919 (w), 1630 (w), 1604 (m), 1564 (s), 1504 (m), 1481 (w), 1439 (w), 1417 (w), 1371 (s), 1308 (w), 1292 (w), 1264 (m), 1227 (m), 1193 (w), 1164 (s), 1070 (m), 1024 (s), 944 (w), 927 (w), 892 (w), 854 (s), 818 (m), 785 (w), 754 (w), 742 (w), 692 (w), 674 (w) cm⁻¹; HRMS (ESI): \( m/z \) calc'd for C₁₇H₂₀O₃S⁺H⁺: 305.1211 [M+H]⁺; found: 305.1207; elemental analysis calc'd (%) for C₁₇H₂₀O₃S: C 67.08, H 6.62, S 10.53; found: C 66.83, H 6.57, S 10.54.

**Compound 429.** Synthesised according to representative procedure D from N-Me-carprofen¹² (598 mg, 2.08 mmol) to afford compound 429 as yellow solid (645 mg, 1.58 mmol, 76%). The compound was contaminated by some DCC, and was characterized only by ¹H NMR before being used without further purification in the next step. ¹H NMR (500 MHz, CDCl₃): δ 8.21 (d, \( J = 9.2 \) Hz, 2H), 8.04 (d, \( J = 4.5 \) Hz, 1H), 8.03 (d, \( J = 1.4 \) Hz, 1H), 7.43 (dd, \( J = 8.6, 2.1 \) Hz, 1H), 7.40 (d, \( J = 1.0 \) Hz, 1H), 7.32 (d, \( J = 8.7 \) Hz, 1H), 7.26 (dd, \( J = 8.3, 1.5 \) Hz, 1H), 7.18 (d, \( J = 9.2 \) Hz, 2H), 4.19 (q, \( J = 7.2 \) Hz, 1H), 3.86 (s, 3H), 1.74 (d, \( J = 7.2 \) Hz, 3H).

**Compound 270.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 90 :10), from compound 429 (645 mg, 1.58 mmol) to afford compound 270 as white powder (1.21 g, 3.39 mmol, 40%). m.p.: 133–135 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.99 (d, \( J = 1.9 \) Hz, 1H), 7.94 (d, \( J = 8.1 \) Hz, 1H), 7.39 (dd, \( J = 2.0, 8.4 \) Hz, 1H), 7.34 (s, 1H),
7.28 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 4.34 (s, 1H), 3.82 (s, 3H), 3.74 (q, J = 7.0 Hz, 1H), 3.36 (s, 3H), 3.31 (s, 3H), 1.57 (d, J = 7.2 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 191.9 (e), 142.2 (e), 141.8 (e), 139.5 (e), 125.3 (o), 124.3 (e), 123.8 (e), 120.4 (e), 120.3 (o), 119.7 (o), 119.4 (o), 109.3 (o), 107.6 (o), 68.9 (o), 51.1 (o), 42.2 (o), 42.1 (o), 29.2 (o), 18.7 (o); IR (neat): v = 3022 (w), 2922 (w), 2552 (w), 1630 (w), 1600 (w), 1493 (w), 1466 (s), 1415 (m), 1369 (s), 1356 (s), 1334 (m), 1307 (w), 1172 (s), 1140 (m), 1072 (w), 1063 (w), 1026 (s), 995 (m), 957 (w), 923 (w), 849 (m), 835 (w), 810 (s), 796 (s), 759 (w), 759 (w), 725 (w), 686 (w) cm⁻¹; HRMS (ESI): m/z calcd for C19H20ClNO2S+: 384.0801 [M+Na]⁺; found: 384.0790; elemental analysis calcd (%) for C19H20ClNO2S: C 63.06, H 5.57, N 4.03, S 9.22; found: C 62.76, H 5.59, N 3.73, S 9.21.

**Compound 430.** Synthesised according to representative procedure D from racemic zaltoprofen (2 g, 6.70 mmol) to afford compound 430 as a beige amorphous solid (2.44 g, 5.82 mmol, 87%).

1H NMR (500 MHz, CDCl3): δ 8.26-8.18 (m, 3H), 7.67 (d, J = 7.9 Hz, 1H), 7.61 (dd, J = 8.0, 1.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.44 (td, J = 7.4, 1.8 Hz, 1H), 7.36-7.30 (m, 1H), 7.24 (d, J = 7.9, 1.9 Hz, 1H), 7.18 (d, J = 9.3 Hz, 2H), 4.40 (s, 2H), 3.99 (q, J = 7.1 Hz, 1H), 1.62 (s, J = 7.2 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 191.6 (e), 171.5 (e), 155.3 (e), 141.4 (e), 140.0 (e), 138.4 (e), 136.1 (e), 134.0 (e), 132.6 (o), 131.8 (o), 131.5 (o), 130.8 (o), 128.6 (o), 126.9 (o) 126.2 (o), 125.2 (o, 2C), 122.2 (o, 2C), 51.1 (e), 45.3 (o), 18.3 (o); IR (neat): v = 3115 (w), 3080 (w), 2980 (w), 2936 (w), 2115 (w), 1758 (s), 1670 (s), 1615 (w), 1589 (m), 1519 (s), 1488 (m), 1458 (m), 1428 (w), 1377 (w), 1344 (s), 1284 (s), 1238 (w), 1202 (s), 1158 (s), 1114 (s), 1068 (s), 1041 (m), 1022 (m), 1011 (m), 993 (w), 924 (w), 892 (w), 863 (s), 845 (m), 832 (w), 811 (w), 755 (s), 729 (m), 695 (w), 677 (w), 661 (w) cm⁻¹; HRMS (ESI): m/z calcd for C23H17NO2S+: 442.0725 [M+Na]⁺; found: 442.0732

**Compound 271.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (EtOAc/MeOH = 90 :10), from compound 430 (1.11 g, 2.65 mmol) to afford compound 271 as an amorphous pink gum (444 mg, 1.19 mmol, 45%). 1H NMR (400 MHz, CDCl3): δ 8.19 (dd, J = 8.0, 1.4 Hz, 1H), 7.59 (dd, J = 8.0, 1.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (ddd, J
\[ \delta = 7.9, 7.2, 1.6 \text{ Hz}, 1H), 7.37 (d, J = 2.0 \text{ Hz}, 1H), 7.30 (d, d, J = 8.1, 7.2, 1.3 \text{ Hz}, 1H), 7.16 (d, d, J = 8.0, 2.0 \text{ Hz}, 1H), 4.35 (s, 2H), 4.28 (s, 1H), 3.52 (q, J = 7.3 \text{ Hz}, 1H), 3.36 (s, 3H), 3.30 (s, 3H), 1.42 (d, J = 7.2 \text{ Hz}, 3H); ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta 191.6 \text{ (e), 190.7 (e), 145.6 (e), 140.5 (e), 137.5 (e), 136.2 (e), 132.4 (o), 132.2 (e), 131.4 (o), 131.2 (o), 130.8 (o), 128.7 (o), 126.7 (o), 126.5 (o), 69.1 (o), 51.1 (e), 49.9 (o), 42.2 (o), 42.1 (o), 18.4 (o); IR (neat): } \tilde{\nu} = 3011 \text{ (w), 2924 (w), 2552 (w), 1737 (m), 1667 (s), 1563 (s), 1459 (s), 1428 (m), 1411 (m), 1374 (s), 1282 (s), 1238 (m), 1175 (s), 1127 (m), 1074 (w), 1024 (s), 942 (w), 886 (w), 853 (m), 806 (w), 797 (w), 753 (s), 729 (m), 690 (w), 661 \text{ (w) cm}^{-1}; HRMS (ESI): } m/z \text{ calcd for C}_{20}\text{H}_{20}\text{O}_3\text{S}_2\text{Na}: 395.0752 \text{ [M+Na]}^+; \text{ found: 395.0750. }

\[ \text{Compound 279:} \text{ 4-bromo-1H-indole (3 g, 15.4 mmol) was dissolved in THF (22 mL, 0.7 M) and cooled to 0 °C with an ice bath. NaH (60% in mineral oil, 0.60 g, 25.1 mmol, 1.02 equiv) was added portion-wise and the reaction was allowed to warm up to room temperature over 1 h. TsCl (3.0 g, 15.69} \]
mmol, 1.02 equiv) was added (CAUTION: exotherm) and the reaction stirred at rt for 16 h. The reaction was poured into 5% aqueous NaHCO$_3$ solution (183 mL) and extracted with Et$_2$O (3x 100 mL). The combined organic layers were washed once with brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The resulting dark brown solid was recrystallised from ethanol to afford compound 279 as a beige solid. (4.33 g, 12.4 mmol, 80%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.94 (dt, $J$ = 0.8, 8.2 Hz, 1H), 7.76 (d, $J$ = 8.4 Hz, 2H), 7.62 (d, $J$ = 3.7 Hz, 1H), 7.38 (dd, $J$ = 0.8, 7.8 Hz, 1H), 7.24 (d, $J$ = 7.9 Hz, 2H), 7.17 (t, $J$ = 8.1 Hz, 1H), 6.72 (dd, $J$ = 3.7, 0.8 Hz, 1H), 2.35 (s, 3H), $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.3 (e), 135.0 (e), 131.4 (e), 130.0 (o, 2C), 126.8 (o, 2C), 126.2 (o), 125.5 (o), 115.0 (e), 112.5 (o), 108.8 (o), 21.6 (o), in agreement with previously reported data$^{13}$; HRMS (ESI): $m/z$ calcd for C$_{15}$H$_{12}$BrNO$_2$S$^+$ [M+H]$^+$ 349.9845; found 349.9846.

**Compound 280.** SIPr (0.04 g, 0.09 mmol, 3 mol%) and Pd$_2$(dba)$_3$ (0.09 g, 0.09 mmol, 3 mol%) were weighed into a flame dried 2-neck flask, which was then evacuated and backfilled with N$_2$ three times. LiHMDS (1 M in toluene, 7 mL, 7.22 mmol, 2.3 equiv) was added, followed by compound 279 (1.10 g, 3.14 mmol, 1.0 equiv), tert-butyl acetate (0.5 mL, 4.08 mmol, 1.3 equiv) and toluene (7 mL, 0.44 M). The reaction was left to stir overnight at room temperature, then partitioned between an aqueous saturated solution of NH$_4$Cl and Et$_2$O. The layers were separated, and the aqueous layer was washed 3 times with Et$_2$O. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 93:7) to afford compound 280 as a pale brown viscous oil (0.861 g, 2.23 mmol, 71% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.89 (d, $J$ = 8.4 Hz, 1H), 7.76 (d, $J$ = 8.6 Hz, 2H), 7.57 (d, $J$ = 4.1 Hz, 1H), 7.27-7.24 (m, 1H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.11 (dd, $J$ = 7.4, 0.8 Hz, 1H), 6.72 (dd, $J$ = 3.7, 0.8 Hz, 1H), 3.70 (s, 2H), 2.34 (s, 3H), 1.37 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.3 (e), 144.9 (e), 135.3 (e), 134.8 (e), 130.4 (e), 129.8 (o, 2C), 127.6 (e), 126.8 (o, 2C), 126.1 (o), 124.6 (o), 124.1 (o), 112.4 (o), 107.4 (o), 81.0 (e), 40.2 (e), 27.9 (o, 3C), 21.5 (o); IR (neat): $\tilde{\nu}$ = 3123 (w), 3035 (w), 2976 (w), 1690 (s), 1597 (w), 1529 (w), 1452 (m), 1460 (m), 1424 (s), 1370 (s), 1312 (m), 1279 (s), 1247 (s), 1212 (w), 1177 (s), 1163 (s), 1147 (s), 1124 (s), 1105 (s), 1088 (m), 1079 (m), 1029 (m), 998 (w), 972 (w), 938 (m), 901 (w), 884 (w), 857 (w), 833 (m), 812 (w), 787 (w), 754 (s), 741 (s), 733 (s), 694 (m), 676 (s), 657 (m), 624 (m), 570 (m), 552 (m), 518 (m), 486 (w), 457 (w), 435 (s), 414 (m), 382 (w), 342 (m), 327 (w), 306 (m), 286 (s), 267 (s), 248 (m), 229 (m), 210 (m), 191 (s), 171 (m), 157 (m), 140 (m), 125 (w), 109 (w), 98 (m), 87 (m), 77 (m), 66 (w), 55 (w), 45 (w), 35 (w), 25 (w), 15 (w).
724 (m), 703 (w), 687 (w), 653 (w), 668 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₂₁H₂₃NO₄S⁺Na⁺: 408.1240 [M+Na⁺]; found: 408.1242.

**Compound 281.** iPr₂NH (1.5 mL, 11.0 mmol, 1.8 equiv) was dissolved in THF (9 mL) and cooled to -10 °C using an ice/brine bath, and nBuLi (2.5 M in hexanes, 4 mL, 1.6 equiv, 9.8 mmol) was added dropwise. The reaction was stirred at -10 °C for 15 minutes, then 280 (2.4 g, 6.1 mmol, 1.0 equiv) was added dropwise. The reaction was stirred at -10 °C for 30 minutes, then MeI (0.8 mL, 12.3 mmol, 2.0 equiv) was added. The reaction was stirred at room temperature for 1 h, then quenched with aqueous saturated solution of NH₄Cl. The layers were separated, and the aqueous layer was washed 3 times with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/EtOAc, 94:6) to afford 281 as a pale-yellow oil (471 mg, 1.2 mmol, 19%). ¹H NMR (500 MHz, CDCl₃): δ 7.88 (dt, J = 8.3, 0.8 Hz, 1H); 7.76 (d, J = 8.4 Hz, 2H); 7.57 (d, J = 3.8 Hz, 1H); 7.28-2.4 (m, 1H); 7.22 (d, J = 8.0 Hz, 2H); 7.15 (d, J = 7.5 Hz, 1H); 6.78 (dd, J = 3.8, 0.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 173.3 (e), 144.8 (e), 135.3 (e), 134.8 (e), 134.0 (e), 129.8 (o, 2C), 129.6 (e), 126.8 (o, 2C), 124.7 (o), 121.2 (o), 112.1 (o), 107.4 (o), 80.7 (e), 43.8 (o), 27.8 (o, 3C), 21.5 (o), 17.4 (o); IR (neat): ν = 2977 (w), 2934 (w), 1723 (s), 1597 (m), 1528 (w), 1482 (w), 1455 (w), 1423 (w), 1392 (w), 1366 (s), 1326 (m), 1307 (w), 1282 (m), 1254 (m), 1214 (m), 1179 (s), 1164 (s), 1151 (s), 1133 (s), 1089 (s), 1022 (m), 1000 (m), 930 (w), 890 (w), 847 (m), 812 (m), 759 (s), 703 (m), 679 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₂₂H₂₅NO₄S⁺Na⁺: 422.1397 [M+Na⁺]; found: 422.1396.

**Compound 282.** Compound 281 (1.39 g, 3.48 mmol, 1.0 equiv) and NaI (1.04 g, 6.97 mmol, 2 equiv) were dissolved in MeCN (3.5 mL) under N₂, and TMSCl (0.9 mL, 6.97 mmol, 2 equiv) was added. The reaction was heated at 45 °C for 2 h, then cooled to rt and quenched with water (9 mL) and extracted 3 times with EtOAc. The combined organic layers were washed with water and then with saturated aqueous sodium thiosulphate solution to remove inorganic salts and iodine, respectively, and the organic layer was dried over MgSO₄, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (DCM/MeOH = 98:2) to afford 282 (589 mg, 1.71 mmol, 50% yield) as cream-coloured solid, whose identity was confirmed by ¹H NMR and HRMS only.
1H NMR (500 MHz, CDCl3): δ 7.90 (dt, J = 8.4, 0.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 3.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 6.76 (dd, J = 3.8, 0.7 Hz, 1H), 4.04 (q, J = 7.5 Hz, 1H), 2.35 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H); HRMS (ESI): m/z calcd for C18H17NO4S+Na+: 366.0770 [M+Na]+; found: 366.0771.

**Compound 431.** Synthesised according to representative procedure D from compound 282 (361 mg, 1.05 mmol) to afford compound 431 as pale green amorphous solid (393 mg, 0.85 mmol, 80%). 1H NMR (500 MHz, CDCl3) δ 8.18 (d, J = 9.3 Hz, 2H), 7.97 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 3.7 Hz, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.26–7.23 (m, 2H), 7.06 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 3.7 Hz, 1H), 4.29 (q, J = 7.1 Hz, 1H), 2.36 (s, 3H), 1.67 (d, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 171.8 (e), 155.4 (e), 141.2 (e), 135.3 (e), 135.0 (e), 132.0 (e), 130.0 (o, 2C), 129.3 (e), 127.0 (o, 2C), 126.7 (o), 125.1 (o, 2C), 125.0 (o), 122.3 (o, 2C), 121.6 (o), 112.9 (o), 106.4 (o), 43.2 (o), 21.6 (o), 17.5 (o); IR (neat): ν = 3117 (w), 3084 (w), 2987 (w), 2856 (w), 2114 (w), 1757 (s), 1615 (w), 1592 (s), 1522 (s), 1489 (w), 1450 (w), 1424 (w), 1401 (w), 1373 (m), 1360 (m), 1344 (s), 1324 (w), 1307 (w), 1284 (w), 1203 (m), 1179 (s), 1164 (s), 1130 (s), 1087 (s), 1074 (s), 1053 (s), 1021 (m), 1013 (m), 996 (m), 952 (w), 923 (w), 892 (m), 864 (m), 838 (w), 812 (w), 759 (s), 712 (w), 702 (w), 674 (s) cm⁻¹; HRMS (CI(NH₃)): m/z calcd for C₂₄H₂₀N₂O₆S+H+: 465.1120 [M+H]+; found: 465.1119.

**Compound 277.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98 :2) followed by trituration of the solid obtained from the product containing fractions, from compound 431 (1.20 g, 3.41 mmol) to afford compound 277 as white powder (224 mg, 0.54 mmol, 63%). m.p.: 113–116 °C; 1H NMR (500 MHz, CDCl3): δ 7.84 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 3.8 Hz, 1H), 7.25–7.21 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.79 (dd, J = 3.7, 0.7 Hz, 1H), 4.17 (s, 1H), 3.83 (q, J = 7.2 Hz, 1H), 3.31 (s, 3H), 3.26 (s, 3H), 2.35 (s, 3H), 1.49 (d, J = 7.2 Hz, 3H) (one multiplet (1H) is masked by residual CHCl₃); 13C NMR (125 MHz, CDCl3): δ 191.2 (e), 144.9 (e), 136.2 (e), 135.3 (e), 134.7 (e), 129.8 (o, 2C), 129.7 (e), 126.9 (o, 2C), 125.7 (o), 124.7 (o), 121.4 (o), 111.6 (o), 107.3 (o), 70.0 (o), 47.9 (o), 42.1 (o), 42.0 (o), 21.5 (o), 17.6 (o); IR (neat): ν = 3087 (w).
2996 (w), 2918 (w), 1590 (m), 1568 (s), 1494 (w), 1481 (w), 1454 (w), 1420 (m), 1371 (s), 1357 (s), 1296 (m), 1283 (m), 1178 (s), 1163 (s), 1128 (s), 1086 (s), 1030 (s), 2703 (m), 680 (s), 667 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₂₁H₂₄NO₄S₂+H⁺: 418.1141 [M+H⁺]; found: 418.1148; elemental analysis calcd (%): C 60.41, H 5.55, N 3.35, S 15.36; found: C 60.32, H 5.64, N 3.25, S 15.36.

**Compound 432.** Compound 282 (645 mg, 1.88 mmol, 1 equiv) was dissolved in MeOH (59 mL, 0.032 M) and a 5M aq solution of KOH (6 mL, 0.32 M) was added. The reaction was heated at reflux for 20 h, and then cooled to rt, and the MeOH removed in vacuo. The residue was diluted with H₂O (5 mL) the acidified to pH 1 with conc. HCl. During the addition, a solid precipitated, which was filtered off, the filter cake washed with 2N HCl, and the solid was dried in a vacuum desiccator overnight to afford an off-white solid (313 mg, 1.65 mmol) that was used without further purification by diluting it in THF (14 mL) at 0 °C under N₂. MeI (1 mL, 16.5 mmol, 10 equiv) was added, followed by NaH (60% in oil, 158 mg, 6.60 mmol, 4 equiv) is small portions. After stirring at r.t. for 3 h, reaction was quenched with H₂O (20 mL) and washed with EtOAc (3 × 15 mL). The aqueous layer was acidified to pH 2-3 with 2N HCl, and then extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under vacuum to afford compound a pink solid (322 mg, 1.58 mmol) that was used without further purification according to representative procedure D to afford 432 as pale green amorphous solid (365 mg, 1.12 mmol, 71%). ¹H NMR (500 MHz, CDCl₃): δ 8.18 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.28-7.25 (m, 1H), 7.16-7.10 (m, 4H), 6.63 (d, J = 3.0 Hz, 1H), 4.38 (q, J = 7.2 Hz, 1H), 3.83 (s, 3H), 1.73 (d, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.5 (e), 155.8 (e), 137.0 (e), 131.4 (e), 129.1 (o), 126.9 (e), 125.0 (o, 2C), 122.4 (o, 2C), 121.9 (o), 117.8 (o), 108.8 (o), 98.9 (o), 43.7 (o), 33.0 (o), 17.5 (o); IR (neat): ν = 3081 (w), 2930 (w), 2854 (w), 2114 (w), 1756 (s), 1614 (w), 1592 (m), 1521 (s), 1489 (m), 1445 (w), 1419 (w), 1344 (s), 1304 (m), 1275 (w), 1240 (w), 1206 (s), 1156 (s), 1132 (s), 1073 (s), 1048 (m), 1012 (m), 996 (w), 934 (w), 892 (m), 863 (m), 841 (w), 748 (s), 710 (m), 679 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₈H₁₆N₂O₄+H⁺: 325.1183 [M+H⁺]; found: 325.1182.
Compound 278. Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration of the solid obtained from the product containing fractions, from compound 432 (365 mg, 1.12 mmol) to afford compound 278 as cream-coloured powder (199 mg, 0.72 mmol, 64%). m.p.: 119–121 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.22-7.16 (m, 2H), 7.06 (dd, $J = 6.0$, 2.0 Hz, 1H), 7.03 (d, $J = 3.1$ Hz, 1H), 6.58 (d, $J = 3.2$ Hz, 1H), 4.24 (s, 1H), 3.96 (q, $J = 7.3$ Hz, 1H), 3.78 (s, 3H), 3.33 (s, 3H), 3.27 (s, 3H), 1.56 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 136.7 (e), 135.6 (e), 128.3 (o), 127.5 (e), 121.7 (o), 117.4 (o), 107.5 (o), 99.5 (o), 68.5 (o), 48.1 (o), 42.2 (o), 42.0 (o), 32.9 (o), 17.4 (o); IR (neat): $\tilde{\nu} = 3090$ (w), 3072 (w), 3006 (w), 2994 (w), 2693 (w), 2914 (w), 2861 (w), 1713 (w), 1679 (w), 1562 (s), 1515 (w), 1492 (s), 1444 (m), 1424 (m), 1416 (m), 1376 (s), 1360 (m), 1339 (m), 1309 (m), 1291 (m), 1278 (m), 1258 (w), 1240 (w), 1180 (s), 1168 (s), 1128 (m), 1082 (s), 1062 (w), 1032 (s), 996 (m), 948 (m), 906 (w), 882 (w), 856 (s), 804 (w), 781 (m), 759 (s), 709 (s), 671 (m) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{15}$H$_{19}$NO$_2$S+H$^+$: 278.1209 [M+H]$^+$; found: 278.1217; elemental analysis calcd (%) for C$_{15}$H$_{19}$NO$_2$S: C 64.95, H 6.90, N 5.05, S 11.56; found: C 64.99, H 6.92, N 4.94, S 11.40.
**Compound 433.** In a flame dried 2-neck 250 mL RB flask under N₂, compound 288 (11.9 g, 56.53 mmol, 1 equiv), paraformaldehyde (2.55 g, 84.80 mmol, 1.5 equiv), and K₂CO₃ (7.81 g, 56.53 mmol, 1 equiv) were dissolved in dry DMF (40 mL, 1.4 M) and heated at 100 °C for 1 h. After cooling to room temperature, H₂O (200 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (5 x 100 mL), dried (MgSO₄), filtered and concentrated **in vacuo**. The residue was purified by FCC (PE:EtOAc 4:1) to afford compound 289 as a bright yellow oil. (3.00 g, 13.53 mmol, 24%). ¹H NMR (500 MHz, CDCl₃): δ 7.02 (m, 3H), 6.85 (d, J = 8.1 Hz, 1H), 6.28 (d, J = 1.3 Hz, 1H), 5.85 (d, J = 1.3 Hz, 1H), 3.89 (s, 6H), 3.83 (s, 3H). Then, following a reported procedure¹⁴, pyrrole (1.90 mL, 27.06 mmol, 2 equiv) was added to a solution of KO'Bu (3.03 g, 27.06 mmol, 2 equiv) in 8% aqueous DMSO (61 mL) under N₂. A solution of compound 289 (3.0 g, 13.53 mmol, 1 equiv) in DMSO (27 mL) was added dropwise at rt, and the reaction was left to stir at rt for 3 h. The reaction was poured into an ice-water bath (135 mL), then washed with DCM (3 x 50 mL). The aqueous layer was acidified to pH 1 with conc HCl, then extracted with DCM (3 x 100 mL). The combined organic layers from the second extraction were washed with H₂O (5 x 50 mL), brine (1 x 50 mL), dried (MgSO₄), filtered and concentrated **in vacuo**. The crude residue was purified by FCC (98:2 DCM:MeOH) to afford compound 290 (3.71 g, 13.48 mmol, quant) as a pale brown amorphous solid whose identity was confirmed by ¹H NMR only before being used in the next step. ¹H NMR (500 MHz, DMSO-d6): δ 6.89 (d, J = 8.4 Hz, 1H), 6.82 (td, J = 2.2, 9.1 Hz, 2H), 6.67 (t, J = 2.1 Hz, 2H), 5.90 (t, J = 2.2 Hz, 2H), 4.43 (dd, J = 8.6, 13.9 Hz, 1H), 4.09 (dd, J = 6.9, 13.8 Hz, 1H), 3.94 (dd, J = 6.6, 8.5 Hz, 1H), 3.72 (s, 3H); 3.71 (s, 3H). Synthesised according to representative procedure D from compound 290 (2.29 g, 8.32 mmol) to afford compound 433 as pale brown solid (1.06 g, 2.67 mmol, 32%). m.p.: 68–70 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.22 (d, J = 9.2 Hz, 2H), 7.07 (d, J = 9.2 Hz, 2H), 6.94 (dd, J = 8.3, 2.0 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 2.1 Hz, 1H), 6.65 (t, J = 2.0 Hz, 2H), 6.16 (t, J = 2.1 Hz, 2H), 4.62 (dd, J = 13.7, 9.0 Hz, 1H), 4.24 (dd, J = 13.8, 5.8 Hz, 1H), 4.19 (dd, J = 9.0, 5.8 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 170.2 (e), 155.1 (e), 149.5 (e), 149.3 (e), 145.5 (e), 127.0 (e), 125.2 (o, 2C); 122.3 (o, 2C); 121.0 (o, 2C), 120.1 (o), 111.6 (o), 110.9 (o), 108.8 (2C, o), 56.0 (o), 55.9 (o), 53.6 (o), 52.4 (e)); IR (neat): ν = 3120 (w), 3079 (w), 2989 (w),
2953 (w), 2836 (w), 1751 (s), 1592 (m), 1525 (s), 1492 (m), 1466 (m), 1453 (m), 1440 (w), 1422 (w), 1347 (s), 1285 (m), 1272 (w), 1249 (m), 1233 (m), 1203 (m), 1182 (w), 1162 (w), 1125 (s), 1088 (s), 1072 (m), 1060 (w), 1037 (w), 1022 (s), 968 (w), 943 (w), 896 (m), 864 (m), 849 (w), 841 (w), 819 (w), 769 (w), 754 (w), 738 (w), 724 (s), 701 (m) cm\(^{-1}\); HRMS (ESI): \(m/z\) calcd for C\(_{21}\)H\(_{20}\)N\(_2\)O\(_6\)+H\(^+\): 397.1394 [M+H]\(^+\); found: 397.1391; elemental analysis calcd (%) for C\(_{21}\)H\(_{20}\)N\(_2\)O\(_6\): C 63.63, H 5.09, N 7.07; found: C 63.51, H 5.26, N 7.24.

**Compound 285.** Synthesised according to representative procedure E, except that the crude compound was purified by FCC (DCM/MeOH = 98:2), from compound 433 (3.99 g, 10.06 mmol) to afford compound 285 as cream-coloured solid (1.70 g, 4.85 mmol, 48%). m.p.: 78–80 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.86–6.77 (m, 3H), 6.57 (t, \(J = 2.0\) Hz, 2H), 6.04 (t, \(J = 2.0\) Hz, 2H), 4.58 (dd, \(J = 13.6, 8.6\) Hz, 1H), 4.28 (s, 1H), 4.08 (dd, \(J = 13.6, 6.0\) Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.75–3.63 (m, 1H), 3.33 (s, 3H), 3.28 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 187.8 (e), 148.9 (e), 148.2 (e), 131.4 (e), 121.1 (o, 2C), 120.1 (o), 111.1 (o), 111.0 (o), 107.7 (o, 2C), 70.8 (o), 57.6 (o), 55.85 (o), 55.80 (o), 52.3 (e), 41.94 (o), 41.89 (o); IR (neat): \(\tilde{\nu} = 3113\) (w), 3075 (w), 3015 (w), 2929 (w), 1698 (w), 1646 (s), 1561 (s), 1525 (m), 1494 (w), 1466 (m), 1374 (s), 1325 (s), 1307 (m), 1253 (m), 1243 (m), 1175 (s), 1147 (m), 1085 (s), 1029 (s), 994 (m), 967 (m), 941 (m), 876 (w), 856 (s), 776 (w), 740 (s), 702 (m), 679 (w) cm\(^{-1}\); HRMS (ESI): \(m/z\) calcd for C\(_{18}\)H\(_{23}\)NO\(_4\)+Na\(^+\): 372.1245 [M+Na]\(^+\); found: 372.1250.

**Representative Procedure F:** In a 2-neck RB flask under N\(_2\), 2-aminoethanol (10.0 mL, 163.7 mmol, 1.0 equiv) and NaOAc (13.6 g, 165.4 mmol, 1.01 equiv) were dissolved in AcOH (25 mL, 6.5 M) and H\(_2\)O (76 mL, 2.2 M), and the reaction was heated to 90 °C for 5 mins. 2,5-dimethoxytetrahydrofuran (21 mL, 163.7 mmol, 1.0 equiv) was added, and the reaction was heated at 90 °C for 18 h. After cooling to room temperature, the reaction was diluted with EtOAc and washed once with brine and once with water. The combined organic layers were dried (MgSO\(_4\)), filtered and
concentrated in vacuo to afford a brown liquid that was purified by FCC (petroleum ether:EtOAc = 3:2) to afford compound 291 as a clear viscous liquid (8.74 g, 78.64 mmol, 48%). This was combined with a second batch of 1.26 g prepared using the same method for use in the next step.

**Compound 291.** $^1$H NMR (500 MHz, CDCl$_3$): 6.71 (t, J = 2.1 Hz, 2H); 6.18 (t, J = 2.2 Hz, 2H); 4.03 (t, J = 5.3 Hz, 2H); 3.87 (t, J = 5.4 Hz, 2H), in agreement with previously reported data$^{15}$.  

**Compound 292.** Triphenylphosphine (35 g, 135.0 mmol, 1.5 equiv) was dissolved in dry DCM (692 mL, 0.13 M) under N$_2$ and iodine (34 g, 135.0 mmol, 1.5 equiv) was added at rt in small portions. The reaction was left to stir at rt for 10 mins, before imidazole (15.3 g, 224.9 mmol, 2.5 equiv) was added in small portions, and the reaction was stirred at rt for a further 10 mins. Compound 291 (10 g, 90.0 mmol, 1 equiv) was added to the reaction dropwise, and the reaction was stirred at rt for 1 h, before being quenched with sat. aq. sodium thiosulfate solution (692 mL), and stirred for a further 5 mins. The layers were then separated, the aqueous was extracted with DCM (2 x 200 mL), and the combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified by FCC (95:5 PE:EtOAc) to afford compound 292 as a light brown liquid (12.7 g, 57.31 mmol, 64%). $^1$H NMR (400 MHz, CDCl$_3$): δ ppm 6.68 (t, J = 2.2 Hz, 2H); 6.19 (t, J = 2.0 Hz, 2H); 4.25 (t, J = 7.4 Hz, 2H); 3.39 (t, J = 7.6 Hz, 2H), in agreement with previously reported data$^{16}$.  

**Scheme 1:**
Compound 434. A flame-dried 2-neck 250 mL flask under N\textsubscript{2} containing \textsuperscript{3}Pr\textsubscript{2}NH (6 mL, 42.81 mmol, 1.8 equiv) in THF (25 mL) was cooled to \(-10\) °C using an ice/brine bath before adding \textsuperscript{3}BuLi (2.5 M in hexanes, 16 mL, 39.65 mmol, 1.6 equiv) dropwise. The reaction was then left to stir at \(-10\) °C for 30 minutes before a solution of methyl 2-(3,4-dimethoxyphenyl)acetate (5 g, 24.78 mmol, 1 equiv) in THF (49 mL) was added dropwise. The reaction was left to stir at \(-10\) °C for 30 mins, then compound 292 (10.95 g, 49.56 mmol, 2 equiv) was added. The reaction was then left to stir at room temperature for 1 h before being quenched with H\textsubscript{2}O and extracted 3 times with EtOAc. The combined organic layers were washed once with brine, dried over MgSO\textsubscript{4}, filtered and concentrated under vacuum to afford a pale-yellow oil (2.69 g, 8.87 mmol, 37%) that was dissolved in THF/H\textsubscript{2}O (1:1, 35 mL, 0.25 M) before NaOH (1.77 g, 44.35 mmol, 5 equiv) was added. The reaction was stirred at reflux for 15 h, then carefully acidified to pH 2 using 2N HCl. The reaction was then quickly extracted 3 times with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were dried over MgSO\textsubscript{4}, filtered and concentrated under vacuum to afford a brown solid (2.55 g, 8.1 mmol, quant.) that was used according to representative procedure D to afford 434 as pale-brown amorphous solid (1.81 g, 4.41 mmol, 48%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 8.25 (d, \(J = 9.3\) Hz, 2H), 7.15 (d, \(J = 9.4\) Hz, 2H), 6.97-6.88 (m, 3H), 6.67 (t, \(J = 2.1\) Hz, 2H), 6.22 (t, \(J = 2.1\) Hz, 2H), 4.05-3.98 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.91-3.83 (m, 1H), 3.63 (t, \(J = 7.8\) Hz, 1H), 2.73-2.62 (m, 1H), 2.41-2.30 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 171.2 (e), 155.3 (e), 149.4 (e), 149.9 (e), 145.4 (e), 129.0 (e), 125.1 (o, 2C), 122.2 (o, 2C), 120.5 (o, 2C), 120.4 (o), 111.6 (o), 111.0 (o), 108.5 (o, 2C), 56.02 (o), 55.92 (o), 47.9 (o), 46.7 (e), 34.2 (e); IR (neat): \(\tilde{\nu} = 3080\) (w), 2933 (w), 2855 (w), 2115 (w), 1755 (m), 1703 (w), 1615 (w), 1591 (m), 1515 (s), 1500 (m), 1489 (m), 1463 (m), 1452 (m), 1420 (w), 1344 (s), 1283 (m), 1261 (s), 1236 (s), 1205 (s), 1157 (m), 1141 (s), 1111 (s), 1089 (m), 1025 (m), 940 (w), 862 (m), 809 (w), 764 (w), 726 (s), 683 (w) cm\textsuperscript{-1}; HRMS (ESI): \(m/z\) calcd for C\textsubscript{22}H\textsubscript{22}N\textsubscript{2}O\textsubscript{6}+H\textsuperscript{+}: 411.1551 [M+H]\textsuperscript{+}; found: 411.1551.
Compound 286. Synthesised according to representatative procedure E, from compound 434 (1.81 g, 4.41 mmol), except that crude compound was purified by FCC (DCM/MeOH = 98:2), to afford compound 286 as cream-coloured solid (716 mg, 1.97 mmol, 45%). m.p.: 92–93 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 6.82–6.78 (m, 3H), 6.62 (t, $J = 2.1$ Hz, 2H), 6.13 (t, $J = 2.1$ Hz, 2H), 4.30 (s, 1H), 3.89–3.84 (m, 7H), 3.81–3.74 (m, 1H), 3.36 (s, 3H), 3.29 (s, 3H), 3.19 (t, $J = 8.0$ Hz, 1H), 2.60–2.50 (m, 1H), 2.18–2.09 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 189.9 (e), 148.9 (e), 147.8 (e), 133.3 (e), 120.6 (o, 2C), 120.1 (o), 111.1 (o), 111.0 (o), 107.8 (o, 2C), 69.8 (o), 55.84 (o), 55.79 (o), 52.5 (o), 47.4 (e), 42.1 (o), 41.9 (o), 34.4 (e); IR (neat): $\nu = 3016$ (w), 2927 (w), 2843 (w), 1606 (w), 1590 (w), 1559 (s), 1515 (s), 1451 (m), 1417 (m), 1360 (s), 1322 (w), 1308 (w), 1289 (w), 1257 (s), 1225 (s), 1172 (s), 1140 (s), 1087 (m), 1065 (w), 1029 (s), 1019 (s), 998 (m), 982 (w), 971 (w), 946 (w), 857 (m), 844 (s), 813 (m), 767 (m), 749 (w), 721 (s), 684 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{19}$H$_{25}$NO$_4$S$+$H$^+$: 364.1583 [M$+$H]$^+$; found: 364.1579; elemental analysis calcd (%) for C$_{19}$H$_{25}$NO$_4$S: C 62.79, H 6.93, N 3.85, S 8.82; found: C 62.61, H 6.96, N 3.83, S 8.64.

Compound 295. Synthesised according to representative procedure F, from 3-bromopropan-1-amine hydrobromide 293 (10 g, 45.68 mmol) to afford compound 295 as a brown oil (3.40 g, 18.25 mmol, 40%). $^1$H NMR (500 MHz, CDCl$_3$): δ 6.68 (t, $J = 2.1$ Hz, 2H), 6.16 (t, $J = 2.1$ Hz, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 3.31 (t, $J = 6.2$ Hz, 2H), 2.26 (quint, $J = 6.2$ Hz, 2H); in agreement with previously reported data$^{17}$. 

![Diagram](attachment:image.png)
Compound 435. In a flame dried 2-neck RB flask under N\(_2\), \(^3\)Pr\(_2\)NH (2.3 mL, 16.44 mmol, 1.8 equiv) was dissolved in THF (13 mL) and the solution was cooled to -10 °C using an ice/brine bath. \(^n\)BuLi (2.5 M in hexanes, 6 mL, 14.62 mmol, 1.6 equiv) was added dropwise, and the reaction was stirred at -10 °C for 15 mins. A solution of methyl phenylacetate (1.3 mL, 9.14 mmol, 1.0 equiv) in THF (25 mL) was added dropwise, and the reaction was stirred at -10 °C for 30 mins. Compound 295 (3.4 g, 18.27 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 1 hour. The reaction was quenched with water, the layers were separated and the aqueous was extracted three times with EtOAc. The combined organic layers were washed once with brine, dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude residue was purified by FCC (hexane/Et\(_2\)O = 9:1) to afford compound 435 as a pale brown oil (1.14 g, 4.43 mmol, 48%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.39-7.20 (m, 5H); 6.60 (t, \(J = 2.2\) Hz, 2H); 6.12 (t, \(J = 2.0\) Hz, 2H); 3.91-3.80 (m, 2H); 3.65 (s, 3H); 3.50 (t, \(J = 6.6\) Hz, 1H); 2.13-2.00 (m, 1H); 1.84-1.62 (m, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): δ 175.8 (e), 141.7 (e), 128.5 (o, 2C), 127.0 (o), 126.3 (o, 2C), 120.4 (o, 2C), 108.1 (o, 2C), 53.3 (e), 52.2 (o), 49.6 (o), 31.8 (e), 26.3 (e); IR (neat): \(\tilde{\nu} = 3029\) (w), 2951 (w), 2872 (w), 1729 (s), 1601 (w), 1584 (w), 1547 (w), 1498 (m), 1453 (m), 1434 (m), 1353 (m), 1280 (m), 1208 (m), 1151 (s), 1088 (s), 1072 (m), 1030 (w), 1005 (w), 969 (w), 919 (w), 821 (w), 721 (s), 697 (s) \(\text{cm}^{-1}\); HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{19}\)NO\(_2\)+H\(^+\): 258.1489 [M+H]\(^+\); found: 258.1487.

Compound 436. Compound 435 (1.14 g, 4.43 mmol) was used according to representative procedure C to afford a sticky brown solid (0.98 g, 4.03 mmol, 91%) which was used immediately according to representative procedure D to afford compound 436 as a beige amorphous solid (1.19 g, 3.26 mmol, 81%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 8.22 (d, \(J = 9.1\) Hz, 2H), 7.43-7.28 (m, 5H), 7.14 (d, \(J = \)
9.1 Hz, 2H), 6.63 (t, $J = 2.1$ Hz, 2H), 6.15 (t, $J = 2.1$ Hz, 2H), 3.91 (t, $J = 6.4$ Hz, 2H), 3.72 (t, $J = 7.2$ Hz, 1H), 1.96-1.69 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.3 (c), 155.4 (c), 137.4 (c), 131.4 (c), 129.1 (o, 2C), 128.0 (o), 127.9 (o, 2C), 125.2 (o, 2C), 122.3 (o, 2C), 120.5 (o, 2C), 108.3 (o, 2C), 51.3 (o), 49.2 (e), 30.3 (e), 29.4 (e); IR (neat): $\tilde{\nu} = 3115$ (w), 3071 (w), 2990 (w), 2928 (w), 2115 (m), 1924 (w), 1760 (m), 1708 (w), 1616 (w), 1590 (m), 1519 (s), 1489 (m), 1466 (w), 1454 (m), 1423 (w), 1380 (w), 1343 (s), 1321 (s), 1288 (w), 1261 (w), 1244 (w), 1204 (w), 1164 (w), 1115 (s), 1091 (s), 1063 (s), 1048 (s), 1010 (m), 982 (w), 956 (w), 931 (w), 900 (s), 865 (s), 857 (s), 813 (w), 770 (w), 746 (s), 719 (w), 708 (m), 675 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{21}$H$_{20}$N$_2$O$_4$+: 365.1496 [M+H]$^+$; found: 365.1494.

**Compound 287.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration of the solid obtained from the product containing fractions, from compound 436 (1.19 g, 0.98 mmol) to afford compound 287 as an off white powder (398 mg, 1.25 mmol, 38%). m.p. = 68-70 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.31-7.24 (m, 4H), 7.23-7.18 (m, 1H), 6.61 (t, $J = 1.9$ Hz, 2H), 6.11 (t, $J = 2.0$ Hz, 2H), 4.30 (s, 1H), 3.92-3.77 (m, 2H), 3.35 (s, 3H), 3.32-3.26 (m, 4H), 2.14-2.03 (m, 1H), 1.82-1.62 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.2 (e), 141.4 (e), 128.4 (o, 2C), 127.4 (o, 2C), 126.6, 120.4 (o, 2C), 107.8 (o, 2C), 69.7 (o), 56.1 (o), 49.5 (e), 42.1 (o), 41.9 (o), 30.1 (e), 29.9 (e); IR (neat): $\tilde{\nu} = 3023$ (w), 2926 (w), 2238 (w), 1724 (w), 1562 (s), 1499 (w), 1451 (w), 1375 (s), 1302 (w), 1281 (m), 1176 (s), 1119 (w), 1088 (m), 1069 (w), 1024 (m), 988 (w), 968 (w), 908 (s), 856 (w), 721 (vs), 698 (vs) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{23}$NO$_2$S$^+$: 318.1522 [M+H]$^+$; found: 318.1524.

**Compound 437.** Synthesised according to representative procedure D from 2-(1H-pyrrol-1-yl)acetic acid (1.89 g, 15.10 mmol) to afford compound 437 as pale-brown amorphous solid (1.89 g, 7.68 mmol, 51%). The compound was contaminated by some DCC, and was characterized only by $^1$H NMR before being used without further purification in the next step. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.28 (d, $J = 9.2$ Hz, 2H), 7.32 (d, $J = 9.2$ Hz, 2H), 6.75 (t, $J = 2.0$ Hz, 2H), 6.26 (t, $J = 2.1$ Hz, 2H), 4.94 (s, 2H).
Compound 306. Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 95:5), from compound 437 (1.00 g, 4.06 mmol) to afford compound 306 as white solid (555 mg, 2.78 mmol, 68%). m.p.: 95–97 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.65 (t, \(J = 2.0\) Hz, 2H), 6.17 (t, \(J = 2.0\) Hz, 2H), 4.44 (s, 2H), 4.07 (s, 1H), 3.37 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 186.2 (e), 121.8 (o, 2C), 108.7 (o, 2C), 68.8 (o), 56.9 (e), 42.1 (o, 2C); IR (neat): \(\tilde{\nu}\) = 3106 (w), 3068 (w), 3023 (w), 3066 (m), 2921 (w), 2240 (w), 1723 (w), 1548 (s), 1493 (w), 1424 (w), 1403 (w), 1375 (s), 1324 (m), 1288 (m), 1174 (s), 1164 (s), 1089 (m), 1064 (m), 1028 (s), 991 (m), 974 (m), 964 (m), 916 (m), 859 (m), 816 (w), 762 (m), 726 (s), cm\(^{-1}\); HRMS (ESI): m/z calcd for C\(_9\)H\(_{13}\)NO\(_2\)S+H\(^+\): 200.0740 [M+H]\(^+\); found: 200.0742.

\[
\text{NaOAc (1.01 equiv)} \\
\text{AcOH (6.5 M)} \\
\text{H}_2\text{O (2.2 M)} \\
\text{DCE (1.6 M)} \\
\text{90 °C, 16 h}
\]

Compound 438: Synthesised according to representative procedure F, from racemic alanine (2 g, 22.45 mmol) to afford compound 438 as a sticky brown gum that was used without further purification (3.13 g, 22.49 mmol, quant). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\): ppm 6.75 (t, \(J = 2.2\) Hz, 2H), 6.21 (t, \(J = 2.2\) Hz, 2H), 4.81 (q, \(J = 7.0\) Hz, 1H), 1.77 (d, \(J = 7.4\) Hz, 3H), in agreement with previously reported data\(^18\).

Compound 439. Synthesised according to representative procedure D from compound 438 (1.52 g, 7.99 mmol) to afford compound 439 as viscous yellow oil (1.42 g, 4.56 mmol, 57%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.26 (d, \(J = 9.1\) Hz, 2H), 7.24 (d, \(J = 9.1\) Hz, 2H), 6.84 (t, \(J = 2.1\) Hz, 2H), 6.25 (t, \(J = 2.1\) Hz, 2H), 5.04 (q, \(J = 7.3\) Hz, 1H), 1.89 (d, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 168.9 (e), 155.0 (e), 153.5 (e), 125.3 (o, 2C), 122.2 (o, 2C), 119.7 (o, 2C), 109.3 (o, 2C), 106.8 (o), 18.0 (o); IR (neat): 3116 (w), 2989 (w), 2922 (w), 2865 (w), 1764 (s), 1702 (m), 1662 (s), 1615 (w), 1591 (m), 1521 (s), 1489 (s), 1453 (w), 1410 (w), 1346 (s), 1302...
Compound 307. Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98 : 2) followed by trituration of the solid obtained from the product containing fractions, from compound 439 (2.49 g, 9.56 mmol) to afford compound 307 as off-white solid (1.66 g, 7.79 mmol, 81%). m.p.: 86–87 °C; ¹H NMR (500 MHz, CDCl₃): δ 6.74 (t, J = 2.1 Hz, 2H), 6.17 (t, J = 2.1 Hz, 2H), 4.52 (q, J = 7.4 Hz, 1H), 4.02 (s, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 1.68 (d, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 189.2 (e), 119.8 (o, 2C), 108.1 (o, 2C), 68.2 (o), 61.7 (o), 41.9 (o), 41.8 (o), 18.0 (o); IR (neat): ν = 3099 (w), 2996 (w), 2916 (w), 1537 (s), 1493 (w), 1458 (w), 1435 (w), 1403 (w), 1382 (s), 1363 (m), 1327 (w), 1300 (s), 1282 (m), 1270 (w), 1173 (s), 1090 (m), 1064 (w), 1027 (s), 994 (w), 958 (w), 945 (w), 881 (w), 855 (s), 751 (w), 727 (s), 703 (m), 679 (w) cm⁻¹; HRMS (CI(CH₄)): m/z calced for C₁₀H₁₂NO₂S+H⁺: 214.0902 [M+H⁺]; found: 214.0890; elemental analysis calcd (%) for C₁₀H₁₄NO₂S: C 56.31, H 7.09, N 6.57, S 15.03; found: C 56.18, H 7.11, N 6.40, S 14.53.

Compound 441. In a flame dried 2-neck RB flask under N₂, ¹Pr₂NH (3.3 mL, 23.50 mmol, 1.8 equiv) was dissolved in dry THF (18 mL), and the solution was cooled to -10 °C with an ice/brine bath. n-BuLi (2.5 M in hexanes, 8.4 mL, 20.90 mmol, 1.6 equiv) was added dropwise, and the reaction was stirred at -10 °C for 15 mins. A solution of 440 (2 g, 13.06 mmol, 1.0 equiv) in THF (36 mL) was added dropwise, and the reaction was stirred at -10 °C for 30 mins. Allyl bromide (2.3 mL, 26.12 mmol, 2.0 equiv) was added, and the reaction was warmed to rt, and stirred for 1 h. The reaction was quenched with water, extracted three times with ethyl acetate, and the
combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to give a brown oil (2.09 g, 10.81 mmol, 83%). This oil was dissolved in THF/H₂O (1:1, 43 mL, 0.25 M), and powdered NaOH (2.16 g, 54.05 mmol, 5.0 equiv) was added. The reaction was stirred at reflux for 16 h, then cooled to rt and the layers were separated. The aqueous was carefully acidified with 2N HCl, and extracted three times with DCM. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to afford a sticky brown solid (1.62 g, 9.81 mmol, 91%). The solid was then used according to representative procedure D to afford compound 441 as an amorphous cream-coloured solid (1.10 g, 3.84 mmol, 39%). ¹H NMR (500 MHz, CDCl₃): δ 8.26 (d, J = 9.3 Hz, 2H), 7.23 (d, J = 9.2 Hz, 2H), 6.84 (t, J = 2.1 Hz, 2H), 6.24 (t, J = 2.1 Hz, 2H), 5.80-5.69 (m, 1H), 5.24 (dq, J = 17.1, 1.5 Hz, 1H), 5.18 (dq, J = 10.3, 1.1 Hz, 1H), 4.90 (dd, J = 8.4, 7.0 Hz, 1H), 3.06-2.99 (m, 1H), 2.95-2.91 (m, 1H). This compound contained DCC, and was therefore characterised by ¹H NMR only before being used in the next step.

**Compound 308.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2), from compound 441 (1.10 g, 3.84 mmol) to afford compound 308 as a beige coloured solid (293 mg, 1.22 mmol, 32%). m.p. = 85-87 °C; ¹H NMR (500 MHz, CDCl₃): δ 6.73 (t, J = 2.2 Hz, 2H), 6.16 (t, J = 2.2 Hz, 2H), 5.69 (quin d, J = 6.9, 3.6, 6.9 Hz, 1H), 5.10 (dq, J = 17.0, 1.5 Hz, 1H), 5.01 (dq, J = 10.3, 1.4 Hz, 1H), 4.40 (dd, J = 5.1, 10.2 Hz, 1H), 4.14 (s, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.00-2.92 (m, 1H), 2.74-2.64 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 187.3 (e), 134.2 (o), 120.1 (o, 2C), 117.5 (e), 108.2 (o, 2C), 69.2 (o), 66.3 (o), 42.0 (o), 41.8 (o), 36.3 (o); IR (neat): ν 3135 (w), 3075 (w), 3001 (w), 2917 (w), 2917 (w), 1704 (w), 1641 (w), 1571 (s), 1488 (m), 1412 (m), 1387 (s), 1327 (m), 1313 (s), 1269 (m), 1239 (w), 1172 (w), 1135 (m), 1112 (m), 1086 (s), 1073 (m), 1053 (w), 1026 (s), 1003 (m), 959 (m), 946 (w), 925 (s), 906 (w), 851 (s), 786 (w), 757 (w), 730 (s), 680 (m), 658 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₂H₁₇NO₂S+H [M+H]⁺ 240.1053; found 240.1051.
**Compound 442**: Synthesised according to representative procedure F from racemic phenylglycine (2 g, 12.12 mmol) to afford compound 442 as a sticky brown gum that was used without further purification (2.60 g, 12.92 mmol, 98%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.46 – 7.30 (m, 5H), 6.74 (t, $J = 3.0$ Hz, 2H), 6.21 (t, $J = 3.0$ Hz, 2H), 5.90 (s, 1H), in agreement with previously reported data$^{18}$. 

**Compound 444**. Synthesised according to representative procedure D from compound 442 (2.6 g, 12.92 mmol) to afford compound 444 as pale-green amorphous solid (2.76 g, 8.56 mmol, 66%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.30–8.23 (m, 2H), 7.50–7.39 (m, 5H), 7.31–7.26 (m, 2H), 6.82 (t, $J = 2.2$ Hz, 2H), 6.25 (t, $J = 2.2$ Hz, 2H), 6.12 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.3 (e), 154.8 (e), 145.7 (e), 129.4 (o), 129.3 (o, 2C), 127.9 (o, 2C), 125.3 (o, 2C), 122.2 (o, 2C), 120.9 (o, 2C), 109.4 (o, 2C), 65.4 (o); IR (neat): $\tilde{\nu}$ = 2934 (w), 2836 (w), 2162 (w), 1757 (m), 1614 (w), 1591 (m), 1450 (s), 1489 (s), 1463 (m), 1419 (w), 1345 (s), 1205 (s), 1157 (s), 1142 (s), 1115 (s), 1089 (s), 1026 (s), 959 (w), 907 (w), 862 (m), 807 (w), 763 (w), 728 (s), 682 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{18}$H$_{14}$N$_2$O$_4$Na$^+$: 345.0851 [M+Na]$^+$; found: 345.0850. 

**Compound 309**. Synthesised according to representative procedure E, except that crude compound was purified by FCC on a BIOTAGE flash chromatography system (gradient 0-10% MeOH in DCM), from compound 444 (2.76 g, 8.56 mmol) to afford compound 309 as white solid (1.02 g, 3.70 mmol, 43%). m.p.: 125–126 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39-7.28 (m, 5H), 6.69 (t, $J = 2.1$ Hz, 2H), 6.16 (t, $J = 2.1$ Hz, 2H), 5.62 (s, 1H), 4.31 (s, 1H), 3.43 (s, 3H), 3.40 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 186.0 (e), 137.5 (e), 128.6 (o, 2C), 128.5 (o, 2C), 128.1 (o), 121.0 (o, 2C), 108.3 (o, 2C), 70.7 (o), 69.9 (o), 42.2 (o), 42.0 (o); IR (neat): $\tilde{\nu}$ = 3279 (w), 3114 (w), 3075 (w), 3016 (m), 2929
(m), 1698 (w), 1646 (s), 1532 (s), 1525 (m), 1466 (m), 1373 (s), 1325 (s), 1307 (m), 1253 (m), 1243 (m), 1175 (s), 1146 (m), 1086 (s), 1029 (s), 995 (m), 967 (m), 941 (m), 917 (m), 876 (w), 856 (s), 776 (m), 742 (s), 703 (m), 672 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₅H₁₇NO₂S⁺Na⁺: 298.0878 [M+Na⁺]; found: 298.0868.

**Compound 443:** Synthesised according to representative procedure F from racemic phenylalanine (2 g, 12.12 mmol) to afford compound 443 as a sticky brown gum that was used without further purification (2.61 g, 12.12 mmol, quant). ¹H NMR (500 MHz, CDCl₃): δ ppm 7.29 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.73 (t, J = 1.8 Hz, 2H), 6.23 (t, J = 1.8 Hz, 2H), 4.53 (dd, J = 10.4, 4.8 Hz, 1H), 2.65-2.60 (m, 1H); 2.52-2.34 (m, 3H), in agreement with previously reported data¹⁸.

**Compound 445.** Synthesised according to representative procedure D from compound 443 (2.62 g, 12.17 mmol) to afford compound 445 as a pale-green amorphous solid (1.55 g, 4.61 mmol, 38%); ¹H NMR (500 MHz, CDCl₃): δ 8.23 (d, J = 2.6 Hz, 2H), 7.34-7.27 (m, 3H), 7.14 (dd, J = 7.6, 1.6 Hz, 2H), 7.10-7.05 (m, 2H), 6.14 (t, J = 2.1 Hz, 2H), 6.23 (t, J = 2.1 Hz, 2H), 5.05 (t, J = 7.9 Hz, 1H), 3.55 (dd, J = 13.7, 7.7 Hz, 1H), 3.42 (dd, J = 13.7, 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 167.6 (e), 154.4 (e), 145.4 (e), 135.2 (e), 128.8 (o, 2C), 128.6 (o, 2C), 127.2 (o), 125.0 (o, 2C), 121.9 (o, 2C), 119.8 (o, 2C), 109.1 (o, 2C), 63.2 (o), 39.2 (e); IR (neat): ν = 3277 (w), 3115 (w), 3085 (w), 3030 (w), 2934 (w), 2857 (w), 2857 (w), 1760 (s), 1702 (w), 1667 (m), 1617 (m), 1592 (m), 1520 (s), 1486 (s), 1455 (m), 1446 (m), 1420 (w), 1389 (w), 1344 (s), 1312 (s), 1277 (s), 1243 (m), 1202 (s), 1174 (m), 1157 (m), 1125 (s), 1107 (m), 1093 (s), 1071 (s), 1032 (m), 1024 (m), 1012 (m), 990 (w), 969 (m), 916 (w), 895 (m), 865 (m), 843 (m), 807 (w), 789 (w), 755 (m), 746 (m), 746 (s), 719 (s), 698 (s), 680 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₉H₁₆N₂O₄⁺H⁺: 337.1183 [M+H⁺]; found: 337.1186.

**Compound 310.** Synthesised according to representative procedure E, except that crude compound was purified by FCC using a BIOTAGE flash chromatography system (gradient 0-10% MeOH in EtOAc) from compound 445 (1.45 g, 4.31 mmol) to afford compound 310 as brown powder (0.78 g, 2.71 mmol, 63%). m.p.: 90–92 °C; ¹H NMR (500 MHz,
CDCl$_3$): $\delta$ 7.23-7.13 (m, 3H), 7.07-7.02 (m, 2H), 6.70 (t, $J = 2.1$ Hz, 2H), 6.12 (t, $J = 2.1$ Hz, 2H), 4.53 (dd, $J = 9.7$, 5.4 Hz, 1H), 4.17 (s, 1H), 3.54 (dd, $J = 10.1$, 5.4 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.16 (dd, $J = 10.1$, 9.7 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 186.7 (e), 138.2 (e), 128.9 (o, 2C), 128.3 (o, 2C), 126.5 (o), 120.3 (o, 2C), 108.2 (o, 2C), 69.6 (o), 68.1 (o), 42.1 (o), 41.8 (o), 38.5 (e); IR (neat): $\tilde{\nu}$ = 3113 (w), 3075 (w), 3015 (w), 2929 (w), 1698 (w), 1646 (m), 1374 (s), 1325 (s), 1307 (m), 1253 (m), 1243 (m), 1175 (s), 1147 (m), 1085 (s), 1029 (s), 994 (m), 967 (m), 941 (m), 918 (m), 976 (w), 976 (w), 740 (s), 702 (m), 679 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{16}$H$_{19}$NO$_2$S$^+$Na$^+$: 312.1029 [M+Na]$^+$; found: 312.1027; elemental analysis calcd (%) for C$_{16}$H$_{19}$NO$_2$S: C 66.41, H 6.62, N 4.84, S 11.08; found: C 66.35, H 6.56, N 4.72 S 11.09.

**Compound 446.** Homophenylalanine (2 g, 11.16 mmol) and NaOAc (915 mg, 11.16 mmol, 1.0 equiv) were dissolved in AcOH (1.7 mL), water (5 mL), and 1,2-DCE (7 mL). After heating at 90 °C for 5 minutes, 2,5-dimethoxytetrahydrofuran (1.5 mL, 11.16 mmol, 1 equiv) was added, and the reaction was heated at 90 °C for 16 h before being cooled to room temperature and diluted with ethyl acetate. After washing with brine, and then water, the combined organic layers were dried over MgSO$_4$, filtered and concentrated under vacuum to afford 4-phenyl-2-(1H-pyrrol-1-yl)butanoic acid (2.25 g, 9.81 mmol, 88%) that was used without further purification according to representative procedure D to afford compound 446 as pale-green amorphous solid (1.94 g, 9.81 mmol, 56%); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.25 – 8.20 (m, 2H), 7.36 – 7.22 (m, 4H), 7.19 (m, 4H), 6.82 (t, $J = 2.1$, 2H), 6.28 (t, $J = 2.1$, 2H), 4.81 – 4.73 (m, 1H), 2.78 – 2.66 (m, 1H), 2.66 – 2.45 (m, 3H), 2.45 – 2.27 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.1 (e), 154.6 (e), 139.3 (e), 128.4 (o, 2C), 128.3 (o, 2C), 128.2 (e), 126.3 (o), 124.9 (o, 2C), 121.9 (o, 2C), 119.8 (o, 2C), 109.1 (o, 2C), 60.4 (o), 33.5 (e), 31.3 (e); IR (neat): $\tilde{\nu}$ = 3079 (w), 2934 (w), 2836 (w), 2115 (w), 1754 (s), 1614 (m), 1591 (m), 1516 (s), 1489 (s), 1463 (m), 1419 (w), 1345 (s), 1262 (s), 1237 (s), 1205 (s), 1157 (s), 1142 (s), 1115 (s), 1089 (s), 1026 (m), 959 (w), 907 (w), 862 (m), 808 (w), 763 (w), 728 (s), 682 (w) cm$^{-1}$; HRMS (CI(CH$_4$)): $m/z$ calcd for C$_{20}$H$_{18}$N$_2$O$_4$+H$^+$: 351.1339 [M+H]$^+$; found: 351.1337.
**Compound 311.** Synthesised according to representative procedure E, except that crude compound was purified by FCC using a BIOTAGE flash purification system (gradient 0-10% MeOH in DCM), from compound 446 (1.45 g, 4.31 mmol) to afford compound 311 as white solid (0.95 g, 3.13 mmol, 56%). m.p.: 65–68 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.31–7.26 (m, 2H), 7.21–7.11 (m, 3H), 6.73 (s, 2H), 6.21 (s, 2H), 4.28 (dd, J = 10.9, 4.2 Hz, 1H), 4.09 (s, 1H), 3.33 (s, 6H), 2.67-2.44 (m, 3H), 2.29-2.20 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 188.2 (e), 140.9 (e), 128.6 (o, 2C), 128.4 (o, 2C), 126.0 (o), 120.1 (o, 2C), 108.3 (o, 2C), 68.7 (o), 65.6 (o), 42.1 (o), 41.9 (o), 33.5 (e), 32.2 (e); IR (neat): \( \tilde{\nu} \approx \) 3076 (w), 3001 (w), 2953 (w), 2919 (w), 2861 (w), 2816 (w), 1571 (s), 1510 (w), 1487 (w), 1454 (w), 1435 (w), 1415 (s), 1390 (s), 1350 (w), 1313 (w), 1301 (w), 1277 (w), 1263 (w), 1235 (w), 1183 (s), 1169 (s), 1125 (s), 1089 (s), 1071 (w), 1062 (w), 1050 (w), 1028 (s), 1000 (w), 948 (w), 927 (w), 927 (w), 909 (w), 857 (m), 798 (w), 760 (m), 748 (m), 760 (s), 698 (s), 678 (m) cm⁻¹; HRMS (ESI): \( m/z \) calcld for C₁₇H₂₁NO₂S⁺: 304.1366 [M⁺]; found: 304.1362.

**Representative Procedure G:** Following a reported procedure¹⁹, in a flame dried 2-neck 250 mL RB flask, 2-coumaranone (2.5 g, 18.64 mmol, 1 equiv) and compound 327 (8.10 g, 22.37 mmol, 1.2 equiv) were dissolved in dry toluene (40 mL, 0.46 M) and protected from light with aluminium foil. The reaction was heated at reflux for 48 h, then cooled to rt and concentrated in vacuo. The crude residue was purified by FCC (2.5% EtOAc in n-hexane) to afford compound 328 as a pale yellow oil (1.50 g, 6.87 mmol, 46%).

**Compound 328.** ¹H NMR (400 MHz, CDCl₃): δ 7.52 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.22 (quint. d, J = 2.0, 7.6 Hz, 2H), 6.58 (s, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.94 (q, J = 7.5 Hz, 1H), 1.62 (d, J = 7.3 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), in agreement with previously reported data²⁰.
**Compound 447**: Compound 328 (1.53 g, 7.01 mmol, 1 equiv) was dissolved in EtOH/H$_2$O (1:1, 44 mL, 0.16 M) and NaOH (0.56 g, 14.02 mmol, 2 equiv) was added. The reaction was stirred at rt for 2.5 h, then carefully acidified to pH 3 using 2N HCl. The reaction was then quickly extracted with DCM (x3), the combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo (the organic layers were left on the rotavap for ca. 30 mins, taking care not to increase the water bath temperature above 30 °C. The residual solvent was then removed on a hi-vacuum line) to afford compound 447 as a light brown solid (1.32 g, 6.94 mmol, quant.). m.p. = 58-60 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.52 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.28-7.23 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.62 (s, 1H), 4.00 (q, J = 7.2 Hz, 1H), 1.66 (d, J = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 178.0 (e), 155.4 (e), 154.8 (e), 128.0 (e), 124.1 (o), 122.7 (o), 120.8 (o), 111.1 (o), 103.5 (o), 39.7 (o), 15.5 (o); IR (neat): $\tilde{\nu}$ = 2989 (w); 2946 (w); 2889 (w); 2616 (w); 2533 (w); 2050 (w); 1941 (w); 1903 (w); 1790 (w); 1693 (s); 1606 (m); 1586 (w); 1454 (s); 1412 (m); 1375 (m); 1348 (w); 1327 (w); 1286 (m); 1256 (s); 1230 (m); 1215 (s); 1171 (s); 1154 (m); 1110 (w); 1070 (m); 1006 (w); 932 (s); 882 (m); 859 (w); 816 (m); 741 (s); 731 (s); 670 (s) cm$^{-1}$, HRMS (ESI): m/z calcd for C$_{11}$H$_{10}$O$_3$-H: 189.0557 [M-H]-; found: 189.0556.

**Compound 448.** Synthesised according to representative procedure D from compound 447 (1.52 g, 7.99 mmol) to afford compound 448 as viscous yellow oil (1.42 g, 4.56 mmol, 57%). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.26 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.32-7.22 (m, 4H), 6.70 (s, 1H), 4.24 (q, J = 7.3 Hz, 1H), 1.78 (d, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 170.0 (e), 155.3 (e), 154.86 (e), 154.81 (e), 145.4 (e), 128.1 (e), 125.2 (o, 2C), 124.3 (o), 122.9 (o), 122.3 (o, 2C), 120.9 (o), 111.1 (o), 103.8 (o), 40.1 (o), 15.6 (o); IR (neat): $\tilde{\nu}$ = 3116 (w), 3096 (w), 2990 (w), 2936 (w), 2856 (w), 2116 (w), 1810 (w), 1763 (w), 1615 (m), 1592 (m), 1521 (s), 1489 (m), 1454 (s), 1379 (w), 1345 (s), 1254 (w), 1201 (s), 1154 (s), 1120 (s), 1063 (s), 1011 (m), 993 (w), 939 (w), 897 (m), 888 (w), 864 (s), 847 (w), 807 (w), 779 (w), 748 (s), 710 (w), 679 (w) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{17}$H$_{13}$NO$_5$+H$^+$: 312.0827 [M+H]$^+$; found: 312.0830.
Compound 321. Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration in Et₂O of the solid obtained from the product containing fractions, from compound 448 (1.42 g, 4.56 mmol) to afford compound 321 as white solid (638 mg, 2.41 mmol, 53%). m.p.: 70–74 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.50 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.24-7.16 (m, 2H), 6.54 (s, 1H), 4.40 (s, 1H), 3.72 (q, J = 7.2 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 188.5 (e), 159.4 (e), 154.6 (e), 128.7 (e), 123.4 (o), 122.4 (o), 120.5 (o), 111 (o), 102.5 (o), 68.7 (o), 44.8 (o), 42.11 (o), 42.08 (o), 16.1 (o); IR (neat): ʋ = 3093 (w), 3015 (w), 3000 (w), 2980 (w), 2914 (w), 1561 (s), 1472 (w), 1455 (s), 1384 (s), 1366 (s), 1327 (w), 1310 (w), 1299 (w), 1255 (m), 1179 (s), 1141 (m), 1106 (w), 1053 (w), 994 (s), 957 (w), 937 (m), 883 (w), 852 (s), 816 (w), 803 (s), 740 (s), 708 (w), 693 (w), 657 (m) cm⁻¹; HRMS (ESI): m/z calcd for C₁₄H₁₆O₃S⁺Na⁺ [M+Na]^+: 287.0718; found: 287.0720.

Compound 449. Synthesised from ethyl 1-(benzofuran-3-yl)propanote¹⁰ (1.09 g, 5.73 mmol), to afford compound 449 as pale-brown amorphous solid (1.38 g, 4.43 mmol, 78%). ¹H NMR (500 MHz, CDCl₃): δ 8.22 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 7.7 Hz, 1H), 7.67 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.38-7.32 (m, 1H), 7.32-7.27 (m, 1H), 7.19 (d, J = 9.1 Hz, 2H), 4.21 (q, J = 7.4 Hz, 1H), 1.77 (d, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 171.5 (e), 155.5 (e), 150.4 (e), 149.8 (e), 136.5 (e), 126.5 (e), 125.2 (o, 2C), 124.5 (o), 122.9 (o), 122.3 (o, 2C), 119.8, 111.9 (o), 36.3 (o), 17.0 (o); IR (neat): ʋ = 3115 (w), 3071 (w), 2990 (w), 2928 (w), 2854 (w), 2115 (m), 1924 (w), 1760 (m), 1708 (w), 1616 (w), 1590 (m), 1519 (s), 1489 (m), 1466 (w), 1454 (m), 1423 (w), 1380 (w), 1343 (s), 1321 (s), 1288 (w), 1261 (w), 1244 (w), 1204 (s), 1164 (w), 1115 (s), 1091 (s), 1063 (s), 1048 (s), 1010 (m), 982 (w), 956 (w), 931 (w), 900 (s), 865 (s), 857 (s), 813 (w), 770 (w), 746 (s), 719 (w), 708 (m), 675 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₇H₁₆O₃S⁺Na⁺: 334.0691 [M+Na]^+: found: 334.0695.
**Compound 322.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration in Et₂O of the solid obtained from the product containing fractions, from compound 449 (1.38 g, 4.43 mmol) to afford compound 322 as an off-white powder (400 mg, 1.51 mmol, 34%); m.p.: 52-55 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.62 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.46 (dt, J = 8.2, 0.8 Hz, 1H), 7.29-7.25 (m, 1H), 7.23-7.18 (m, 1H), 4.39 (s, 1H), 3.69 (q, J = 7.2 Hz, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 190.8 (e), 155.4 (e), 141.4 (o), 127.4 (e), 124.1 (o), 122.3 (o), 122.2 (e), 120.2 (o), 111.4 (o), 68.5 (o), 42.11 (o), 42.05 (o), 41.0 (o), 17.5 (o); IR (neat): ν ~ = 3109 (w); 2994 (w); 2975 (w); 2915 (w); 2915 (w); 1615 (w); 1577 (s); 1555 (s); 1471 (w); 1453 (s); 1415 (m); 1404 (m); 1382 (s); 1362 (s); 1329 (m); 1307 (w); 1280 (w); 1250 (w); 1172 (s); 1145 (m); 1120 (w); 1094 (m); 1083 (m); 1061 (m); 1039 (s); 1023 (s); 992 (m); 980 (m); 945 (w); 890 (w); 757 (s); 716 (w); 698 (w); 684 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₄H₁₆O₃S+: 287.0712 [M+Na]+; found: 287.0718.

**Compound 451:** Synthesised according to representative procedure B, from compound 450 (4.1 g, 20.32 mmol) to afford compound 451 as a pale brown oil (3.08 g, 14.18 mmol, 70%). ¹H NMR (500 MHz, CDCl₃): δ 7.67 (dt, J = 0.9, 8.1 Hz, 1H), 7.30 (dt, J = 0.9, 8.2 Hz, 1H), 7.26-7.22 (m, 1H), 7.15-7.11 (m, 1H), 7.00 (s, 1H), 4.04 (q, J = 7.1 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 175.7
(e), 137.0 (e), 126.8 (e), 126.3 (o), 121.8 (o), 119.3 (o), 119.2 (o), 114.0 (e), 109.3 (o), 52.0 (o), 36.8 (o), 32.7 (o), 18.1 (o), in agreement with previously reported data 

**Compound 452.** Compound 451 (3.08 g, 14.18 mmol, 1.0 equiv) was dissolved in THF/H₂O (1:1, 55 mL, 0.25 M) and NaOH (2.84 g, 70.9 mmol, 5.0 equiv) was added. The reaction was heated at reflux for 15 h, then carefully acidified to pH 2 using 2N HCl. The reaction was then quickly extracted three times with DCM and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to afford a pale-brown solid (2.87 g, 14.12 mmol, quant.) that was used without further purification according to representative procedure D to afford compound 452 as pale-green amorphous solid (3.96 g, 12.21 mmol, 86%).

**1H NMR (500 MHz, CDCl₃):** δ 8.20 (d, J = 9.3 Hz, 2H), 7.74 (dt, J = 8.0, 0.9 Hz, 1H), 7.34 (dt, J = 8.3, 1.0 Hz, 1H), 7.31-7.27 (m, 2H), 7.17 (d, J = 9.3 Hz, 2H), 7.09 (s, 1H), 4.29 (q, J = 7.4 Hz, 1H), 3.80 (s, 3H), 1.74 (d, J = 7.2 Hz, 2H); **13C NMR (125 MHz, CDCl₃):** δ 171.5 (e), 155.9 (e), 145.2 (e), 137.0 (e), 131.5 (e), 129.1 (o), 125.1 (o, 2C), 122.3 (o, 2C), 121.8 (o), 119.0 (o), 112.1 (e), 108.8 (o), 101.2 (o), 45.2 (o), 34.2 (o), 17.5 (o); IR (neat): ν = 3081 (w), 2934 (w), 2837 (w), 2115 (w), 1760 (m), 1653 (w), 1615 (w), 1591 (m), 1513 (s), 1488 (s), 1463 (m), 1418 (w), 1345 (s), 1259 (s), 1234 (s), 1203 (s), 1158 (s), 1140 (s), 1097 (s), 1024 (s), 962 (w), 930 (w), 913 (w), 913 (w), 884 (w), 862 (s), 806 (w), 782 (w), 758 (m), 722 (s), 682 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₈H₁₆N₂O₄+H⁺: 325.1183 [M+H]⁺; found: 325.1181.

**Compound 323.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (Et₂O followed by a gradient of 1-2% MeOH in DCM) followed by trituration in Et₂O of the solid obtained from the product containing fractions, from compound 452 (2.35 g, 7.24 mmol) to afford compound 323 as cream-coloured powder (677 mg, 2.44 mmol, 34%); m.p.: 71-73 °C; **1H NMR (500 MHz, CDCl₃):** δ 7.64 (dt, J = 7.8, 0.8 Hz, 1H), 7.28 (dt, J = 8.4, 1.1 Hz, 1H), 7.23-7.17 (m, 1H), 7.10-7.05 (m, 1H), 6.97 (s, 1H), 4.39 (s, 1H), 3.80 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 1.54 (d, J = 7.2 Hz, 3H); **13C NMR (125 MHz, CDCl₃):** δ 192.8 (e), 137.0 (e), 127.3 (e), 126.1 (o), 121.4 (o), 119.4 (o), 118.6 (o), 116.6 (e), 109.1 (o), 68.1 (o), 42.11 (o), 42.05 (o), 41.95 (o), 32.6 (o), 18.3 (o); IR (neat): ν = 3123 (w); 3086 (w); 3047
Compound 332: Following a reported procedure, in a flame dried, 3-neck 500 mL RB flask under N₂, powdered NaOH (4.22 g, 105.7 mmol, 10 equiv) was suspended in dry DCM (330 mL, 0.03 M), and the suspension was cooled to -20 °C using a temperature controlled cryogenic bath. Compound 331 (2 g, 10.57 mmol, 1 equiv), TBAB (0.17 g, 0.53 mmol, 5 mol%) and TsCl (20 g, 105.7 mmol, 10 equiv) were added in that order, and the reaction was stirred at -20 °C for 20 h, before being quenched with 2N HCl (151 mL) at -20 °C. The reaction was allowed to warm up to rt and the layers were separated. The organic layer was washed twice with brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified by FCC (95:5 then 4:1 PE:EA, with the product eluting during 4:1 PE:EA) to afford compound 332 as a light brown oil (3.25 g, 9.46 mmol, 90%). 

1H NMR (500 MHz, CDCl₃): δ 7.97 (dt, J = 0.9, 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 1.2 Hz, 1H), 7.49 (dt, J = 1.0, 7.9 Hz, 1H), 7.35-7.29 (m, 1H), 7.25-7.20 (m, 3H), 7.25 (s, 3H), 3.71 (s, 3H), 3.69 (d, J = 1.0 Hz, 2H), 2.34 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 170.9 (e), 135.2 (e), 134.9 (e), 130.3 (e), 129.8 (o, 2C), 126.8 (o, 2C),...
124.8 (o), 124.7 (o), 123.2 (o), 119.4 (o), 114.9 (e), 113.6 (o), 52.1 (o), 30.7 (e), 21.5 (o); in agreement with previously reported data.

**Compound 453.** Compound 332 (1.5 g, 4.37 mmol) was used according to representative procedure B to afford a pale yellow liquid (474 mg, 1.33 mmol, 30%) and its identity was verified by $^1$H NMR (500 MHz, CDCl$_3$): δ 7.96 (dt, $J = 0.9$, 8.3 Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.55 (dt, $J = 8.0$, 1.0 Hz, 1H), 7.51 (s, 1H), 7.33-7.28 (m, 1H), 7.24-7.20 (m, 3H), 3.92 (q, $J = 7.3$ Hz, 1H), 3.66 (s, 3H), 2.34 (s, 3H), 1.59 (d, $J = 7.3$ Hz, 3H). Some of this material (345 mg, 0.96 mmol, 1 equiv) was dissolved in 1,4-dioxane/H$_2$O (2:1, 45 mL, 0.02 M), and a 5% aqueous solution of KOH (3 mL) was added. The reaction was stirred at rt for 4 h, then acidified to pH 2-3 with 2N HCl, and extracted with 3 times with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered and concentrated under vacuum. The crude residue was purified by flash chromatography on SiO$_2$ (CH$_2$Cl$_2$/MeOH, 98:2) to afford compound 453 as an off white solid (330 mg, 0.96 mmol, quant.). m.p. = 108-110 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 10.75 (br s, 1H), 7.95 (d, $J = 8.2$ Hz, 1H), 7.75 (d, $J = 8.1$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.53 (s, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 3.93 (q, $J = 7.2$ Hz, 1H), 2.33 (s, 3H), 1.61 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 179.7 (e), 144.9 (e), 135.2 (e), 135.1 (e), 129.9 (o, 2C), 129.6 (e), 126.8 (o, 2C), 124.8 (o), 123.6 (o), 123.2 (o), 120.9 (e), 119.8 (o), 113.7 (o), 36.7 (o), 21.5 (o), 17.0 (o); IR (neat): $\tilde{\nu}$ ≈ 2979 (w), 2941 (w), 2639 (w), 1920 (w), 1744 (w), 1700 (s), 1594 (w), 1562 (w), 1492 (w), 1446 (m), 1420 (w), 1397 (w), 1373 (s), 1304 (m), 1282 (m), 1247 (w), 1233 (w), 1210 (w), 1187 (m), 1172 (s), 1134 (s), 1122 (s), 1108 (m), 1086 (s), 1050 (w), 1016 (m), 997 (m), 959 (m), 865 (w), 811 (m), 794 (w), 760 (m), 749 (s), 729 (m), 701 (m), 665 (s) cm$^{-1}$; HRMS (ESI neg): m/z calcd for C$_{18}$H$_{17}$NO$_4$S-H$^-$: 342.0806 [M-H]$^-$; found: 342.0800.

**Compound 454.** Synthesised according to representative procedure D from compound 453 (300 mg, 0.87 mmol) to afford compound 454 as a pale green amorphous solid (317 mg, 0.68 mmol, 78%). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.21 (d, $J = 9.1$ Hz, 2H), 8.01 (dt, $J = 8.3$, 0.3 Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 2H), 7.62 (dt, $J = 7.9$, 0.9 Hz, 1H), 7.61 (s, 1H), 7.39-7.33 (m, 1H), 7.30-7.27 (m, 1H), 7.22
(d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 9.2$ Hz, 2H), 4.19 (q, $J = 7.2$ Hz, 1H), 2.34 (s, 3H), 1.74 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.3 (e), 155.3 (e), 145.3 (e), 145.1 (e), 135.2 (e), 135.1 (e), 129.9 (o, 2C), 129.3 (e), 126.8 (o, 2C), 125.1 (o, 2C), 123.8 (o), 123.4 (o), 122.2 (o, 2C), 120.5 (e), 119.5 (o), 113.9 (o), 37.1 (o), 21.5 (o), 17.0 (o); IR (neat): $\tilde{\nu} = 3115$ (w), 2984 (w), 2938 (w), 2116 (w), 1916 (w), 1760 (s), 1615 (w), 1592 (m), 1522 (s), 1489 (m), 1447 (m), 1369 (m), 1346 (s), 1325 (w), 1307 (w), 1283 (w), 1204 (s), 1188 (s), 1173 (s), 1120 (s), 1087 (s), 1074 (s), 1012 (w), 1000 (w), 957 (w), 897 (w), 864 (w), 846 (w), 812 (w), 763 (w), 745 (m), 732 (s), 702 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{24}$H$_{20}$N$_2$O$_6$S$^+$Na$: 487.0934$ [M+Na]$^+$; found: 487.0936.

**Compound 324.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration in Et$_2$O of the solid obtained from the product containing fractions, from compound 454 (317 mg, 0.68 mmol) to afford compound 324 as pale green powder (177 mg, 0.42 mmol, 62%). m.p.: 49–51 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.95 (dt, $J = 8.3$, 0.8 Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 2H), 7.55 (dt, $J = 8.0$, 1.0 Hz, 1H), 7.45 (d, $J = 0.8$ Hz, 1H), 7.30-7.26 (m, 1H), 7.23-7.16 (m, 3H), 4.23 (s, 1H), 3.66 (q, $J = 7.2$ Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.32 (s, 3H), 1.52 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 190.8 (e), 144.8 (e), 135.34 (e), 135.28 (e), 130.4 (e), 129.8 (o, 2C), 126.7 (o, 2C), 124.8 (e), 124.6 (o), 123 (o), 122.9 (o), 120.1 (o), 113.7 (o), 68.4 (o), 42.11 (o), 42.04 (o), 42.01 (o), 21.5 (o), 17.6 (o); IR (neat): $\tilde{\nu} = 3015$ (w), 2925 (w), 1570 (s), 1494 (w), 1446 (s), 1358 (s), 1304 (m), 1277 (m), 1168 (s), 1120 (s), 1101 (s), 1087 (s), 1020 (s), 998 (m), 961 (m), 899 (w), 854 (m), 812 (m), 764 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{21}$H$_{23}$NO$_4$S$^+$H$: 418.1141$ [M+H]$^+$; found: 418.1145.
Compound 456. Synthesised according to representative procedure D, from compound 455 (1.99 g, 9.78 mmol) to afford compound 456 as a pale green amorphous solid (1.56 g, 4.81 mmol, 49%). ¹H NMR (500 MHz, CDCl₃): δ 8.24 (d, J = 9.2 Hz, 2H), 7.62 (dt, J = 7.9, 0.9 Hz, 1H), 7.32 (dt, J = 8.3, 0.9 Hz, 1H), 7.28-7.23 (m, 1H), 7.17 (d, J = 9.2 Hz, 2H), 7.16-7.11 (m, 1H), 6.93 (s, 1H), 3.76 (s, 3H), 3.23 (t, J = 7.6 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), in agreement with previously reported data²⁴.

Compound 325. Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 98:2) followed by trituration in Et₂O of the solid obtained from the product containing fractions, from compound 456 (1.56 g, 4.81 mmol) to afford compound 325 as an off-white powder (577 mg, 2.07 mmol, 43%). m.p.: 68–70 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.61 (d, J = 7.8 Hz, 1H), 7.28–7.25 (m, 1H), 7.22–7.18 (m, 1H), 7.10–7.06 (m, 1H), 6.86 (s, 1H), 4.37 (s, 1H), 3.73 (s, 3H), 3.35 (s, 6H), 3.08–3.02 (m, 2H), 2.58–2.54 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 190.5 (e), 136.9 (e), 127.8 (e), 126.1 (o), 121.4 (o), 119.0 (o), 118.5 (o), 114.6 (e), 109.0 (o), 69.1 (o), 42.2 (o, 2C), 41.7 (e), 32.5 (o), 21.5 (e); IR (neat): ʋ = 3057 (w), 3025 (w), 3002 (w), 2911 (w), 2852 (w), 1614 (w), 1555 (s), 1485 (m), 1472 (m), 1448 (m), 1417 (m), 1373 (s), 1321 (m), 1308 (m), 1280 (w), 1245 (m), 1201 (w), 1165 (s), 1127 (m), 1104 (w), 1060 (w), 1032 (s), 1011 (m), 990 (m), 954 (w), 926 (w), 849 (s), 802 (w), 790 (w), 778 (w), 758 (w), 734 (s), 724 (s), 684 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₅H₁₉NO₂S⁺H⁺: 278.1209 [M+H⁺]; found: 278.1216; elemental analysis calcd (%) for C₁₅H₁₉NO₂S: C 64.95, H 6.90, N 5.05, S 11.56; found: C 64.92, H 6.82, N 5.00, S 11.57.
**Compound 350.** NaH (60% in oil, 430 mg, 10.74 mmol, 1.2 equiv) was added in small portion to a solution of tert-butyl 4-(1H-pyrrole-2-carbonyl)piperazine-1-carboxylate (2.5 g, 8.95 mmol) in dry DMF (36 mL) at 0 °C under N₂. After stirring at room temperature for 1 h, ethyl 2-bromoacetate (1.1 mL, 9.84 mmol, 1.1 equiv) was added. After stirring at room temperature for 16 h, the reaction was quenched and extracted 3 times with EtOAc. The combined organic layers were washed first with water, then brine, and then dried over MgSO₄, filtered and concentrated under vacuo to afford a pale-brown oil (2.62 g, 7.17 mmol, 80%) that was dissolved in 1,4-dioxane (118 mL) before a 5% aqueous solution of NaOH (118 mL) was added. After at room temperature for 1 h, the reaction was then acidified to pH 2-3 with 2N HCl, then extracted with CH₂Cl₂ (4 × 100 mL). The combined organic layers were passed through a phase separator cartridge, and the filtrate was concentrated under vacuum to afford a brown gum (2.39 g, 7.09 mmol, quant.) that was then used without further purification according to representative procedure B to afford 350 as pale-brown amorphous solid (1.54 g, 3.36 mmol, 47%). ¹H NMR (500 MHz, CDCl₃): δ 8.29-8.24 (m, 2H), 7.93-7.32 (m, 2H), 6.84 (dd, J = 2.5, 1.6 Hz, 1H), 6.47 (dd, J = 3.8, 1.5 Hz, 1H), 6.25-6.19 (m, 1H), 5.16 (s, 2H), 3.80–3.60 (m, 4H), 3.49-3.43 (m, 4H), 1.47 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 166.6 (e), 162.7 (e), 154.9 (e), 154.3 (e), 145.2 (e), 126.6 (o), 125.0 (o, 2C), 124.0 (e), 122.0 (o, 2C), 114.0 (o), 107.8 (o), 80.0 (e), 50.1 (e), 28.1 (o, 3C) (Two resonances of methylene carbon nuclei of piperazine are not visible due to slow rotation of Boc group); HRMS (ESI): m/z calcd for C₂₂H₂₆N₄O₇⁺Na⁺: 481.1694 [M+Na]⁺; found: 481.1710.

**Compound 351.** Synthesised according to representative procedure E, except that crude compound was purified by FCC using a BIOTAGE flash chromatography system (gradient 0-30% MeOH in EtOAc), from compound 350 (770 mg, 1.68 mmol) to afford compound 351 as white solid (538 mg, 1.31 mmol, 78%). m.p.: 125–127 °C; ¹H NMR (500 MHz, CDCl₃): δ 6.75 (dd, J = 2.5, 1.7 Hz, 1H), 6.33 (dd, J = 3.8, 1.6 Hz, 1H), 6.14 (dd, J = 3.7, 2.7 Hz, 1H), 4.73 (s, 2H), 4.13 (s, 1H), 3.74–3.67 (m, 4H), 3.36 (s, 6H), 1.47 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 185.0 (e), 163.2 (e), 154.6 (e), 126.5 (o), 125.0 (e), 112.9 (o), 107.4 (o), 80.2 (e), 67.9 (o),
55.0 (e), 42.2 (o. 2C), 28.3 (o, 3C) (Two signals of methylene carbon nuclei of piperazine are not visible due to slow rotation of the Boc group); IR (neat): $\tilde{\nu} = 3082$ (w), 2975 (w), 2917 (w), 2867 (w), 1674 (s), 1624 (s), 1561 (s), 1470 (m), 1455 (m), 1418 (s), 1378 (s), 1325 (m), 1305 (m), 1280 (m), 1242 (s), 1183 (s), 1164 (s), 1138 (m), 1123 (s), 1072 (m), 1055 (w), 1022 (m), 997 (m), 970 (w), 954 (w), 917 (w), 856 (m), 842 (w), 826 (w), 806 (w), 784 (w), 770 (w), 736 (m), 706 (w), 691 (w), 672 (w), 657 (w) cm$^{-1}$; HRMS (ESI): $m/z$ calcld for C$_{19}$H$_{29}$N$_3$O$_5$S$: 434.1720 [M+Na]$^+ $; found: 434.1731.

Compound 457. Following a reported procedure$^{25}$, in a flame dried 2-neck 25 mL RB flask under N$_2$, L-tryptophan (1 g, 3.28 mmol, 1.0 equiv) and NaOH (0.26 g, 6.57 mmol, 2.0 equiv) were dissolved in dry DMSO (7 mL, 0.5 M) and stirred at 40 °C for 2 h. MeI (0.6 mL, 9.86 mmol, 3.0 equiv) was added and the reaction was stirred at 40 °C for 16 h. Water was added to the reaction, and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with water (x5), dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified by FCC (7:3 PE:EtOAc) to afford compound 457 as a colourless liquid (933 mg, 2.81 mmol, 85%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.24-7.20 (m, 1H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.85 (s, 1H), 5.05 (br d, $J = 7.2$ Hz, 1H), 4.63 (q, $J = 6.9$ Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.27 (s, 2H), in agreement with previously reported data$^{25}$. 

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**Compound 356.** Following a reported procedure\textsuperscript{25}, compound 457 (0.93 g, 2.81 mmol, 1.0 equiv) was dissolved in DMSO (9 mL, 0.3 M) and a 1M aqueous solution of NaOH (0.7 M) was added. The reaction was stirred at rt for 16 h, then diluted with H\textsubscript{2}O and washed with EtOAc (x3). The aqueous layer was acidified with 2N HCl, then extracted with DCM (x3). The combined DCM layers were washed with H\textsubscript{2}O (x5), dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo to afford compound 356 as a light brown powder which was used without further purification (0.89 g, 2.79 mmol, quant.). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.60 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.21-7.17 (m, 1H), 7.10-7.06 (m, 1H), 6.91 (s, 1H), 5.09 (br s, 1H), 4.60 (q, J = 6.1 Hz, 1H), 3.73 (s, 3H), 3.39-3.23 (m, 2H), in agreement with previously reported data\textsuperscript{25}.

**Compound 357.** To a flame dried, 2-neck RB flask under N\textsubscript{2} was added compound 356 (2.28 g, 7.16 mmol, 2.0 equiv) and EDCI•HCl (1.03 g, 5.37 mmol, 1.5 equiv), followed by dry DCM (14 mL, 0.25 M). The reaction was stirred at rt for 5 mins, before 4-nitrophenol 211 (0.50 g, 3.58 mmol, 1.0 equiv) was added, and the reaction was allowed to stir at rt for 20 h. The reaction was diluted with DCM and washed with sat. aq. NaHCO\textsubscript{3} solution (x3). The organic layer was dried, filtered and concentrated in vacuo, and the crude residue was purified by FCC (petroleum ether/EtOAc = 4:1) to afford compound 357 as a pale yellow amorphous solid (0.701 g, 1.60 mmol, 44%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.20 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.29-7.24 (m, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 9.1 Hz, 2H), 6.96 (s, 1H), 5.13 (br d, J = 7.2 Hz, 1H), 4.83 (q, J = 7.5 Hz, 1H), 3.79 (s, 3H), 3.45 (dd, J = 5.8, 14.5 Hz, 1H), 3.38 (dd, J = 6.1, 14.8 Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 170.4 (e), 155.3 (e), 155.1 (e), 145.4 (e), 137.0 (e), 127.9 (e), 127.6 (o), 125.1 (o, 2C), 122.3 (o), 122.1 (o, 2C), 119.4 (o), 118.8 (o), 109.4 (o), 80.4 (e), 54.6

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(o), 32.3 (o), 28.3 (o, 3C), 27.7 (e); HRMS (ESI): m/z calcd for C_{23}H_{25}N_{3}O_{6}+Na^+ [M+Na]^+ 462.1636; found 462.1647.

**Compound 358.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by trituration in Et_2O, from compound 357 (701 mg, 1.59 mmol) to afford compound 358 as a light brown powder (310 mg, 0.79 mmol, 50%), m.p. = 40-43 °C; [α]_D = -11.16 (MeOH, l = 0.25 dm, c = 8.6); Chiral HPLC analysis (Chiralpak AD-H), 25% isopropanol/hexane at 0.75 mL/min. flow rate, 254 nm; tR (major) 8.52 min., tR (minor) 9.69 min., 92% enantiomeric excess.; ^1H NMR (500 MHz, CDCl_3): δ 7.62 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.92 (s, 1H), 5.32 (d, J = 8.4 Hz, 1H), 4.36 (q, J = 6.6 Hz, 1H), 4.27 (s, 1H), 3.74 (s, 3H), 3.25 (s, 3H), 3.21-3.20 (m, 1H), 3.14 (dd, J = 6.9, 14.2 Hz, 1H), 3.06 (s, 3H), 1.43 (s, 9H); ^13C NMR (100 MHz, CDCl_3): δ 187.5 (e), 136.7 (e), 128.6 (e), 127.5 (o), 121.4 (o), 119.3 (o), 118.6 (o), 110.2 (e), 109.0 (o), 83.3 (e), 69.2 (o), 57.6 (o), 41.8 (o), 41.6 (o), 32.6 (o), 28.9 (e), 28.4 (o, 3C); IR (neat): 3397 (br, w), 3008 (w), 2976 (w), 2924 (w), 1696 (s), 1565 (s), 1483 (s), 1474 (s), 1437 (m), 1389 (s), 1376 (s), 1364 (s), 1326 (m), 1247 (m), 1162 (s), 1020 (s), 937 (w), 894 (w), 854 (m), 739 (s), 685 (w); HRMS (ESI): m/z calcd for C_{20}H_{28}N_{2}O_{4}S+H^+ [M+H]^+ 393.1843; found: 393.1842.
Representative Procedure H: Indole (2 g, 17.07 mmol, 1.0 equiv) was dissolved in dry DMF (68 mL, 0.25 M) under N₂, and cooled to 0 °C. NaH (60% in oil, 0.8 g, 32.78 mmol, 1.2 equiv) was added in small portions, and the reaction stirred at rt for 1 h. Methyl bromoacetate (1.8 mL, 18.78 mmol, 1.1 equiv) was added and the reaction was
allowed to stir at rt for 16 h. The reaction was quenched with water, and extracted with EtOAc (3x 100 mL). The combined organic layers were washed with water (x5), brine (once), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by FCC (9:1 hexane:Et₂O) to afford compound 383 as a colourless oil (1.63 g, 8.62 mmol, 50%).

**Compound 383.** ¹H NMR (500 MHz, CDCl₃): δ ppm 7.64 (dt, J = 0.9, 7.9 Hz, 1H); 7.26-7.21 (m, 2H), 7.16-7.11 (m, 1H), 7.10 (d, J = 3.1 Hz, 1H), 6.57 (dd, J = 0.6, 3.2 Hz, 1H), 4.87 (s, 2H), 3.74 (s, 3H); in agreement with previously reported data²⁶.

**Compound 379.** Synthesised according representative procedure C, from compound 383 (1.63 g, 8.62 mmol) to afford compound 379 as a cream powder that was used without further purification (1.30 g, 7.42 mmol, 87%). ¹H NMR (500 MHz, DMSO-d₆): δ 12.94 (br s, 1H); 7.54 (d, J = 7.9 Hz, 1H); 7.37 (d, J = 8.2 Hz, 1H); 7.32 (d, J = 3.2 Hz, 1H); 7.12 (t, J = 7.7 Hz, 1H); 7.02 (t, J = 7.3 Hz, 1H); 6.44 (d, J = 3.1 Hz, 1H); 5.00 (d, J = 2.4 Hz, 2H), in agreement with previously reported data²⁶.

**Compound 458.** Synthesised according to representative procedure D, from compound 379 to afford compound 458 as a bright yellow amorphous solid (1.90 g, 6.41 mmol, 88%). ¹H NMR (500 MHz, CDCl₃): δ 8.25 (d, J = 9.3 Hz, 2H), 7.68 (dt, J = 0.9, 8.0 Hz, 1H), 7.34 (dd, J = 0.8, 8.3 Hz, 1H), 7.31-7.26 (m, 2H), 7.20-7.15 (m, 2H), 6.63 (dd, J = 0.8, 3.2 Hz, 1H), 5.15 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 166.2 (e), 154.7 (e), 145.6 (e), 136.5 (e), 128.8 (e), 128.3 (o), 125.3 (o, 2C), 122.5 (o), 122.1 (o), 121.4 (o), 120.3 (o, 2C), 108.7 (o), 103.3 (o), 47.9 (e); IR (neat): 3111 (w), 3078 (w), 2931 (w), 2856 (w), 2115 (w), 1786 (m), 1667 (m), 1615 (w), 1589 (m), 1519 (s), 1487 (m), 1461 (s), 1417 (w), 1392 (w), 1341 (s), 1332 (s), 1290 (s), 1245 (m), 1204 (s), 1161 (m), 1130 (s), 1105 (s), 1012 (m), 961 (w), 953 (w), 920 (m), 864 (m), 848 (s), 816 (m), 798 (m), 764 (w), 755 (m), 737 (s), 710 (s), 677 (w), 661 (w); HRMS (ESI): m/z calcd for C₁₆H₁₁DN₂O₄+H⁺ [M+H]⁺ 298.0933; found 298.0929.
Compound 381. Synthesised according representative procedure E, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by trituration in Et₂O, from compound 458 (1.90 g, 6.42 mmol) to afford compound 381 as a cream powder (1.12 g, 4.51 mmol, 70%). m.p. = 90-95 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.64 (dt, J = 1.0, 7.9 Hz, 1H), 7.31 (dd, J = 0.8, 8.4 Hz, 1H), 7.23-7.19 (m, 1H), 7.14-7.11 (m, 1H), 7.10 (d, J = 3.2 Hz, 1H), 4.68 (s, 2H), 3.99 (s, 1H), 3.34 (s, 6H), ¹³C NMR (100 MHz, CDCl₃): δ 185.3 (e), 136.4 (e), 128.6 (e), 128.5 (e), 121.8 (o), 120.9 (o), 119.6 (o), 109.4 (o), 102.0 (o), 69.1 (o), 53.7 (o), 41.9 (o, 2C); IR (neat/cm⁻¹): 3122 (w), 3076 (w), 3030 (w), 3011 (w), 2988 (w), 2909 (w), 1723 (w), 1608 (w), 1557 (s), 1513 (w), 1483 (w), 1463 (m), 1428 (m), 1385 (s), 1363 (m), 1335 (s), 1319 (s), 1257 (m), 1177 (s), 1152 (s), 1119 (w), 1088 (w), 1041 (s), 1012 (w), 997 (w), 974 (w), 956 (w), 946 (w), 926 (m), 861 (s), 767 (s), 749 (s), 725 (s), 692 (m); HRMS (ESI): m/z calcd for C₁₃H₁₅NO₂S+H+. [M+H]⁺ 250.0896; found: 250.0899.

![Chemical Structure](image)

Compound 384. Following a reported procedure²⁷, indole (3 g, 25.61 mmol, 1.0 equiv) was dissolved in THF (43 mL, 0.6 M) and cooled to 0 °C. NaH (60% in oil, 2.4 g, 102.4 mmol, 2.5 equiv) was added in small portions, and the reaction was allowed to stir at 0 °C for 30 mins, before benzenesulfonyl chloride (3.9 mL, 30.73 mmol, 1.2 equiv) was added. The reaction was allowed to stir at room temperature for 16 h, then quenched with water and extracted with EtOAc (x3). The combined organic layers were washed with water (x5), then once with brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified by FCC (petroleum ether/EtOAc = 95:5) to afford compound 384 as colourless solid, 6.58 g, 25.57 mmol, quant. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.00 (d, J = 8.4 Hz, 1H), 7.90-7.86 (m, 2H), 7.57 (d, J = 3.7 Hz, 1H), 7.55-7.51 (m,
2H), 7.46-7.41 (m, 2H), 7.34-7.29 (m, 1H), 7.25-7.21 (m, 1H), 6.647 (dd, J = 0.8, 3.6 Hz, 1H); in agreement with previously reported data.\(^{27}\)

**Compound d-384.** Following a reported procedure,\(^{27}\) compound 384 (3 g, 11.66 mmol, 1.0 equiv) was dissolved in dry THF (19 mL, 0.6 M) under N₂, and the solution was cooled to -78 °C using a dry ice/acetone bath. nBuLi (2.5 M in hexanes, 12 mL, 29.15 mmol, 2.5 equiv) was added dropwise. Once the addition was complete, the reaction was allowed to stir at rt for 1 h, during which time it turned dark brown. The reaction was then cooled back to -78 °C, and D₂O (3 mL, 1 mL/1 g of 384) was added dropwise. Once the addition was complete, the reaction was allowed to warm up to rt over 1 h, during which time the reaction turned pale yellow and a white precipitate could be seen. The reaction was quenched with solid K₂CO₃ and dry Et₂O (117 mL, 0.1 M with respect to 384) was added. The suspension was stirred for 30 mins and the solid was filtered through cotton wool. The solid was washed with Et₂O and the filtrate was concentrated *in vacuo*. The residue was purified by FCC (petroleum ether/EtOAc = 95:5) to afford compound d-384 as an off-white solid (2.11 g, 8.17 mmol, 70%). \(^{1}H\) NMR (400 MHz, CDCl₃): δ ppm 8.00 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.56-7.50 (m, 2H), 7.47-7.41 (m, 2H), 7.35-7.29 (m, 1H), 7.25-7.20 (m, 1H), 6.66 (2, 1H); in agreement with previously reported data.\(^{27}\)

**Compound d-382.** Following a reported procedure, in a 2-neck RB flask under N₂, compound d-384 (2.1 g, 8.17 mmol, 1.0 equiv) was dissolved in MeOH (11 mL, 0.77 M), and a 2 M aqueous NaOH solution (14 mL, 0.6 M) was added. The reaction was heated at reflux for 16 h, then the MeOH was removed *in vacuo*. The residue was extracted with DCM (3 x 20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford compound ### as a white solid which was used in the next step without further purification (804 mg, 6.80 mmol, 84%). \(^{1}H\) NMR (400 MHz, CDCl₃): δ ppm 8.13 (br s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.57 (s, 1H).); in agreement with previously reported data.\(^{27}\)
**Compound d-383.** Synthesised according to representative procedure H, from compound **d-382** (804 mg, 6.80 mmol) to afford compound **d-383** as a colourless oil that darkened on prolonged exposure to air (641 mg, 3.37 mmol, 50%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (dt, $J = 1.0, 7.9$ Hz, 1H), 7.26-7.21 (m, 2H), 7.16-7.12 (m, 1H), 6.57 (s, 1H), 4.87 (s, 2H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.1 (e), 136.5 (e), 128.6* (e), 122.1 (o), 121.2 (o), 119.9 (o), 108.9 (o), 102.4 (o), 52.5 (o), 47.7 (e) (the triplet for the $^{13}$C nucleus in the deuterated position overlaps with the peak marked by an asterisk and is not visible); IR (neat): 3051 (w), 2952 (w), 1739 (s), 1613 (w), 1496 (w), 1461 (s), 1437 (m), 1421 (m), 1392 (w), 1356 (m), 1329 (m), 1306 (w), 1275 (m), 1211 (s), 1173 (s), 1113 (w), 1063 (w), 1011 (w), 954 (w), 928 (w), 901 (w), 844 (w), 798 (w), 740 (s), 697 (w), 659 (m); HRMS (CI (CH$_4$)): $m/z$ calcd for C$_{11}$H$_{10}$DNO$_2$+H$^+$ [M+H]$^+$ 191.0295; found 191.0931.

**Compound d-379.** Synthesised according to representative procedure C, from compound **d-383** (641 mg, 3.37 mmol) to afford compound **d-379** as an off-white powder that was used without further purification (559 mg, 3.17 mmol, 94%). M.p. = 130-132 °C; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 12.93 (br s, 1H), 7.54 (dt, $J = 1.0, 7.9$ Hz, 1H), 7.37 (dq, $J = 1.0, 8.4$ Hz, 1H), 7.14-7.09 (m, 1H), 7.05-7.00 (m, 1H), 6.43 (d, $J = 0.9$ Hz, 1H), 5.00 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 170.5 (e), 136.3 (e), 128.1* (e), 121.1 (o), 120.3 (o), 119.1 (o), 109.7 (o), 100.8 (o), 47.0 (e) (the triplet for the $^{13}$C nucleus in the deuterated position overlaps with the peak marked by an asterisk and is not visible); IR (neat): 3050 (w), 2966 (w), 2932 (w), 2647 (w), 2551 (w), 2331 (w), 1932 (w), 1894 (w), 1709 (vs), 1615 (w), 1512 (w), 1494 (w), 1486 (w), 1464 (s), 1431 (m), 1402 (m), 1393 (m), 1363 (w), 1332 (m), 1305 (w), 1275 (w), 1230 (s), 1194 (s), 1170 (s), 1113 (w), 1067 (w), 1050 (w), 1010 (w), 900 (m), 851 (m), 844 (m), 800 (s), 773 (w), 758 (w); HRMS (CI (CH$_4$)): $m/z$ calcd for C$_{10}$H$_8$DNO$_2$+H$^+$ [M+H]$^+$ 177.0769; found 177.0777.

**Compound d-380.** Synthesised according to representative procedure D, from compound **d-379** (534 mg, 3.03 mmol) to afford compound **d-380** as a bright yellow amorphous solid (552 mg, 1.86 mmol, 61%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.25 (d,
J = 9.3 Hz, 2H), 7.68 (dt, J = 1.0, 7.9 Hz, 1H), 7.34 (dd, J = 0.8, 8.3 Hz, 1H), 7.31-7.26 (m, 3H), 7.21-7.16 (m, 1H), 6.62 (d, J = 0.8 Hz, 1H), 5.15 (s, 2H); 13C NMR (100 MHz, CDCl3): δ 166.3 (e), 154.7 (e), 145.6 (e), 136.4 (e), 128.8* (e), 126.4 (o), 125.3 (o, 2C), 122.5 (o), 122.1 (o, 2C), 121.4 (o), 120.3 (o), 115.8 (o), 108.7 (o), 103.1 (o), 47.9 (e) (the triplet for the 13C nucleus in the deuterated position overlaps with the peak marked by an asterisk and is not visible); IR (neat): 3111 (w), 3078 (w), 2931 (w), 2856 (w), 2115 (w), 1786 (m), 1667 (m), 1615 (w), 1589 (m), 1519 (s), 1487 (m), 1461 (s), 1417 (w), 1392 (w), 1341 (s), 1332 (s), 1290 (s), 1245 (m), 1204 (s), 1161 (m), 1130 (s), 1105 (s), 1012 (m), 961 (w), 953 (w), 920 (m), 864 (m), 848 (s), 816 (m), 798 (m), 764 (w), 755 (m), 737 (s), 710 (s), 677 (w), 661 (w); HRMS (ESI): m/z calcd for C16H12DN2O4 [M+H]+: 298.0933; found 298.0929.

**Compound d-381.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (98:2 DCM:MeOH) followed by trituration in Et2O, from compound d-380 (552 mg, 1.86 mmol) to afford compound d-381 as cream flakes (288 mg, 1.15 mmol, 62%). m.p. = 96-100 °C; 1H NMR (500 MHz, CDCl3): δ 7.63 (dt, J = 0.9, 7.9 Hz, 1H), 7.31 (dd, J = 0.9, 8.3 Hz, 1H), 7.23-7.18 (m, 1H), 7.14-7.09 (m, 1H), 4.68 (s, 2H), 3.99 (s, 1H), 3.33 (s, 6H); 13C NMR (100 MHz, CDCl3): δ 185.3 (e), 136.3 (e), 128.5* (e), 121.8 (o), 120.9 (o), 119.6 (o), 109.4 (o), 101.8 (o), 69.2 (o), 53.4 (e), 41.9 (o, 2C) (the triplet for the 13C nucleus in the deuterated position overlaps with the peak marked by an asterisk and is not visible); IR (neat): 3417 (w), 3115 (w), 3076 (w), 3029 (w), 3011 (w), 2988 (w), 2909 (w), 2324 (w), 1937 (w), 1902 (w), 1769 (w), 1731 (w), 1607 (w), 1557 (s), 1460 (s), 1427 (m), 1384 (s), 1356 (m), 1330 (m), 1315 (m), 1250 (w), 1171 (s), 1149 (s), 1041 (s), 1011 (m), 997 (m), 974 (w), 946 (w), 926 (m), 896 (m), 863 (m), 843 (s), 808 (s), 750 (s), 742 (s), 692 (w), 661 (m); HRMS (ESI): m/z calcd for C13H14DN2O2+H+ [M+H]+ 251.0959; found 251.0963.
**Compound 395.** Following a reported procedure, to a flame dried 2-neck RB flask under N₂ were added successively [RuCl₂(p-cymene)]₂ (0.39 g, 0.64 mmol, 5 mol%), MesCO₂H (0.63 g, 3.86 mmol, 30 mol%), triphenylphosphine (0.66 g, 2.58 mmol, 20 mol%), K₂CO₃ (3.56 g, 25.78 mmol, 2.0 equiv), 68 (1.8 mL, 12.89 mmol, 1.0 equiv), dry 1,4-dioxane (51 mL, 0.25 M) and methyl 2-bromopropionate (4.3 mL, 38.66 mmol, 3.0 equiv). The reaction was stirred at 120 °C for 18 h, then cooled to room temperature and concentrated in vacuo. The crude residue was purified by FCC (petroleum ether/ethyl acetate = 4:1) to afford compound 395 as a pale yellow oil. (2.10 g, 8.70 mmol, 68%). 

**Compound 392.** Compound 395 (2.10 g, 8.70 mmol, 1.0 equiv) was dissolved in EtOH/H₂O (2.5:1, 18 mL, 0.48 M), and solid KOH (0.6 g, 10.47 mmol, 1.2 equiv) was added. The reaction was stirred at 50 °C for 2 h, then the EtOH was removed in vacuo. The aqueous layer was washed three times with Et₂O, then neutralised with 2M HCl, and concentrated to dryness to afford compound 392 as a beige solid which was characterised by H NMR (500 MHz, CDCl₃): δ 8.71 (dq, J = 4.9, 1.0 Hz, 1H), 7.93 (t, J = 1.8 Hz, 1H), 7.86 (dt, J = 7.7, 1.3 Hz, 1H), 7.79-7.69 (m, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.37 (dt, J = 7.7, 1.4 Hz, 1H), 7.27-7.22 (m, 1H), 3.83 (q, J = 7.3 Hz, 1H), 3.67 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H). This compound was synthesised for preliminary results only, so was not fully characterised.
NMR only. $^1$H NMR (500 MHz, DMSO-d6): $\delta$ 8.64 (dt, $J$ = 4.9, 1.4 Hz, 1H), 7.97 (t, $J$ = 1.7 Hz, 1H), 7.89-7.82 (m, 2H), 7.77 (dt, $J$ = 7.3, 1.7 Hz, 1H), 7.34-7.27 (m, 3H), 3.30 (q, $J$ = 7.2 Hz, 1H), 1.28 (d, $J$ = 7.0 Hz, 3H).

**Compound 393.** Compound 392 (1.03 g, 4.53 mmol, 1.0 equiv) and 4-nitrophenol 208 (0.82 g, 5.89 mmol, 1.3 equiv) were dissolved in THF (0.18 M) and triethylamine (0.7 mL, 4.98 mmol, 1.1 equiv) and DCC (1.21 g, 5.89 mmol, 1.3 equiv) were added. The reaction was stirred at room temperature for 18 h, then filtered through Celite. The Celite pad was washed with DCM, and the filtrate was concentrated in vacuo. The crude residue was purified by FCC (petroleum ether/ethyl acetate = 4:1) to afford compound 393 as an amorphous off-white solid (1.38 g, 3.96 mmol, 87%). This compound contained some DCC, and was characterised by $^1$H NMR only before being used in the next step. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.70 (d, $J$ = 4.9 Hz, 1H), 8.22 (d, $J$ = 9.1 Hz, 2H), 8.02 (t, $J$ = 1.7 Hz, 1H), 7.88 (dt, $J$ = 7.7, 1.2 Hz, 1H), 7.82 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.64 (d, $J$ = 8.0 Hz, 1H), 7.51 (t, $J$ = 7.6 Hz, 1H), 7.45 (dt, $J$ = 7.8, 1.5 Hz, 1H), 7.33-7.28 (m, 1H), 7.19 (d, $J$ = 9.1 Hz, 2H), 4.08 (q, $J$ = 7.3 Hz, 1H), 1.67 (d, $J$ = 7.1 Hz, 3H).

**Compound 394.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (98:2 DCM:MeOH), from compound 393 (1.08 g, 3.57 mmol) to afford compound 394 as an off-white solid (256 mg, 0.86 mmol, 24%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (d, $J$ = 4.9 Hz, 1H), 7.92 (s, 1H), 7.83 (dt, $J$ = 7.4, 1.7 Hz, 1H), 7.77-7.72 (m, 2H), 7.43-7.36 (m, 2H), 7.24-7.20 (m, 1H), 4.32 (s, 1H), 3.64 (q, $J$ = 7.2 Hz, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 1.51 (d, $J$ = 7.2 Hz, 3H). This compound was synthesised for preliminary results only, and so was not fully characterised.
Compound 408. NaO\textsubscript{t}Bu (9.14 g, 95.11 mmol, 2.0 equiv) was suspended in dry DMF (119 mL), and a solution of 407 (5 mL, 47.56 mmol, 1.0 equiv) and TOSMIC (11.3 g, 57.07 mmol, 1.2 equiv) in dry DMF (119 mL) was added dropwise. The reaction was stirred at room temperature for 3 h, then diluted with ethyl acetate and washed three times with brine, then three times with water. The organic layer was dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The crude residue was purified by FCC (petroleum ether/EtOAc = 3:2) to afford compound 408 as an amorphous white solid (6.51 g, 45.15 mmol, 95%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.60 (br s, 1H), 8.53 (dq, J = 4.9, 1.0 Hz, 1H), 7.61 (td, J = 7.8, 1.9 Hz, 1H), 7.49 (dt, J = 8.1, 1.1 Hz, 1H), 7.03 (ddd, J = 7.4, 5.0, 1.1 Hz 1H), 6.84 (q, J = 2.5 Hz, 1H), 6.72 (q, J = 2.7 Hz, 1H), in agreement with previously reported data\textsuperscript{29}.

Compound 409. Compound 408 (6.4 g, 44.39 mmol, 1.0 equiv) was added to a solution of KOH (5.0 g, 88.78 mmol, 2.0 equiv) in dry DMF (114 mL, 0.39 M), and the reaction was stirred at rt for 30 mins. Methyl bromoacetate (8.4 mL, 88.78 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 2 h. The reaction was diluted with ethyl acetate and washed five times with water, then the organic layer was dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The residue was purified by FCC (DCM/MeOH = 96:4) to afford compound 409 as a colourless oil (1.24 g, 5.71 mmol, 13%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.51 (dq, J = 4.9, 0.8 Hz, 1H), 7.60 (td, J = 7.7,
1.9 Hz, 1H), 7.45 (dt, J = 8.0, 1.1 Hz, 1H), 7.31 (t, J = 2.1 Hz, 1H), 7.05-7.00 (m, 1H), 6.70 (t, J = 2.6 Hz, 1H), 6.69-6.67 (m, 1H), 4.67 (s, 2H), 3.77 (s, 3H). This compound was synthesised for preliminary results only, so was not fully characterised.

**Compound 411.** Compound 409 (1.02 g, 4.74 mmol, 1.0 equiv) was dissolved in EtOH (7 mL, 0.7 M) and a 2M aqueous solution of KOH (2.5 mL) was added. The reaction was stirred at 50 °C for 2 h, then the EtOH was removed in vacuo. The remaining aqueous solution was washed three times with Et₂O, then neutralised with 2M HCl and concentrated to dryness. The solid residue was dried in a vacuum desiccator overnight to afford an off-white powder (1.11 g, 5.49 mmol). This was immediately suspended in THF (30 mL, 0.18 M) and Et₃N (0.8 mL, 6.04 mmol, 1.1 equiv) was added, followed by 211 (0.99 g, 7.14 mmol, 1.3 equiv) and DCC (1.47 g, 7.14 mmol, 1.3 equiv). The reaction was stirred at room temperature overnight, before being filtered through Celite, and the pad was washed with DCM/MeOH (1:1). The filtrate was concentrated in vacuo and purified by FCC (DCM/MeOH = 98:2) to afford compound 411 as a pale yellow amorphous solid. This compound was contaminated with 211, and so was characterised by ¹H NMR only before being used in the next step. ¹H NMR (500 MHz, CDCl₃): δ 8.43 (dq, J = 5.2, 0.9 Hz, 1H), 8.19 (d, J = 9.2 Hz, 2H), 7.72-7.68 (m, 1H), 7.53 (dt, J = 8.0, 1.0 Hz, 1H), 7.27 (t, J = 2.0 Hz, 1H), 7.14-7.09 (m 3H), 6.69-6.66 (m, 2H), 4.78 (s, 2H).

**Compound 412.** Synthesised according to representative procedure E, except that crude compound was purified by FCC (DCM/MeOH = 95:5) followed by recrystallisation from EtOAc of the solid collected from the product containing fractions, from compound 411 (2.69 g, 8.32 mmol) to afford compound 412 (152 mg, 0.56 mmol, 7%). ¹H NMR (500 MHz, CDCl₃): δ 8.54 (dq, J = 4.9, 0.9 Hz, 1H), 7.64 (td, J = 7.9, 1.9 Hz, 1H), 7.47 (dt, J = 8.1, 1.2 Hz, 1H), 7.28 (t, J = 2.0 Hz, 1H), 7.07 (dd, J = 7.5, 4.9, 1.1 Hz, 1H), 6.75 (dd, J = 2.8, 1.8 Hz, 1H), 6.68 (t, J = 2.6 Hz, 1H), 4.59 (s, 2H), 4.26 (s, 1H), 3.36 (s, 6H). This compound was synthesised for preliminary results only, so was not fully characterised.
3.4 HFIP Mediated Electrocyclisation of Sulfoxonium Ylides

Representative procedure I: In a flame dried Schlenck tube equipped with a J-Young key and a Teflon stirrer bar under N₂, compound 85 (189 mg, 0.66 mmol, 1.0 equiv) was dissolved in HFIP (3.3 mL, 0.2 M), and K₂CO₃ was added. The tube was sealed and placed in a pre-heated oil bath at 60 °C for 18 h. The reaction was cooled to rt and concentrated in vacuo. The residue was purified by FCC (hexane/EtOAc = 98:2) to afford compound 87 as sticky purple amorphous solid (125 mg, 0.60 mmol, 91%).

**Compound 87.** ¹H NMR (500 MHz, CDCl₃): δ ppm 7.40 (d, J = 7.7 Hz, 1H); 7.37-7.26 (m, 5H); 7.20 (d, J = 7.7 Hz, 1H); 7.12 (d, J = 7.0 Hz, 2H); 4.68 (s, 1H); 3.68 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 213.6 (e), 141.2 (e), 138.0 (e), 137.1 (e), 128.6 (o, 2C), 128.3 (o, 2C), 127.9 (o), 127.7 (o), 127.2 (o), 125.9 (o), 124.7 (o), 59.6 (o), 42.8 (o), in agreement with previously reported data; HRMS (CI (CH₄)): m/z calcd for C₁₅H₁₂O [M+H⁺] 209.0961; found 209.0968.

**Compound 229.** Synthesised according to representative procedure I at 60 °C, from compound 213 (148 mg, 0.66 mmol), to afford compound 229 as a yellow oil (44 mg, 0.30 mmol, 46%). ¹H NMR (500 MHz, CDCl₃): δ 7.33-7.26 (m, 4H), 3.62 (d, J = 22.4 Hz, 1H), 3.51 (d, J = 22.6 Hz, 1H), 3.49 (q, J = 7.6 Hz, 1H), 1.42 (d, J = 7.5 Hz, 3H), in agreement with previously reported data.

**Compound 230.** Synthesised according to representative procedure I at 60 °C, from compound 214 (185 mg, 0.66 mmol) to afford compound 230 as a sticky pale yellow solid (114 mg, 0.56 mmol, 79%). ¹H NMR (500 MHz, CDCl₃): δ 7.18 (d, J = 7.5 Hz, 1H), 7.09-7.06 (m, 2H), 3.58 (d, J = 22.5 Hz, 1H), 3.51-3.43 (m, 2H), 2.47 (d, J = 7.2 Hz, 2H), 1.86 (sept, J = 6.8 Hz, 1H), 1.40
(d, J = 7.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 218.3 (e), 141.0 (e), 140.6 (e), 136.1 (e), 128.4 (o), 125.3 (o), 123.7 (o), 47.5 (o), 45.4 (e), 43.0 (e), 30.3 (o), 22.3 (o, 2C), 15.5 (o); IR (neat): $\tilde{\nu}$ = 3006 (w), 2970 (w), 2958 (w), 2932 (w), 2909 (w), 2867 (w), 2849 (w), 2741 (w), 1701 (vs), 1671 (vs), 1611 (m), 1567 (m), 1497 (w), 1466 (w), 1428 (m), 1397 (m), 1384 (w), 1350 (s), 1303 (w), 1285 (w), 1257 (s), 1244 (s), 1221 (s), 1192 (w), 1164 (w), 1149 (w), 1116 (w), 1091 (w), 1059 (w), 1018 (w), 982 (w), 957 (w), 930 (m), 889 (m), 843 (m), 788 (m), 731 (w), 711 (w), 685 (m) cm$^{-1}$; HRMS (CI(CH$_4$)): m/z calcd for C$_{14}$H$_{18}$O+H$^+$ [M+H]$^+$ 203.1436; found 203.1437

Compound 231. Synthesised according to representative procedure I at 60 °C, from compound 215 (168 mg, 0.66 mmol) to afford compound 231 as a pale yellow oily solid (75 mg, 0.42 mmol, 65%) alongside compound 232 as a colourless liquid (57 mg, 0.16 mmol, 25%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.20-7.18 (m, 1H), 6.86-6.83 (m, 2H), 3.82 (s, 3H), 3.58 (d, J = 22.3 Hz, 1H), 3.49 (d, J = 23.0 Hz, 1H), 3.43 (q, J = 7.5 Hz, 1H), 1.38 (d, J = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 218.0 (e), 159.1 (e), 137.5 (e), 135.4 (e), 125.0 (o), 113.7 (o), 110.0 (o), 55.4 (o), 47.1 (o), 43.2 (e), 15.8 (o); IR (neat): $\tilde{\nu}$ = 2982 (w), 2968 (w), 2930 (w), 2893 (w), 2871 (w), 2837 (w), 2039 (w), 1899 (w), 1736 (s), 1698 (w), 1690 (m), 1583 (w), 1491 (s), 1467 (m), 1446 (m), 1430 (w), 1389 (w), 1373 (w), 1300 (m), 1271 (s), 1226 (s), 1184 (m), 1167 (w), 1146 (s), 1087 (s), 1046 (s), 1021 (s), 989 (w), 948 (w), 927 (w), 895 (w), 831 (s), 788 (w), 762 (m), 738 (w); 697 (w), 666 (w) cm$^{-1}$; HRMS (CI(CH$_4$)): m/z calcd for C$_{11}$H$_{12}$O$_2$+H$^+$ [M+H]$^+$: 177.0916; found: 177.0912.

Compound 232. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ ppm 7.28 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.34 (hept, J = 5.8 Hz, 1H), 3.82 (s, 3H), 2.18 (s, 3H), 1.72 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 206.8, 159.9, 130.2, 127.5 (2C), 114.2 (2C), 88.8, 70.5 (hept, J = 32.1 Hz), 55.3, 25.2, 21.0 (the two quartets for the CF$_3$ groups were not visible); $^{19}$F NMR (400 MHz, CDCl$_3$): $\delta$ -72.6 (q, J = 9.6 Hz, 3F), -72.8 (q, J = 9.1 Hz, 3F); IR (neat): $\tilde{\nu}$ = 2941 (w), 1722 (s), 1610 (m), 1583 (w), 1513 (s), 1465 (w), 1357 (s), 1286 (s), 1256 (s), 1219 (s), 1193 (s), 1101 (s), 1033 (s), 901 (s), 832 (m), 784 (w), 742 (w), 687 (w)
cm⁻¹; HRMS (ESI): m/z calcd for C₁₄H₁₄F₆O₃⁺Na⁺ [M+Na]⁺ 367.0739; found: 367.0741.

**Compound 233.** To a flame dried microwave vial under N₂ was added compound 216 (171 mg, 0.66 mmol, 1.0 equiv), followed by HFIP (3.3 mL, 0.2 M). K₂CO₃ (91 mg, 0.66 mmol, 1.0 equiv) was added, the vial was sealed, and the reaction was heated at 80 °C in the microwave for 2 h. The reaction was cooled to rt and concentrated in vacuo. The residue was purified by FCC (9:1 petroleum ether:EtOAc) to afford compound 233 as a pale pink amorphous solid (102 mg, 0.56 mmol, 86%). ¹H NMR (500 MHz, CDCl₃): 7.30 (br s, 1H), 7.29-7.27 (m, 1H), 7.22-7.20 (m, 1H), 3.60 (d, J= 22.7 Hz, 1H), 3.50 (d, J= 22.8 Hz, 1H), 3.44 (q, J= 7.4 Hz, 1H), 1.40 (d, J= 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 216.5 (e), 141.7 (e), 138.0 (e), 133.0 (e), 127.8 (o), 125.4 (o), 125.0 (o), 47.4 (o), 42.8 (e), 15.4 (o); IR (neat): ν = 2980 (w), 2934 (w), 2908 (w), 2645 (w), 1742 (s), 1703 (m), 1669 (m), 1600 (w), 1561 (w), 1475 (s), 1450 (m), 1420 (m), 1397 (w), 1384 (w), 1366 (w), 1280 (w), 1245 (w), 1186 (s), 1155 (w), 1111 (w), 1074 (w), 1060 (w), 1038 (w), 983 (w), 960 (w), 936 (w), 903 (m), 882 (m), 850 (w), 833 (s), 786 (w), 759 (w), 718 (w), 661 (w), 656 (w) cm⁻¹; HRMS (CI(CH₄)): m/z calcd for C₁₀H₉³⁵ClO⁺H⁺ [M+H⁺]: 181.0432; found 181.0433.

**Compound 234.** Synthesised according to representative procedure I at 90 °C, from compound 217 (200 mg, 0.66 mmol) to afford compound 234 as a yellow powder (121 mg, 82%, 0.54 mmol). m.p. = 100-103 °C; ¹H NMR (400 MHz, CDCl₃): 7.46-7.42 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 3.60 (d, J = 22.6 Hz, 1H), 3.50 (d, J = 22.9 Hz, 1H), 3.42 (q, J = 7.4 Hz, 1H), 1.40 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 216.4 (e), 142.3 (e), 138.4 (e), 130.7 (o), 128.0 (o), 125.8 (o), 121.0 (e), 47.4 (o), 42.7 (e), 15.4 (o); IR (neat): ν = 3011 (w), 2921 (w), 2744 (w), 2639 (w), 2558 (w), 1747 (w), 1701 (s), 1668 (s), 1588 (m), 1555 (m), 1473 (w), 1423 (m), 1412 (m), 1393 (w), 1358 (w), 1341 (m), 1287 (m), 1241 (s), 1099 (m), 1059 (w), 1014 (w), 959 (m), 931 (m), 889 (m), 860 (m), 824 (s), 759 (m), 713 (w), 682 (w) cm⁻¹; HRMS (CI (CH₄)): m/z calcd for C₁₀H₉⁷⁹BrO⁺H⁺ [M+H⁺]: 226.0930; found 226.0933.
**Compound 235.** Synthesised according to representative procedure I at 90 °C, from compound 218 (193 mg, 0.66 mmol) to afford compound 235 as a colourless liquid (89 mg, 0.42 mmol, 63%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.61–7.55 (m, 2H), 7.40 (d, $J = 7.9$ Hz, 1H), 3.66 (d, $J = 22.6$ Hz, 1H), 3.57 (d, $J = 22.5$ Hz, 1H), 3.53 (q, $J = 7.3$ Hz, 1H), 1.44 (d, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 216.0 (e), 147.3 (e), 137.1 (e), 129.9 (e, $J = 32.0$ Hz), 124.60 (o, $J = 3.7$ Hz), 124.58 (o), 124.1 (e, $J = 272$ Hz), 121.8 (o, $J = 3.9$ Hz), 47.8 (o), 42.7 (e), 15.2 (o); $^{19}$F NMR (376 MHz, CDCl$_3$): δ -62.4 (s, 3F); IR (neat): $\tilde{\nu}$ = 2976 (w), 1753 (s), 1627 (w), 1437 (m), 1372 (w), 1334 (s), 1284 (s), 1243 (m), 1184 (s), 1153 (s), 1121 (s), 1068 (s), 913 (w), 894 (m), 834 (m), 750 (w), 718 (w), 690 (w) cm$^{-1}$; HRMS (Cl(CH$_4$)): m/z calcd for C$_{12}$H$_{14}$O$_3$+H$: 207.1016$ [M+H]$^+$; found 207.1012

**Compound 237.** Synthesised according to representative procedure I, from compound 227 (159 mg, 0.66 mmol) to afford compound 237 as a colourless liquid (112 mg, 0.34 mmol, 51%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.28 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 5.09 (s, 1H), 4.14 (sept, $J = 5.8$ Hz, 1H), 3.83 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 203.1 (e), 160.9 (e), 129.6 (o, 2C), 124.5 (e), 121.7 (e, q, $J = 284.5$ Hz), 121.2 (e, q, $J = 281.6$ Hz), 114.7 (o, 2C), 88.4 (e), 72.9 (o, sept, $J = 32.7$ Hz), 55.3 (o), 25.8 (o); IR (neat): $\tilde{\nu}$ = 2938 (w), 1730 (s), 1610 (s), 1585 (w), 1513 (s), 1361 (s), 1466 (w), 1361 (s), 1286 (s), 1260 (s), 1219 (s), 1192 (s), 1125 (s), 1102 (s), 1031 (m), 905 (w), 879 (w), 833 (w), 741 (w), 687 (m) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{13}$H$_{12}$F$_6$O$_3$+Na$: 353.0583$ [M+Na]$^+$; found 353.0584.

**Compound 239.** Synthesised according to representative procedure I, from compound 228 (184 mg, 0.66 mmol) to afford compound 239 as a colourless liquid (168.7 mg, 0.46 mmol, 70%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 5.75 (hept, $J = 6.1$ Hz, 1H), 3.08 (t, $J = 7.6$ Hz, 2H), 2.88 (t, $J = 7.7$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 169.2 (e), 143.1 (e), 129.2 (e, q, $J = 32.5$ Hz), 128.6 (o, 2C), 126.6 (o, q, $J = 3.7$ Hz, 2C), 124.2 (e, q, $J = 271.5$ Hz), 120.4 (e, q, $J = 283.6$ Hz, 2C), 66.6 (o, hept, $J = 33.8$ Hz), 34.4 (e), 30.1 (e); $^{19}$F NMR (376 MHz,
CDCl$_3$: $\delta$ -62.56 (s, 3F), -73.13 (s, 6F); IR (neat): $\tilde{\nu}$ = 2971 (w), 1781 (s), 1621 (w), 1420 (w), 1386 (m), 1357 (m), 1325 (s), 1287 (m), 1268 (m), 1228 (s), 1200 (s), 1165 (s), 1106 (vs), 1067 (vs), 1019 (m), 941 (w), 906 (m), 877 (w), 839 (m) cm$^{-1}$; HRMS (ESI): m/z calcd for C$_{13}$H$_9$F$_9$O$_2$+Na$^+$: 391.0357 [M+Na$^+$]; found 391.0356.

**Compound 114.** Synthesised according to representative procedure I at 60 °C, from compound 220 (165 mg, 0.66 mmol) to afford compound 114 as a yellow oil (102 mg, 0.59 mmol, 88%). $^1$H NMR (500 MHz, CDCl$_3$): 7.35-7.33 (m, 1H), 7.32-7.27 (m, 3H), 5.76-5.68 (m, 1H), 5.07 (dq, J = 1.7, 16.9, 1.5 Hz, 1H), 5.02 (d, J = 10.1 Hz, 1H), 3.59-3.53 (m, 2H), 3.46 (d, J = 22.8 Hz, 1H), 2.74-2.69 (m, 1H), 2.63-2.57 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 217.0 (e), 141.5 (e), 136.8 (e), 134.3 (o), 127.4 (o), 127.3 (o), 124.79 (o), 124.78 (o), 117.7 (o), 52.6 (o), 43.3 (e), 35.6 (e), in agreement with previously reported data.$^{32}$

**Compound 264.** Synthesised according to representative procedure I at 90 °C, from compound 221 (198 mg, 0.66 mmol) to afford compound 264 as a yellow oil (94 mg, 0.42 mmol, 67%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.25-7.17 (m, 6H); 7.08-7.06 (m, 2H); 6.95 (d, J = 7.2 Hz, 1H); 3.79-3.76 (m, 1H); 3.48 (d, J = 22.5 Hz, 1H); 3.34 (dd, J = 13.7, 4.7 Hz, 1H); 3.26 (d, J = 22.8 Hz, 1H); 2.99 (dd, J = 13.7, 8.1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 217.1 (e), 141.3 (e), 138.0 (e), 136.9 (e), 129.4 (o, 2C), 128.2 (o, 2C), 127.5 (o), 127.1 (o), 126.4 (o), 125.1 (o), 124.7 (o), 54.4 (o), 43.2 (e), 37.9 (e); IR (neat): $\tilde{\nu}$ = 3070 (w), 3028 (w), 2922 (w), 1744 (s), 1602 (w), 1533 (w), 1495 (m), 1479 (m), 1454 (m), 1391 (m), 1343 (w), 1308 (w), 1280 (w), 1246 (w), 1234 (w), 1188 (w), 1139 (m), 1074 (m), 1042 (w), 1026 (w), 968 (w), 950 (w), 901 (w), 867 (w), 837 (w), 821 (w), 802 (w), 776 (w), 740 (s), 712 (m), 696 (s) cm$^{-1}$; HRMS (CI(CH$_4$)): m/z calcd for C$_{16}$H$_{14}$O+H$^+$: 223.1117 [M+H$^+$]; found 223.1120.

**Compound 265.** Synthesised according to representative procedure I, from compound 222 (200 mg, 0.68 mmol) to afford compound 265 as a colourless liquid (15 mg, 0.07 mmol, 8%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.38-7.20 (m, 4H), 3.46 (s, 2H), 3.31 (d, J = 3.8 Hz, 1H), 2.03-1.90 (m, 2H), 1.75-1.67 (m, 2H), 1.63 (d, J = 10.7 Hz, 2H), 1.57 (d, J = 11.8 Hz, 1H), 1.34-1.15 (m, 4H), 1.15-1.03 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 218.0 (e), 141.3 (e), 137.5
Compounds 266 and 267. Synthesised according to representative procedure I, from compound 223 (50 mg, 0.16 mmol) to afford compounds 266 and 267 as a white amorphous solid. (28 mg, 0.12 mmol, 74%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J$ = 7.2 Hz, minor), 7.35-7.29 (m, 2H, major), 7.28-7.23 (m, 1H, major), 7.19 (d, $J$ = 7.5 Hz, minor), 7.11 (d, $J$ = 7.9 Hz, 3H, major), 6.90-6.84 (m, 1H, major), 4.62 (s, 1H, major), 3.99 (s, minor), 3.85 (s, 3H, major), 3.79 (s, minor), 3.66 (s, minor), 3.64 (s, 2H, major); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.0 (e, major), 159.5 (e, major), 138.49 (e, major), 138.47 (e, major), 133.2 (e, major), 130.9 (o, minor), 129.4 (o, minor), 128.7 (o, 2C, major), 128.8 (o, minor), 128.3 (o, 2C, major), 127.9 (o, minor), 127.8 (o, minor), 127.2 (o, major), 126.9 (o, minor), 126.0 (o, minor), 124.8 (o, minor), 114.3 (o, major), 114.2 (o, minor), 109.8 (o, major), 90.5 (o, major), 86.9 (o, minor), 56.0 (o, major), 33.2 (e, major), 42.8 (e, major); IR (neat): $\bar{\nu}$ = 3057 (w), 3031 (w), 2979 (w), 2946 (w), 2833 (w), 2833 (w), 2833 (w), 1746 (s), 1713 (w), 1653 (w), 1608 (w), 1582 (w), 1490 (s), 1471 (s), 1452 (m), 1429 (w), 1397 (w), 1386 (w), 1351 (w), 1351 (w), 1305 (m), 1288 (m), 1259 (s), 1221 (m), 1206 (w), 1182 (m), 1152 (w), 1134 (s), 1115 (w), 1069 (m), 1027 (s), 1001 (w), 969 (w), 955 (w), 928 (w), 914 (w), 873 (w), 856 (w), 841 (m), 823 (s), 808 (w), 786 (w), 776 (w), 743 (s), 697 (s), 665 (w); HRMS (CI(CH$_4$)): $m$/z calcd for C$_{16}$H$_{14}$O+H$^+$ [M+H]$^+$ 239.1067. Found: 239.1072.

Compound 272. Synthesised according to representative procedure I, from compound 268 (188 mg, 0.66 mmol) to afford compound 272 as a yellow oil (110 mg, 0.53 mmol, 85%). $^1$H NMR (500 MHz, CDCl$_3$): 6.83 (s, 1H), 6.79 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.54 (d, $J$= 22.4 Hz, 1H), 3.46 (d, $J$= 19.2 Hz, 1H), 3.44 (q, $J$= 8.0 Hz, 1H), 1.39 (d, $J$= 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 218.1 (e), 149.0 (e), 148.8 (e), 135.2 (e), 127.15 (o), 127.14 (o), 125.1 (o), 124.6 (o), 59.0 (o), 44.3 (e), 42.7 (o), 29.8 (e), 29.6 (e), 26.6 (e), 26.4 (e), 26.0 (e); IR (neat): $\bar{\nu}$ = 3025 (w), 2922 (w), 2851 (w), 1745 (s), 1478 (m), 1461 (w), 1449 (m), 1393 (w), 1348 (w), 1260 (w), 1185 (m), 1138 (m), 1073 (w), 1055 (w), 1026 (w), 968 (w), 948 (w), 898 (w), 844 (w), 802 (w), 745 (m), 726 (w); HRMS (CI (NH$_3$)): $m$/z calcd for C$_{15}$H$_{18}$O+H$^+$ 232.1696 [M+NH$_4$]$^+$; found 232.1698.
127.9 (e), 107.8 (o), 107.2 (o), 56.1 (o), 56.0 (o), 47.8 (o), 42.8 (e), 15.6 (o); IR (neat): \( \tilde{\nu} = 3139 \) (w), 2977 (w), 2941 (w), 2844 (w), 1723 (s), 1634 (w), 1607 (w), 1594 (w), 1516 (s), 1446 (m), 1420 (w), 1397 (w), 1347 (w), 1332 (w), 1312 (w), 1277 (m), 1248 (m), 1236 (m), 1224 (s), 1189 (m), 1164 (m), 1143 (s), 1067 (w), 1022 (s), 927 (w), 884 (w), 815 (w), 795 (w), 764 (w), 719 (s); HRMS (CI(CH\(_4\))): \( m/z \) calcd for C\(_{12}\)H\(_{14}\)O\(_3\)+H\(^+\): 207.1016; found: 207.1012.

**Compound 273.** Synthesised according to representative procedure I, from compound 269 to afford compound 273 as an off-white powder (137 mg, 0.61 mmol, 91%). m.p. = 82-85 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): 7.72 (d, J=8.2 Hz, 1H), 7.62 (d, J=8.8 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 7.20-7.23 (m, 2H), 3.94 (s, 3H), 3.81 (d, J=4.0 Hz, 2H), 3.64 (q, J=7.5 Hz, 1H), 1.47 (d, J=7.5 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 218.0 (e), 157.5 (e), 138.2 (e), 134.1 (e), 132.5 (e), 127.0 (o), 125.9 (o), 125.2 (o), 122.6 (o), 119.3 (o), 106.9 (o), 48.5 (o), 41.4 (e), 15.9 (o); IR (neat): \( \tilde{\nu} = 3040 \) (w), 3005 (w), 2977 (w), 2959 (w), 2935 (w), 2898 (w), 2860 (w), 2840 (w), 1733 (s), 1625 (m), 1598 (m), 1516 (w), 1448 (w), 1428 (m), 1396 (w), 1362 (m), 1290 (w), 1274 (w), 1262 (m), 1243 (s), 1226 (m), 1194 (m), 1166 (m), 1150 (m), 1135 (m), 1047 (s), 998 (m), 961 (w), 936 (w), 905 (w), 896 (w), 873 (s), 813 (s), 768 (w), 748 (w), 735 (w), 710 (w), 698 (w), 698 (w), 659 (w) cm\(^{-1}\); HRMS (Cl(CH\(_4\))): \( m/z \) calcd for C\(_{15}\)H\(_{13}\)O\(_2\)+H\(^+\) [M+H\(^+\)]\(^2\): 226.1067; found 227.1075

**Compound 274.** Synthesised according to representative procedure I, from compound 270 (230 mg, 0.66 mmol) to afford compound 274 as a cream powder (121 mg, 0.45 mmol, 69%). m.p. = 165-167°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): 8.02 (d, J= 1.8 Hz, 1H), 7.42 (dd, J=2.1, 8.7 Hz, 1H), 7.29 (d, J= 8.7 Hz, 1H), 7.16 (d, J= 8.0 Hz, 1H), 4.06 (d, J= 4.3 Hz, 2H), 3.98 (s, 3H), 3.63 (q, J= 8.1 Hz, 1H), 1.50 (d, J= 7.5 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 217.3 (e), 142.4 (e), 139.3 (e), 137.5 (e), 125.5 (o), 124.6 (e), 123.8 (e), 121.3 (e), 119.9 (o), 119.3 (o), 117.2 (e), 115.3 (o), 109.4 (o), 47.2 (o), 41.5 (e), 30.6 (o), 16.1 (o); IR (neat): \( \tilde{\nu} = 2932 \) (w), 1741 (s), 1622 (w), 1600 (w), 1580 (w), 1490 (w), 1459 (s), 1433 (w), 1410 (w), 1372 (w), 1359 (w), 1342 (w), 1305 (m), 1275 (s), 1229 (w), 1189 (w), 1157 (w), 1128 (w), 1102 (w), 1078 (w), 1055
(w), 1038 (w), 1002 (w), 940 (m), 917 (m), 886 (m), 806 (s), 795 (s), 770 (m), 738 (w), 730 (w), 710 (w), 685 (w), 660 (m) cm<sup>-1</sup>; HRMS (CI (CH<sub>4</sub>)): m/z calcd for C<sub>17</sub>H<sub>15</sub>ClNO [M+H]<sup>+</sup> 283.0764; found 284.0833.

**Compound 275 and 276.** Synthesised according to representative procedure I, except that reaction time was extended to 48 h, from compound **271** (246 mg, 0.66 mmol) to afford compounds **275** and **276** as a slightly pink solid (120 mg, 0.30 mmol, 62%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 8.21 (dd, J= 1.4, 7.9 Hz, 1H), 8.18 (dd, J= 1.4, 7.9 Hz, 1H), 7.62-7.61 (m, 3H), 7.45-7.42 (m, 2H), 7.38 (br s, 1H), 7.35-7.31 (m, 2H), 7.12 (d, J= 7.9 Hz, 1H), 4.41 (s, 2H), 4.37 (s, 2H), 3.77 (d, J= 22.5 Hz, 1H), 3.72 (d, J= 22.8 Hz, 1H), 3.56 (d, J= 22.7 Hz, 1H), 3.51-3.44 (m, 3H); 1.41 (d, J= 3.7 Hz, 3H), 1.39 (d, J= 3.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 216.3 (e), 219.9 (e), 191.9 (e), 190.5 (e), 145.6 (e), 145.3 (e), 140.2 (e), 140.1 (e), 137.0 (e), 136.7 (e), 136.1 (e), 136.0 (e), 135.5 (e), 133.8 (e), 133.7 (e), 133.6 (e), 132.5 (o), 131.5 (o), 131.4 (o), 130.83 (o), 130.81 (o), 130.6 (o), 127.6 (o), 126.9 (o), 126.8 (o), 125.1 (o), 122.7 (o), 51.0 (e), 48.3 (o), 48.0 (e), 47.7 (o), 42.4 (e), 42.0 (e), 15.4 (o), 15.3 (o); IR (neat): cm<sup>-1</sup> 3055 (w), 2971 (w), 2923 (w), 2901 (w), 1746 (s), 1664 (s), 1586 (m), 1473 (w), 1455 (m), 1430 (m), 1395 (m), 1334 (w), 1282 (s), 1236 (m), 1214 (m), 1189 (m), 1155 (m), 1135 (m), 1110 (m), 1072 (m), 1042 (w), 1025 (w), 993 (w), 966 (w), 945 (w), 906 (w), 871 (w), 860 (w), 818 (m), 752 (s), 720 (m), 698 (w), 686 (w), 662 (w); HRMS (CI (CH<sub>4</sub>)): m/z calcd for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub>S+H<sup>+</sup> [M+H]<sup>+</sup> 294.0715; found 295.0750.

**Compound 283.** Synthesised according to representative procedure I, from compound **277** (40 mg, 0.1 mmol) to afford compound **283** as an off white powder (21 mg, 0.06 mmol, 64%). M.p. = 143-145 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.92 (dt, J = 0.8, 8.6 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 3.7 Hz, 1H), 7.26-7.22 (m, 3H), 6.65 (dd, J = 0.9, 3.8 Hz, 1H), 3.66 (q, J = 7.4 Hz, 1H), 3.62-3.59 (m, 2H), 2.35 (s, 3H), 1.49 (d, J = 7.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 217.7 (e), 145.0 (e), 135.5 (e), 135.2 (e), 134.5 (e), 130.9 (e), 129.9 (o, 2C), 127.1 (o), 126.8 (o, 2C), 120.9 (o), 112.8 (o), 106.4 (o), 47.5 (o), 42.8 (e), 21.6 (o), 15.7 (o); IR (neat): ν = 3147 (w), 3113 (w), 3061 (w), 3027 (w),
2981 (w), 2940 (w), 2876 (w), 1745 (s), 1654 (w), 1529 (w), 1489 (w), 1463 (w), 1427 (m), 1363 (s), 1295 (m), 1275 (m), 1241 (w), 1218 (w), 1178 (s), 1155 (s), 1137 (s), 1118 (s), 1085 (m), 1063 (m), 1016 (m), 1016 (m), 987 (m), 907 (w), 895 (m); 874 (w), 841 (w), 815 (m), 799 (m), 776 (m), 735 (m), 703 (m), 679 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₀H₁₇NO₃S+Na⁺ [M+Na⁺] 362.0821; found 362.0821.

**Compound 284.** Synthesised according to representative procedure I, from compound 278 (30 mg, 0.11 mmol) to afford compound 284 as an off-white powder (14 mg, 0.07 mmol, 65%). M.p. = 105-107 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.28-7.24 (m, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 3.1 Hz, 1H), 6.46 (dd, J = 0.8, 3.1 Hz, 1H), 3.82 (s, 3H), 3.76 (q, J = 7.6 Hz, 1H), 3.68-3.64 (m, 2H), 1.56 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 219.6 (e), 136.5 (e), 134.6 (e), 129.4 (o), 126.5 (e), 124.7 (e), 118.0 (o), 108.8 (o), 98.7 (o), 47.8 (o), 43.1 (o), 33.0 (o), 15.5 (o); IR (neat): ν = 3117 (w), 3096 (w), 2976 (w), 2934 (w), 2901 (w), 2869 (w), 2824 (w), 1872 (w), 1735 (s), 1603 (w), 1508 (w), 1482 (m), 1455 (w), 1442 (w), 1421 (s), 1396 (w), 1386 (w), 1365 (w), 1337 (m), 1300 (m), 1287 (m), 1256 (m), 1239 (s), 1218 (m), 1176 (m), 1165 (m), 1146 (m), 1090 (m), 1065 (w), 1020 (w), 999 (w), 978 (w), 940 (w), 923 (w), 897 (w), 872 (w), 799 (s), 778 (s), 760 (w), 734 (s), 690 (w) cm⁻¹; HRMS (EI (CH₄)): m/z calcd for C₁₅H₁₉NO+H⁺ [M+H⁺] 362.1070; found 200.1067.

**Compound 300.** Synthesised according to representative procedure I, from compound 286 (240 mg, 0.66 mmol) to afford compound 300 as an amorphous white solid (152 mg, 0.57 mmol, 85%), alongside compound 301 (28 mg, 0.1 mmol, 15%). ¹H NMR (500 MHz, CDCl₃): δ 7.07 (s, 1H), 6.82 (s, 1H), 6.68 (q, J = 1.4 Hz, 1H), 6.17 (t, J = 3.6 Hz, 1H), 6.15 (dd, J = 3.6, 1.5 Hz, 1H), 4.13 (t, J = 7.2 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89-3.83 (m, 2H), 3.57 (t, J = 2.1 Hz, 2H), 2.89 (tt, J = 7.3, 2.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 148.4 (e), 146.7 (e), 137.6 (e), 134.9 (e), 132.4 (e), 130.3 (e), 129.7 (e), 121.1 (o), 108.7 (o), 108.2 (o), 103.4 (o), 102.0 (o), 56.4 (o), 56.2 (o), 44.1 (e), 35.8 (e), 22.2 (e); IR (neat): ν = 3096 (w), 3056 (w), 3002 (w), 2932 (w), 2905 (w), 2834 (w), 1733 (w), 1703 (w), 1601 (w), 1580 (w), 1535 (w), 1515 (w), 1488 (s), 1463 (s), 1431 (m), 1412 (w), 1382 (s), 1328 (s), 1313 (s), 1266 (s), 1229 (s), 1210 (s), 1189
(s), 1172 (s), 1144 (m), 1123 (s), 1086 (w), 1065 (s), 1047 (m), 1026 (m), 1002 (s), 968 (w), 914 (w), 886 (w), 845 (m), 830 (m), 799 (w), 789 (w), 761 (w), 745 (w), 716 (s), 680 (w), 661 (w) cm⁻¹; HRMS (CI (CH₄)): m/z calcd for C₁₇H₁₇NO₂+H⁺ [M+H]^+ 268.1338; found 268.1441.

**Compound 301.** ¹H NMR (500 MHz, CDCl₃): δ 6.82 (d, J = 8.2 Hz, 1H), 6.72 (dd, J = 2.0, 8.3 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 1.9, 2.6 Hz, 1H), 6.10 (t, J = 3.3 Hz, 1H), 6.06-6.05 (m, 1H), 4.25 (t, J = 5.3 Hz, 2H), 3.90-3.88 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76 (d, J = 15.8 Hz, 1H), 2.46-2.39 (m, 1H), 2.33-2.26 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 206.4 (e), 148.7 (e), 148.2 (e), 130.3 (e), 124.5 (e), 121.3 (o), 120.5 (o), 111.9 (o), 111.0 (o), 108.4 (o), 107.3 (o), 56.7 (o), 55.81 (o), 55.79 (o), 46.3 (e), 42.4 (e), 35.7 (e); IR (neat): ν = 3101 (w), 2998 (w), 2916 (w), 2841 (w), 1706 (m), 1594 (w), 1537 (m), 1518 (w), 1488 (w), 1449 (w), 1384 (m), 1353 (w), 1328 (m), 1301 (m), 1283 (w), 1249 (m), 1236 (m), 1173 (s), 1136 (m), 1090 (m), 1065 (w), 1024 (s), 958 (w), 883 (w), 895 (m), 822 (w), 800 (w), 762 (w), 722 (s), 680 (w) cm⁻¹; HRMS (ESI): m/z calcd for C¹⁷H₁₇NO₃⁺Na⁺ [M+Na]^+ 308.1257; found 308.1262.

**Compound 312.** Synthesised according to representative procedure I, from compound 306 (100 mg, 0.5 mmol) to afford compound 312 as a colourless oil (21 mg, 0.07 mmol, 15%). ¹H NMR (400 MHz, CDCl₃): δ 6.74 (t, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 2H), 5.65 (s, 1H), 3.93 (hept, J = 5.7 Hz, 1H, 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 197.5, 121.6 (q, J = 285.8 Hz), 120.5 (2C), 120.4 (q, J = 282.7), 111.7 (2C), 89.1, 71.1 (hept, J = 33.4 Hz), 25.9; ¹⁹F NMR (400 MHz, CDCl₃): δ -72.2 (q, J = 9.1 Hz, 3F), -73.6 (q, J = 9.2 Hz, 3F); IR (neat): ν = 3110 (w), 2937 (w), 1740 (m), 1568 (w), 1482 (w), 1419 (w), 1364 (m), 1277 (s), 1220 (s), 1193 (s), 1117 (s), 1103 (s), 1088 (s), 1061 (w), 1034 (w), 959 (w), 907 (w), 882 (w), 769 (w), 728 (s), 687 (s) cm⁻¹; HRMS (CI (NH₃)): m/z calcd for C₁₀H₉F₆NO₂+H⁺ [M+H]^+ 290.0616; found 290.0620.
**Compound 313.** Synthesised according to representative procedure I, from compound 307 (140 mg, 0.66 mmol) to afford compound 313 as a colourless oil (84 mg, 0.28 mmol, 42%). $^1$H NMR (500 MHz, CDCl$_3$): δ 6.75 (t, J = 2.2 Hz, 2H), 6.30 (t, J = 2.2 Hz, 2H), 3.59 (sept, J = 5.9 Hz, 1H), 2.40 (s, 3H), 1.93 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 202.3 (e), 129.0 (q, J = 280 Hz), 120.7 (q, J = 283 Hz), 119.6 (2C), 111.0 (2C), 93.5, 69.9 (hept, J = 33.7 Hz), 25.3, 22.1; $^{19}$F NMR: -72.6 (q, J = 9.1 Hz, 3F), -73.0 (q, J = 9.4 Hz, 3F); IR (neat): $\tilde{v}$ = 2944 (w), 1737 (s), 1477 (w), 1421 (w), 1359 (s), 1283 (s), 1258 (m), 1227 (s), 1194 (s), 1101 (s), 1080 (s), 1044 (w), 1000 (w), 970 (w), 949 (w), 897 (s), 805 (w), 730 (s), 687 (s), 687 (s), 663 (w) cm$^{-1}$; HRMS (CI (NH$_3$)): m/z calcd for C$_{11}$H$_{11}$F$_6$NO$_2$+H$^+$ [M+H]$^+$ 304.0767; found 304.0766.

**Compound 314:** Synthesised according to representative procedure I, from compound 308 (158 mg, 0.66 mmol) to afford compound 314 as a pale brown oil (97 mg, 0.29 mmol, 44%). $^1$H NMR (400 MHz, CDCl$_3$): δ 6.76 (t, J = 2.1 Hz, 2H), 6.32 (t, J = 2.1 Hz, 2H), 5.79-5.65 (m, 1H), 5.26-5.16 (m, 2H), 3.24-3.01 (m, 3H), 2.36 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 202.1, 128.9, 121.3, 121.1 (q, J = 266.4 Hz), 121.0 (q, J = 284.1 Hz), 120.0 (2C), 111.3 (2C), 95.5, 70.0 (hept, J = 33.7 Hz), 40.7, 27.2; $^{19}$F NMR (376 MHz, CDCl$_3$): δ -72.8 (q, J = 10.1 Hz, 3F), -72.9 (q, J = 9.4 Hz, 3F); IR (neat): $\tilde{v}$ = 3142 (w), 3089 (w), 3018 (w), 2945 (w), 1728 (s), 1647 (w), 1586 (w), 1533 (w), 1475 (m), 1441 (w), 1415 (m), 1358 (s), 1318 (w), 1287 (m), 1256 (s), 1226 (s), 1212 (s), 1195 (s), 1164 (m), 1123 (s), 1095 (s), 1070 (s), 1024 (m), 987 (m), 955 (w), 938 (m), 896 (s), 887 (s), 858 (w), 834 (w), 738 (s), 700 (m), 682 (s), 655 (s) cm$^{-1}$; HRMS (CI (CH$_4$)): m/z calcd for C$_{13}$H$_{13}$F$_6$NO$_2$+H$^+$ [M+H]$^+$ 330.0923; found 330.0938.

**Compound 315.** Synthesised according to representative procedure I, from compound 309 (182 mg, 0.66 mmol) to afford compound 315 as a purple liquid (135 mg, 0.37 mmol, 56%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.61 (m, 2H), 7.44 (m, 3H), 6.69 (s, 2H), 6.29 (m, 2H), 2.68 (hept, J = 6.0 Hz, 1H), 2.25 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 200.2, 135.2, 130.0, 128.8 (2C), 127.1 (2C), 122.8 (2C), 121.4 (q, J = 278.8 Hz), 120.9 (q, J = 280.0 Hz), 111.0 (2C), 96.9, 69.7 (hept, J = 33.6 Hz), 24.7; IR (neat): $\tilde{v}$ = 3147 (w), 3098 (w),
3059 (w), 2948 (w), 1732 (s), 1698 (w), 1676 (w), 1592 (w), 1555 (w), 1523 (w), 1468 (m), 14158 (w), 1357 (s), 1317 (w), 1289 (s), 1280 (s), 1255 (m), 1237 (s), 1218 (s), 1189 (s), 1175 (s), 1117 (s), 1083 (s), 1060 (m), 1035 (w), 976 (m), 906 (m), 895 (s), 884 (s), 847 (w), 805 (w) cm⁻¹; HRMS (ESI): m/z calcld for C₁₆H₁₃F₆NO₂⁺Na⁺ 388.0743; found 388.0744.

**Compound 333.** Synthesised according to representative procedure I, from compound 321 (100 mg, 0.38 mmol) to afford compound 333 as an off-white solid (61 mg, 0.33 mmol, 87%). m.p.: 58–61 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.53 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0, 1H), 7.33-7.26 (m, 2H), 3.56-3.48 (m, 2H), 3.44 (d, J = 21.1 Hz, 1H), 1.46 (d, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 214.0 (e), 160.5 (e), 157.5 (e), 125.2 (e), 124.0 (o), 123.2 (o), 119.6 (e), 114.6 (e), 112.0 (o), 43.6 (e), 38.2 (e), 14.3 (o); IR (neat): ν = 3040 (w), 2960 (w), 2941 (w), 2917 (w), 1750 (s), 1728 (m), 1677 (w), 1616 (w), 1500 (w), 1479 (w), 1445 (s), 1430 (s), 1415 (s), 1359 (w), 1312 (w), 1280 (w), 1247 (s), 1199 (w), 1174 (m), 1145 (m), 1078 (m), 1043 (s), 1013 (s), 996 (m), 959 (w), 934 (w), 913 (w), 895 (w), 865 (w), 823 (w), 774 (w), 748 (vs), 726 (m), 711 (m) cm⁻¹; HRMS (CI(CH₄)): m/z calcld for C₁₂H₁₀O₂+H⁺: 187.0754 [M+H]⁺; found 187.0750.

**Compound 334.** Synthesised according to representative procedure I, from compound 322 (50 mg, 0.19 mmol) to afford compound 334 as a cream-coloured amorphous solid (3.5 mg, 0.02 mmol, 13%) alongside compound 335 as a cream-coloured solid (26 mg, 0.14 mmol, 75%). ¹H NMR (500 MHz, CDCl₃): δ 7.56–7.46 (m, 2H), 7.34–7.21 (m, 2H), 3.66–3.54 (m, 2H), 3.52 (d, J = 22.6 Hz, 1H), 1.15 (d, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 214.0, 157.6 (e), 154.6 (e), 125.1 (e), 124.0 (o), 123.2 (o), 121.9 (e), 119.1 (o), 112.0 (o), 45.1 (e), 38.3 (o), 15.5 (o); IR (neat): ν = 3052 (w), 2992 (w), 2932 (w), 2904 (w), 2873 (w), 1955 (w), 1914 (w), 1751 (w), 1622 (m), 1478 (w), 1445 (m), 1431 (w), 1417 (w), 1369 (w), 1349 (m), 1308 (m), 1288 (w), 1263 (w), 1225 (m), 1188 (m), 1167 (m), 1144 (m), 1132 (m), 1110 (m), 1056 (w), 1015 (w), 979 (m), 935 (w), 910 (w), 859 (w), 828 (m), 761 (s), 752 (s), 723 (w), 703 (m), 688 (w), 656 (w) cm⁻¹; HRMS (CI(CH₄)): m/z calcld for C₁₂H₁₀O₂+H⁺: 187.0754 [M+H]⁺; found 187.0751,
**Compound 335.** m.p.: 75–77 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.59 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.44-7.38 (m, 1H), 7.06 (td, $J = 7.6$, 1.0 Hz, 1H), 7.01-6.97 (m, 1H), 5.53 (ddq, $J = 5.9$, 4.0, 2.6 Hz, 1H), 3.06 (dd, $J = 16.2$, 5.8 Hz, 1H), 2.80 (dd, $J = 16.4$, 4.1 Hz, 1H), 1.99 (d, $J = 2.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 203.9 (e), 169.6 (e), 165.1 (e), 133.5 (o), 130.3 (e), 124.5 (o), 122.3 (e), 122.0 (o), 112.1 (o), 85.6 (o), 44.1 (e), 8.6 (o); IR (neat): $\tilde{\nu} = 3087$ (w), 3056 (w), 3015 (w), 2990 (w), 2933 (w), 2908 (w), 1705 (s), 1657 (s), 1603 (s), 1476 (w), 1453 (s), 1445 (s), 1411 (w), 1376 (m), 1346 (m), 1335 (s), 1285 (s), 1233 (m), 1208 (s), 1181 (w), 1155 (m), 1114 (m), 1100 (m), 1057 (s), 1014 (w), 985 (m), 972 (s), 946 (m), 891 (m), 870 (w), 849 (m), 801 (m), 767 (s), 756 (s), 731 (m), 691 (w), 655 (w) cm$^{-1}$; HRMS (CI(CH$_4$)): $m/z$ calcd for C$_{12}$H$_{10}$O$_2$+H$^+$: 187.0754 [M+H$^+$]; found 187.0752.

**Compounds 336 and 337.** Synthesised according to representative procedure I, from compound 323 (100 mg, 0.36 mmol) to afford an inseparable mixture of compound 336 and 337 (30 mg, 0.15 mmol, 30%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58 (dt, $J = 8.0$, 1.0 Hz, 1H, 337), 7.35 (dt, $J = 8.2$, 0.9 Hz, 1H, 336), 7.25-7.21 (m, 1H, both), 7.17-7.12 (m, 1H, both), 4.00 (q, $J = 7.1$ Hz, 1H, 337), 3.78 (s, 3H, 337), 3.74 (s, 3H, 336), 3.67 (q, $J = 7.4$ Hz, 1H, 336), 3.56 (d, $J = 22.0$ Hz, 1H, 336), 3.50 (d, $J = 21.9$ Hz, 1H, 336), 2.09 (s, 3H, 337), 1.49 (d, $J = 7.3$ Hz, 3H, both).

**Compound 336.** was also synthesised under the iridium catalysed conditions, and full characterisation is described in the following section.

**Compound 338.** Synthesised according to representative procedure I, from compound 324 (40 mg, 0.1 mmol) to afford compound 338 as an off-white powder (16.1 mg, 0.05 mmol, 50%) alongside compound 339 as a pale pink powder (10 mg, 0.03 mmol, 31%). m.p.: 140–143 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.11 (dt, $J = 8.4$, 0.9 Hz, 1H); 7.74 (d, $J = 8.4$ Hz, 2H); 7.44 (d, $J = 7.8$ Hz, 1H); 7.37-7.30 (m, 1H); 7.27 (dd, $J = 7.7$, 1.1 Hz, 1H); 7.24 (d, $J = 7.8$ Hz, 2H); 3.78 (s, 2H); 3.52 (q, $J = 7.4$ Hz, 1H); 2.36 (s, 3H); 1.44 (d, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 215.0 (e), 145.2 (e), 137.8 (e), 135.6 (e), 135.3 (e), 130.1 (o, 2C), 126.7 (e), 126.6 (o, 2C), 125.5 (e), 124.5 (e), 123.7 (o), 114.4 (o), 44.4 (o), 40.6 (e), 21.6 (o), 15.4 (o); IR (neat): $\tilde{\nu} = 3054$ (w), 2971 (w), 2831 (w), 1657 (s), 1598 (s), 1476 (w), 1454 (s), 1445 (s), 1411 (w), 1376 (m), 1345 (m), 1335 (s), 1285 (s), 1257 (m), 1233 (m), 1208 (s), 1181 (w), 1155 (m), 1114 (m), 1100 (m), 1057 (s), 1054 (w), 985 (m), 972 (s), 946 (m), 891 (m), 870 (w), 849 (m), 801 (m), 767 (s), 756 (s), 731 (m), 691 (w), 655 (w) cm$^{-1}$; HRMS (CI(CH$_4$)): $m/z$ calcd for C$_{12}$H$_{10}$O$_2$+H$^+$: 187.0754 [M+H$^+$]; found 187.0752.
2911 (w), 1749 (m), 1491 (w), 1478 (w), 1446 (m), 1417 (w), 1397 (w), 1364 (s), 1345 (m), 1303 (w), 1294 (w), 1266 (w), 1239 (m), 1218 (w), 1197 (W), 1185 (s), 1164 (s), 1141 (m), 1120 (m), 1103 (w), 1086 (s), 1047 (m), 1008 (m), 955 (w), 931 (w), 913 (m), 808 (m), 796 (m), 759 (m), 745 (s), 700 (w), 666 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₉H₁₇NO₃S+Na⁺: 362.0821 [M+Na]⁺; found 362.0823.

**Compound 339.** m.p.: 88–90 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.86 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.49-7.43 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.15 (td, J = 7.6, 0.9 Hz, 1H), 4.65 (ddq, J = 5.8, 4.2, 2.7 Hz, 1H), 3.15 (dd, J = 17.2, 5.6 Hz, 1H), 2.96 (dd, J = 17.0, 4.2 Hz, 1H), 2.39 (s, 3H), 1.94 (d, J = 2.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 205.0 (e), 163.9 (e), 146.9 (e), 145.1 (e), 132.8 (o), 132.5 (e), 130.6 (e), 130.0 (o, 2C), 127.8 (o, 2C), 124.8 (o), 124.4 (o), 115.6 (o), 66.0 (o), 45.1 (e), 21.6 (o), 8.5 (o); IR (neat): ν = 3675 (w), 2987 (m), 2901 (m), 1752 (w), 1704 (s), 1655 (s), 1597 (m), 1492 (w), 1452 (s), 1412 (m), 1394 (w), 1375 (w), 1354 (s), 1335 (s), 1302 (m), 1286 (m), 1273 (m), 1233 (o), 1203 (m), 1167 (s), 1155 (s), 1117 (s), 1104 (s), 1081 (s), 1058 (s), 1038 (s), 1014 (s), 976 (w), 955 (m), 905 (m), 867 (w), 830 (w), 914 (m), 814 (s), 763 (m), 742 (s), 705 (m), 656 (w), 661 (s) cm⁻¹; HRMS (ESI): m/z calcd for C₁₉H₁₇NO₃S+Na⁺: 362.0821 [M+Na]⁺; found 362.0826.

**Compound 396.** Synthesised according to representative procedure I, from compound 394 (199 mg, 0.66 mmol), to afford compound 396 as a pale brown amorphous solid (20.1 mg, 0.09 mmol, 14%) along with compound 397 as a pale brown amorphous solid (54.6 mg, 0.24 mmol, 38%). ¹H NMR (400 MHz, CDCl₃): δ 8.68 (d, J = 4.9 Hz, 1H), 7.77 (td, J = 7.9, 2.0 Hz, 1H), 7.57 (d, J = 4.1 Hz, 1H), 7.56 (d, J = 4.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.25-7.21 (m, 1H), 3.91 (d, J = 23.3 Hz, 1H), 3.81 (d, J = 23.3 Hz, 1H), 3.54 (q, J = 7.6 Hz, 1H), 1.45 (d, J = 7.5 Hz, 1H). This compound was synthesised for preliminary results only, and so was not fully characterised.

**Compound 397.** ¹H NMR (400 MHz, CDCl₃): δ 8.71 (d, J = 4.8 Hz, 1H), 7.96 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.80-7.72 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.26-7.21 (m, 1H), 3.66 (d, J = 22.6 Hz, 1H), 3.61-3.52 (m, 2H), 1.49 (d, J = 7.5 Hz, 3H). This compound was synthesised for preliminary results only, and so was not fully characterised.
3.5 Iridium Catalysed Cyclisation of Sulfoxonium Ylides

Representative Procedure J: To a flame dried microwave vial under N\textsubscript{2} was added compound \textbf{306} (60 mg, 0.3 mmol, 1.0 equiv) and [Ir(cod)Cl\textsubscript{2}] (2 mg, 0.003 mmol, 1 mol%), and the vial was evacuated and backfilled with N\textsubscript{2} three times. Dry 1,2-DCE (15 mL, 0.02 M) was added, and the solution was degassed with an argon balloon for 30 mins. The vial was then sealed and heated at 80 °C in the microwave (Anton Paar Microwave Synthesis Reactor Monowave 300) for 2 hours. The vial was cooled to rt under a stream of nitrogen, and the solvent was removed \textit{in vacuo}. The residue was purified by FCC (petroleum ether/EtOAc = 9:1) to afford compound \textbf{341} as a dark green powder (27 mg, 0.22 mmol, 74%).

\textbf{Compound 341}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 6.77 (dd, \(J = 2.8, 1.2\) Hz, 1H); 6.27 (t, \(J = 3.1\) Hz, 1H); 6.02 (dq, \(J = 3.5, 1.2\) Hz, 1H); 4.40 (s, 2H); 3.54 (d, \(J = 1.0\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 209.6 (e), 130.2 (e), 115.4 (o), 111.2 (o), 101.8 (o), 54.4 (e), 37.4 (e), in agreement with previously reported data\textsuperscript{33}.

\textbf{Compound 342}. Synthesised according to representative procedure J, from compound \textbf{307} (64 mg, 0.3 mmol) to afford compound \textbf{342} as a dark green powder (26 mg, 0.19 mmol, 64%). m.p.: 46–48 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 6.80-6.71 (m, 1H), 6.32-6.21 (m, 1H), 6.05-5.95 (m, 1H), 4.39 q, \(J = 6.9\) Hz, 1H), 3.62-3.45 (m, 2H), 1.54 (d, \(J = 7.1\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 212.5 (e), 128.2 (e), 114.0 (o), 111.1 (o), 101.4 (o), 59.8 (o), 36.5 (e), 17.3 (o); IR (neat): \(\tilde{\nu}\) = 3500 (w), 3042 (w), 2998 (w), 2978 (w), 2934 (w), 2901 (w), 2873 (w), 1755 (s), 1717 (w), 1625 (w), 1568 (w), 1551 (w), 1468 (w), 1455 (w), 1447 (w), 1399 (w), 1366 (m), 1312 (m), 1294 (m), 1255 (s), 1229 (w), 1193 (w), 1181 (w), 1116 (w), 1103 (w), 1073 (m), 1064 (m), 1032 (m), 1025 (m), 1003 (w), 977 (w), 937 (w), 904
Compound 340. Synthesised according to representative procedure J, from compound 325 (28 mg, 0.1 mmol), to afford compound 340 as a pale-pink powder (17 mg, 0.08 mmol, 85%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.51 (d, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.25-7.20 (m, 1H), 7.16-7.11 (m, 1H), 3.64–3.61 (m, 5H), 3.14-3.09 (m, 2H), 2.78 (t, $J = 6.7$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 208.0 (e), 137.6 (e), 131.8 (e), 126.0 (e), 121.4 (o), 119.3 (o), 118.0 (o), 108.4 (e), 39.5 (e), 37.5 (e), 29.2 (o), 19.8 (e); IR (neat): $\tilde{\nu}$ = 3051 (w), 2978 (w), 2933 (w), 2856 (w), 1906 (w), 1871 (w), 1705 (s), 1615 (w), 1586 (w), 1567 (w), 1470 (s), 1418 (w), 1375 (m), 1345 (w), 1314 (m), 1291 (w), 1273 (w), 1239 (s), 1203 (w), 1178 (m), 1144 (w), 1129 (w), 1034 (m), 1010 (w), 983 (w), 964 (w), 935 (w), 920 (w), 877 (w), 786 (w), 757 (s), 736 (s), 664 (w); elemental analysis calcd (%) for C$_{13}$H$_{13}$NO: C 78.36, H 6.58, N 7.03; found: C 78.30, H 6.60, N 6.98.

Compound 344. Synthesised according to representative procedure J, from compound 309 (28 mg, 0.10 mmol) to afford compound 344 as yellow gum (17 mg, 0.08 mmol, 90%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39-7.33 (m, 3H), 7.10-7.05 (m, 2H), 6.71 (dd, $J = 2.7$, 1.1 Hz, 1H), 6.35 (t, $J = 3.1$ Hz, 1H), 6.12 (dq, $J = 3.5$, 1.1 Hz, 1H), 5.38 (s, 1H), 3.63 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 208.5 (e), 135.9 (e), 129.2 (e), 129.0 (o,), 128.6 (o), 126.2 (o,), 115.3 (o), 111.7 (o), 101.6 (o), 68.1 (o), 36.2 (e); IR (neat): $\tilde{\nu}$ = 3085 (w), 3068 (w), 3028 (w), 2901 (w), 1956 (w), 1759 (s), 1601 (w), 1582 (w), 1555 (w), 1523 (w), 1495 (m), 1470 (m), 1454 (m), 1438 (w), 1401 (m), 1350 (m), 1296 (m), 1279 (m), 1249 (m), 1222 (m), 1193 (w), 1185 (m), 1129 (w), 1094 (m), 1078 (m), 1057 (m), 1030 (w), 1013 (w), 986 (w), 967 (w), 934 (w), 901 (m), 845 (w), 826 (w), 781 (w), 770 (m), 759 (m), 740 (m), 724 (s), 715 (m), 700 (s) cm$^{-1}$; HRMS (Cl(CH$_4$)): $m/z$ calcd for C$_{13}$H$_{11}$NO+H$: 198.0913 [M+H]$^+$; found 198.0922.
**Compound 346.** Synthesised according to representative procedure J, from compound 310 (29 mg, 0.10 mmol) to afford compound 346 as purple gum (20 mg, 0.09 mmol, 95%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): δ 7.26-7.20 (m, 3H), 6.99 (dd, \(J = 6.4, 2.8\) Hz, 2H), 6.50 (d, \(J = 1.9\) Hz, 1H), 6.20 (t, \(J = 3.1\) Hz, 1H), 5.87-5.94 (m, 1H), 4.69-4.61 (m, 1H), 3.44-3.33 (m, 2H), 3.00-3.10 (m, 2H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): δ 211.7 (e), 135.1 (e), 129.2 (o, 2C), 128.7 (e), 128.3 (o, 2C), 126.9 (o), 114.6 (o), 110.8 (o), 101.1 (o), 65.0 (o), 38.5 (o), 36.7 (o); IR (neat): \(\nu\ = 3138\ (w),\ 3113\ (w),\ 3062\ (w),\ 2991\ (w),\ 1970\ (w),\ 1758\ (s),\ 1600\ (w),\ 1585\ (w),\ 1552\ (w),\ 1496\ (w),\ 1468\ (m),\ 1455\ (m),\ 1403\ (w),\ 1343\ (w),\ 1295\ (m),\ 1267\ (w), 1250\ (m), 1214\ (w), 1187\ (m), 1166\ (m), 1128\ (w), 1085\ (m), 1052\ (m), 1028\ (w), 1010\ (w), 998\ (w), 974\ (w), 946\ (w), 921\ (w), 871\ (w), 853\ (m), 836\ (w), 779\ (m), 765\ (m), 747\ (m): 715\ (s): 700\ (s)\ cm\(^{-1}\); HRMS (Cl(CH\(_4\))): \(m/z\) calcd for C\(_{14}\)H\(_{13}\)NO+H\(^+\): 212.1070 [M+H]\(^+\); found 212.1080.

**Compound 348.** Synthesised according to representative procedure J, from compound 311 (91 mg, 0.3 mmol) using 2.5 mol% of [Ir(cod)Cl]\(_2\) at 100 °C to afford compound 348 as yellow oil (54 mg, 0.24 mmol, 79%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): δ 7.29-7.26 (m, 2H), 7.22-7.18 (m, 1H), 7.14-7.12 (m, 2H), 6.80 (dd, \(J = 2.7, 1.2\) Hz, 1H), 6.32-6.30 (m, 1H), 6.04-6.02 (m, 1H), 4.39 (td, \(J = 5.4, 1.0\) Hz, 1H), 3.52 (d, \(J = 22.9\) Hz, 1H), 3.39 (dt, \(J = 22.8, 1.1\) Hz, 1H), 2.67-2.56 (m, 2H), 2.35-2.24 (m, 2H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): δ 212.4 (e), 140.2 (e), 129.0 (e), 128.48 (o, 2C), 128.50 (o, 2C), 126.3 (o), 114.4 (o), 111.4 (o), 101.6 (o), 63.5 (o), 37.1 (e), 33.9 (e), 30.6 (e); IR (neat): \(\nu\ = 3026\ (w),\ 2923\ (w),\ 1759\ (s),\ 1602\ (w),\ 1552\ (w):\ 1496\ (w),\ 1470\ (m),\ 1454\ (m),\ 1403\ (m),\ 1257\ (m),\ 1193\ (w),\ 1180\ (w),\ 1099\ (m),\ 1080\ (w),\ 1058\ (m),\ 1029\ (w),\ 903\ (m),\ 846\ (w),\ 776\ (m),\ 748\ (m),\ 699\ (s)\ cm\(^{-1}\); HRMS (Cl(CH\(_4\))): \(m/z\) calcd for C\(_{15}\)H\(_{15}\)NO+H\(^+\): 226.1226 [M+H]\(^+\); found 226.1232.

**Compound 297.** Synthesised according to representative procedure J, from compound 285 (105 mg, 0.3 mmol) to afford compound 297 as pale-brown amorphous solid (76 mg, 0.28 mmol, 94%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): δ 6.81 (d, \(J = 8.3\) Hz, 1H), 6.69 (br s, 1H), 6.61 (dd, \(J = 8.3, 2.2\) Hz, 1H), 6.41 (d, \(J = 2.1\) Hz, 1H), 6.19 (t, \(J = 3.2\) Hz, 1H), 6.00 (d, \(J = 2.8\) Hz, 1H), 4.49 (dd, \(J = 13.1, 5.4\) Hz, 1H), 4.39 (dd, \(J = 13.1, 7.2\) Hz,
1H), 3.87-3.74 (m, 3H), 3.85 (s, 3H), 3.78 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 205.6 (e), 149.2 (e), 148.6 (e), 128.4 (e), 124.8 (e), 120.4 (o), 119.6 (o), 111.4 (o), 111.0 (o), 108.8 (o), 106.0 (o), 55.84 (o), 55.81 (o), 55.1 (o), 48.8 (e), 37.8 (e); IR (neat): ν = 3135 (w), 3007 (w), 2967 (w), 2938 (w), 2876 (w), 2841 (w), 1724 (s), 1633 (w), 1605 (w), 1550 (w), 1515 (s), 1487 (m), 1464 (m), 1445 (m), 1418 (w), 1400 (w), 1373 (w), 1345 (w), 1328 (w), 1299 (w), 1275 (s), 1245 (s), 1235 (s), 1223 (s), 1187 (m), 1162 (m), 1143 (s), 1128 (m), 1067 (w), 1021 (s), 982 (w), 945 (w), 925 (w), 886 (w), 849 (m), 831 (w), 814 (m): 793 (w), 780 (w), 763 (w), 719 (s) cm⁻¹; HRMS (ESI): m/z calcd for C16H17NO+Na⁺: 294.1101 [M+Na⁺]; found 294.1102.

**Compound 301.** Synthesised according to representative procedure J from compound 286 (109 mg, 0.3 mmol) to afford compound 301 as pale-brown amorphous solid (77 mg, 0.27 mmol, 90%). 1H NMR (500 MHz, CDCl3): δ 6.82 (d, J = 8.2 Hz, 1H), 6.72 (dd, J = 8.3, 2.0 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 2.6, 1.9 Hz, 1H), 6.10 (t, J = 3.3 Hz, 1H), 6.06-6.05 (m, 1H), 4.28-4.22 (m, 2H), 3.92-3.86 (m, 2H), 3.86 (s, 3H), 3.76 (d, J = 15.8 Hz, 1H), 2.46-2.39 (m, 1H), 2.33-2.26 (m, 1H).

**Compound 299.** Synthesised according to representative procedure J, from compound 287 (95 mg, 0.3 mmol) using 5 mol% of [Ir(cod)Cl]2 to afford compound 296 as pale-brown amorphous solid (40 mg, 0.17 mmol, 56%). 1H NMR (500 MHz, CDCl3): δ 7.32-7.27 (m, 2H), 7.25-7.20 (m, 3H), 6.69-6.65 (m, 1H), 6.22 (t, J = 3.0 Hz, 1H), 6.08-6.04 (m, 1H), 4.08 (ddd, J = 15.3, 8.2, 2.7 Hz, 1H), 3.83 (ddd, J = 15.4, 7.9, 3.1 Hz, 1H), 3.80 (s, 2H), 3.75 (dd, J = 11.1, 2.7 Hz, 1H), 2.14-2.05 (m, 1H), 1.82-1.72 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 211.2 (e), 140.1 (e), 128.4 (o, 2C), 128.0 (o, 2C), 127.0 (o), 126.3 (e), 121.2 (o), 108.9 (o), 108.6 (o), 55.6 (o), 45.9 (e), 41.6 (e), 32.2 (e), 30.6 (e); IR (neat): ν = 2927 (w), 1707 (s), 1600 (w), 1484 (m), 1452 (m), 1398 (w), 1352 (w), 1304 (m), 1277 (w), 1208 (w), 1102 (w), 1075 (m), 1030 (w), 971 (w), 939 (w), 910 (w), 878 (w), 826 (w), 795 (m); 758 (m), 698 (s) cm⁻¹; HRMS (ESI): m/z calcd for C16H17NO+Na⁺: 262.1208 [M+Na⁺]; found 262.1209.
**Compound 355.** Synthesised according to representative procedure J from compound 351 (41 mg, 0.1 mmol) using 5 mol% of [Ir(cod)Cl]₂ for 3 hours to afford compound 355 as a purple powder (20.5 mg, 0.06 mmol, 61%). m.p.: 115–116 °C; ¹H NMR (500 MHz, CDCl₃): δ 6.49 (d, J = 3.9 Hz, 1H), 6.07 (d, J = 3.8 Hz, 1H), 4.67 (s, 2H), 3.89–3.71 (m, 4H), 3.52-3.49 (m, 6H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 208.7 (e), 162.2 (e), 154.6 (e), 134.4 (e), 121.6 (e), 115.4 (o), 102.7 (o), 80.3 (e), 55.9 (e), 44.9 (e)*, 43.8 (e)*, 37.2 (e), 28.4 (o, 3C) (peaks marked by an asterisk are very broad due to slow rotation of Boc group); IR (neat): ν ~ = 2978 (w), 2903 (w), 1766 (s), 1690 (s), 1617 (s), 1552 (w), 1475 (s), 1409 (s), 1368 (m), 1283 (m), 1242 (s), 1164 (s), 1132 (s), 1069 (m), 1041 (m), 995 (m), 862 (m), 839 (w), 822 (w), 809 (w), 767 (m), 735 (s), 669 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₇H₂₃N₃O₄⁺Na⁺: 356.1581 [M+Na]⁺; found 356.1585.

**Compound 359.** Synthesised according to representative procedure J, from compound 358 (118 mg, 0.3 mmol) using 2.5 mol% [Ir(cod)Cl]₂ at 100 °C for 3 h to afford compound 359 as a turquoise solid (80.3 mg, 0.26 mmol, 85%). [α]D = -61.28 (MeOH, l = 0.25 dm, c = 8.6); Chiral HPLC analysis (Chiralpak AD-H), 10% isopropanol/hexane at 0.75 mL/min. flow rate; tR (major) 28.29 min., tR (minor) 23.32 min., 57% enantiomeric excess; ¹H NMR (500 MHz, CDCl₃): δ 7.49 (d, J= 7.9 Hz, 1H), 7.29 (d, J= 8.2 Hz, 1H), 7.23 (t, J= 7.3 Hz, 1H), 7.13 (t, J= 7.4 Hz, 1H), 5.61 (br s, 1H), 4.72 (q, J = 7.4 Hz, 1H), 3.86-3.81 (m, 2H), 3.73 (d, J= 19.7 Hz, 1H), 3.63 (s, 3H), 2.70 (t, J= 12.2 Hz, 1H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 204.0 (e), 155.4 (e), 137.7 (e), 130.2 (e), 125.9 (e), 121.7 (o), 119.6 (o), 109.0 (o), 106.4 (e), 79.9 (e), 57.3 (o), 37.5 (e), 28.4 (o, 3C), 28.2 (e); IR (neat): ν = 3368 (w), 2974 (w), 2928 (w), 2869 (w), 1737 (s), 1686 (s), 1616 (w), 1584 (w), 1569 (w), 1510 (s), 1471 (s), 1443 (m), 1409 (w), 1394 (w), 1365 (m), 1338 (m), 1308 (w), 1290 (m), 1235 (s), 1170 (s), 1156 (s), 1114 (w), 1076 (m), 1046 (m), 1010 (m), 1001 (m), 917 (w), 865 (w), 838 (w), 826 (m), 780 (m), 736 (s), 695 (w) cm⁻¹; HRMS (ESI): m/z calcd for C₁₈H₂₂N₂O₃⁺Na⁺ [M+Na]⁺ 337.1527; found 337.1523.
Compound 336. Synthesised according to representative procedure J from compound 323 (83 mg, 0.3 mmol) using 2.5 mol% of [Ir(cod)Cl]₂ at 100 °C to afford compound 336 as cream-coloured solid (49 mg, 0.25 mmol, 82%). m.p.: 91–93 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.53 (d, J = 7.9 Hz, 1H), 7.35 (dt, J = 8.2, 0.9 Hz, 1H), 7.25-7.21 (m, 1H), 7.17-7.12 (m, 1H), 3.74 (s, 3H), 3.67 (q, J = 7.4 Hz, 1H), 3.56 (d, J = 22.0 Hz, 1H), 3.50 (d, J = 21.9 Hz, 1H), 1.49 (d, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 216.5 (e), 139.2 (e), 137.6 (e), 124.2 (e), 121.3 (o), 119.6 (o), 118.6 (o), 117.4 (e), 109.6 (o), 45.3 (o), 37.4 (e), 31.1 (o), 16.4 (o); IR (neat): ν = 3048 (w), 2973 (w), 2931 (w), 2896 (w), 2858 (w), 2827 (w), 1739 (s), 1612 (w), 1558 (w), 1484 (m), 1469 (m), 1448 (w), 1420 (w), 1402 (w), 1382 (m), 1264 (w), 1226 (m), 1182 (w), 1143 (w), 1132 (w), 1113 (w), 1070 (w), 1060 (w), 1011 (m), 958 (w), 930 (w), 904 (w), 856 (w), 805 (w), 746 (s), 669 (w) cm⁻¹; HRMS (Cl(CH₄)): m/z calcd for C₁₃H₁₃NO+H⁺: 200.1070 [M+H]⁺; found 200.1077.
**Compound 368.** Synthesised according to representative procedure J from compound 366 (68 mg, 0.3 mmol) to afford compound 368 as a slightly yellow solid (23.3 mg, 0.16 mmol, 53%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32-7.22 (m, 2H), 7.04 (t, $J = 7.06$ Hz, 1H), 6.82 (d, $J = 8.23$ Hz, 1H), 3.52 (s, 2H), 3.21 (s, 3H); HRMS (Cl(CH$_4$)): $m/z$ calcd for C$_9$H$_9$NOH$^+$ [M+H]$^+$ 148.0757; found 148.0757, in agreement with previously reported data$^{34}$. 

**Compound 115.** Synthesised according to representative procedure J, from compound 220 (75 mg, 0.3 mmol) to afford compound 115 as a pale yellow liquid (42.3 mg, 0.25 mmol, 82%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34-7.27 (m, 3H), 7.23-7.15 (m, 2H), 3.58-3.53 (m, 1H), 2.80-2.70 (m, 1H), 2.37-2.31 (m, 1H), 2.13-2.04 (m, 1H), 1.97-1.92 (m, 1H), 1.19-1.11 (m, 1H), 1.01-0.96 (m, 1H), in agreement with previously reported data$^{32}$. 

**Compound 371.** Synthesised according to representative procedure J from compound 308 (72 mg, 0.3 mmol) to afford compound 371 as a dark green amorphous solid (26.2 mg, 0.16 mmol, 54%) alongside compound 323 as a dark green oil (18.9 mg, 0.12 mmol, 39%). (500 MHz, CDCl$_3$): $\delta$ 6.82-6.78 (m, 1H), 6.26 (t, $J = 3.2$ Hz, 1H), 6.03-5.98 (m, 1H), 5.70-5.57 (m, 1H), 5.18-5.09 (m, 2H), 4.42 (t, $J = 5.5$ Hz, 1H), 3.53 (d, $J = 22.8$ Hz, 1H), 3.43 (d, $J = 22.7$ Hz, 1H), 2.84-2.76 (m, 1H), 2.66-2.55 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 211.8 (e), 131.6 (o), 128.8 (e), 119.7 (e), 114.7 (o), 111.1 (o), 101.4 (o), 63.8 (o), 37.1 (e), 36.6 (e); IR (neat): $\tilde{\nu} = 3080$ (w), 2905 (w), 1734 (s), 1688 (s), 1618 (s), 1549 (w), 1470 (m), 1435 (w), 1404 (w), 1337 (w), 1296 (m), 1276 (w), 1250 (w), 1213 (w), 1180 (w), 1092 (w), 1055 (w), 996 (w), 923 (m), 773 (w), 701 (s); HRMS (Cl (NH$_3$)): $m/z$ calcd for C$_{10}$H$_{11}$NOH$^+$ [M+H]$^+$ 162.0913; found 162.0916. 

**Compound 372.** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.65 (t, $J = 2.1$ Hz, 2H), 6.23 (t, $J = 2.1$ Hz, 2H), 3.19 (dd, $J = 18.8$, 7.5 Hz, 1H), 2.68-2.62 (m, 2H), 2.51-2.45 (m, 2H), 1.41-1.34 (m, 1H), 1.28-1.23 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 208.3 (e), 120.0 (o, 2C), 108.5 (o, 2C), 59.3 (o), 30.6 (e), 25.2 (o), 19.9 (o), 14.8 (e), IR (neat): $\tilde{\nu} = 3099$ (w), 2937 (w), 1734 (s), 1688 (s), 1618 (m), 1514 (w), 1492 (s), 1451 (w), 1426 (w), 1384 (w), 1329 (w), 1309 (w), 1285...
Compound 376: Synthesised according to representative procedure J from compound 375 (50 mg, 0.2 mmol) to afford compound 376 as a colourless oil (9.0 mg, 0.05 mmol, 26%) along with compound 377 as a pale brown amorphous solid (25.1 mg, 0.14 mmol, 74%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.56 (s, 2H), 4.27-4.29 (m, 2H), 5.20-5.27 (m, 2H), 5.79-5.89 (m, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 7.03 (t, $J = 7.3$ Hz, 1H), 7.21-7.25 (m, 2H); in agreement with previously reported data.$^{34}$

Compound 377. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.52 (d, $J = 7.8$ Hz, 2H), 7.31-7.36 (m, 2H), 7.11 (tt, $J = 7.7$, 1.5 Hz, 1H), 4.05 (dd, $J = 5.8$, 10.0 Hz, 1H), 3.75 (dd, $J = 1.5$, 10.0 Hz, 1H), 2.13-2.07 (m, 1H), 1.23-1.17 (m, 1H), 0.80 (q, $J = 4.3$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.3 (e), 139.4 (e), 128.8 (o, 2C), 124.2 (o), 119.7 (o, 2C), 50.3 (e), 21.7 (o), 12.7 (e), 11.3 (o); IR (neat): $\tilde{\nu} = 3081$ (w), 3063 (w), 3008 (w), 2965 (w), 2939 (w), 2889 (w), 1679 (s), 1597 (s), 1584 (s), 1494 (s), 1481 (s), 1457 (w), 1443 (w), 1390 (s), 1353 (m), 1320 (s), 1284 (s), 1233 (s), 1219 (m), 1179 (w), 1171 (w), 1157 (w), 1145 (m), 1097 (w), 1075 (w), 1054 (m), 1025 (s), 1008 (m), 997 (w), 963 (m), 910 (w), 895 (w), 835 (m), 828 (m), 808 (m), 769 (s), 744 (s), 690 (s), 662 (s) cm$^{-1}$; HRMS (CI (NH$_3$)): $m/z$ calcd for C$_{11}$H$_{11}$NO+H$^+$ [M+H]$^+$ 174.0913; found 174.0920.

Compound 385. Synthesised according to representative procedure J from compound 381 (75 mg, 0.30 mmol), to afford compound 385 as a pale-brown powder (42 mg, 0.25 mmol, 82%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.63 (d, $J = 7.9$ Hz, 1H), 7.26-7.19 (m, 2H), 7.18-7.13 (m, 1H), 6.38 (q, $J = 1.1$ Hz, 1H), 4.46 (s, 2H), 3.71 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 208.6 (e), 136.5 (e), 133.5 (e), 130.5 (e), 121.5 (o), 120.8 (o), 120.3 (o), 109.6 (o), 95.7 (o), 52.2 (e), 37.5 (e), HRMS (Cl(CH$_4$)): $m/z$ calcd for: C$_{11}$H$_{9}$NO+H$^+$ [M+H]$^+$ 172.0757; found 172.0765, in agreement with previously reported data.$^{35}$
**Compound 413.** Synthesised according to representative procedure J, from compound 412 (83 mg, 0.3 mmol) to afford compound 413 as a dark green solid (7.7 mg, 0.03 mmol, 13%) along with compound 414 as a dark green solid (4.2 mg, 0.02 mmol, 7%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.54 (d, \(J = 4.9\) Hz, 1H), 7.65 (t, \(J = 7.7\) Hz, 1H), 7.47 (d, \(J = 7.6\) Hz, 1H), 7.30-7.24 (m, 1H), 7.08 (t, \(J = 6.7\) Hz, 1H), 6.77 (d, \(J = 8.7\) Hz, 1H), 4.59 (s, 2H), 3.49 (s, 2H). This compound was synthesised for preliminary results only, so was not fully characterised.

**Compound 414.** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.52 (d, \(J = 4.9\) Hz, 1H), 7.65 (t, \(J = 7.8\) Hz, 1H), 7.44 (d, \(J = 7.0\) Hz, 1H), 7.30-7.25 (m, 1H), 6.80 (s, 1H), 6.06 (s, 1H), 4.65 (s, 2H), 3.66 (s, 2H). This compound was synthesised for preliminary results only, and so was not fully characterised.

**References for Chapter 3**


(15) Schifflner, J. A.; Wöste, T. H.; Oestreich, M. Enantioselective Fujiwara–Moritani Indole and Pyrrole Annulations Catalyzed by Chiral Palladium (II)–
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