An investigation of thiadiazolidines and related compounds for use as ligands in metal mediated catalysis

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Doctor of Philosophy

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Loughborough University June 2011

Supervisor

Dr Benjamin R. Buckley B.Sc., Ph.D., M.R.S.C., F.H.E.A.
“A tidy laboratory means a lazy chemist.”

-Jöns Jacob Berzelius
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# Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
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<td>UV</td>
<td>ultraviolet</td>
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Abstract

An Investigation of Thiadiazolidines and Related Compounds for use as Ligands in Metal Mediated Catalysis

Stephen P. Neary

Keywords: Catalysis, Heck, Thiadiazolidine 1-oxide, NMP, Ligand, Microwave, Palladium, Oxindole, Esermethole

This thesis describes the investigation of thiadiazolidine 1-oxides and structurally related compounds as ligands in palladium catalysis. The introduction will provide background information on subjects related to the work of the main project. Palladium catalysed cross couplings, namely the Heck and Tsuji-Trost reactions, will feature prominently and will be discussed in basic detail. A general outline of different classes of ligands used in palladium catalysis will also be put forward. Extraneous factors which affect catalyst reactivity will also be discussed, including the use of microwave irradiation and the effect of additives. Special attention is paid towards sulfur containing ligands. As their use has been relatively limited this will also include other areas of catalysis. Investigations into the synthesis of esermethole prompt a general background of methods of synthesising oxindoles and also examples of previous syntheses of the compound.

The second chapter begins by describing the initial exploratory work, the testing of a thiadiazolidine 1-oxide compound as a ligand for the Heck reaction. Aryl iodides are successfully coupled to a range of styrenes and α,β-unsaturated esters in excellent yields under microwave conditions. Aryl bromides are also successfully coupled after some optimisation. In many cases the presence of tetrabutylammonium bromide is required to prevent shattering of the sealed microwave vial.

A range of differently substituted thiadiazolidine 1-oxides were synthesised in order to establish a pattern of reactivity based on steric and electronic factors. Structurally related chiral compounds were also synthesised, including the first reported enantiomerically pure thiadiazol-3-one 1-oxide and thiatriaza-indene 3-oxide systems chiral at the sulfur atom.

The synthesis of oxindoles using palladium mediated and non-catalytic chemistry was also investigated. Investigations into the synthesis of esermethole were undertaken; the key stereoinducing reaction, the decarboxylative asymmetric allylic alkylation reaction, achieved a 46% ee. A formal synthesis of esermethole was outlined in 8 steps from commercially available material.

The third chapter is the experimental section and is dedicated to the methods of synthesis and characterization of the compounds mentioned in the previous chapter.

X-ray reports regarding the crystallographic representation of the structures presented in chapter two are provided in appendix A.
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Chapter 1: Introduction

1.1 Palladium Catalysed Cross Coupling Reactions

Palladium catalysis has undeniably become an indispensable tool for both common organic synthesis and also state of the art chemistry. Palladium catalysts are the most commonly used catalyst systems in organic synthesis due to their immense versatility in carbon-carbon and carbon-heteroatom bond formation.

The importance of this chemistry has been recognised by the 2010 Nobel Prize for chemistry being awarded jointly to Richard F. Heck, Akira Suzuki and Ei-ichi Negishi for their immense contributions to the field. Each of whom has a commonly known coupling reaction named after them.

The emergence of palladium catalysis over the last quarter of the 20th century has facilitated a different style of synthesis, whereby components of a target molecule can be synthesised separately and linked together in the final stages as opposed to the more linear synthetic style which before was often predominant in total synthesis. Another reason for the popularity of this type of coupling are the mild conditions employed and exceptional tolerance towards different functional groups, especially alcohols. Some examples of well known palladium-catalysed couplings are outlined in Scheme 1.

Scheme 1

At the most basic level, the majority of these reactions are mechanistically quite similar. The mechanisms of the reactions on the left arrow can be fundamentally described as three steps. The oxidative addition of a Pd(0) catalyst to a -halide or -pseudohalide is always the first step. This is followed by a transmetalation step and
finally, reductive elimination of the product restores the catalyst to the zerovalent state (Scheme 2).

1.1.1 The Heck Reaction

The Heck reaction is the palladium catalysed coupling of an aryl or vinyl halide (or pseudohalide) to an alkene (Scheme 3). Often is the case with organic reactions that, a clear cut set of optimal conditions can be laid out (i.e. solvents, ligands etc.) and reaction scope is clearly defined. Several general procedures can usually cover the entire substrate scope over a range of organic reactions. This cannot be said for Heck chemistry.¹

\[
\begin{array}{c}
R^1_X + R^2 \xrightarrow{\text{Pd(0)}} \text{Base} \rightarrow R^1 = \text{Aryl, Vinyl} \\
X = \text{I, Br, Cl, OTf, N}_2^+
\end{array}
\]

Heck chemistry has been attempted in practically every solvent media conceivable without any being entirely discarded. Slight changes in substrates, base, ligand, temperature etc. can lead to unpredictable results. Patterns of reactivity and selectivity are often blurred and can break quite unexpectedly. Because of this the question of what is the best catalyst, the optimal conditions or the best procedure is difficult to answer.²

The first report of palladium-catalysed olefin arylation using aryl halides was published in 1971 by Mizoroki and co-workers (Scheme 4).³ Independently, a similar transformation under different conditions was published by Heck and Nolley a year later (Scheme 5).⁴
1.1.1.1 The Catalytic Cycle

To begin the catalytic cycle a coordinatively unsaturated 14-electron Pd(0) species is required. This can be generated in situ by reduction of a relatively inexpensive Pd(II) source such as palladium acetate or chloride; or otherwise by ligand dissociation from another Pd(0) source such as palladium triphenylphosphine complex ([Pd(PPh₃)₄]).
Upon contact with an aryl halide (or any similarly reactive compound), the palladium undergoes oxidative addition to the C-X bond. This is a concerted process where the breaking of the C-X bond is simultaneous with the formation of the M-C and M-X bonds. The order of reactivity of C-X bonds is I>>OTf>Br>>Cl.\(^7\) A cis-complex is initially formed and a cis-complex is what proceeds to the next stage of the cycle after some cis-trans isomerisation.\(^8\)

The carboxypalladation step is the main carbon-carbon bond forming step of the reaction. This step is likely to be responsible for substrate selectivity and stereo/regio-discrimination. The R- group of the original alkyl halide or triflate is highly reactive especially towards π-systems; therefore it will migrate to the coordinated olefin. There is no change in oxidation state although a ligand must dissociate to allow the migration to take place.

In the example shown in Scheme 6, β-hydride elimination can only occur after internal rotation around the α and β carbons. There must be a β-hydrogen in a syn-planar position to the halopalladium moiety in order to allow elimination and subsequent product formation. If there is a choice of hydride to eliminate then the outcome is determined by the stability of the alkene products.

Reductive elimination of HX from the hydridopalladium halide, aided by base, regenerates the active catalyst completing the cycle.

### 1.1.1.2 The Asymmetric Heck Reaction

Although the first Heck reactions were reported in the early seventies it was not until 1989 that the first asymmetric results were published independently by Shibasaki (Scheme 7) and Overman (Scheme 8).\(^9,10\)

![Scheme 7](image-url)
The asymmetric induction step is generally considered to be the olefin coordination/insertion step. There are two proposed mechanistic pathways for this insertion involving a chiral bidentate ligand. The first is a cationic pathway that is generally considered to be a superior route for asymmetric induction. This is due to the fact that the ligand is fully attached to the palladium throughout the reaction. In the alternative neutral pathway, the ligand must partially dissociate to allow coordination of the olefin. (Scheme 9)

A reaction can be influenced in favour of the cationic pathway by the addition of halophilic silver salts; these remove the halogen from the palladium and supply a counterion for the stabilisation of positive charge. It is also vital for the formation of a new chiral centre that a β’ hydride is eliminated in product formation (Scheme 10).
1.1.2 The Tsuji-Trost Reaction

Complexation of π-systems to transition metals activates them to attack from nucleophiles. β,γ-Unsaturated organopalladium systems especially allyl and propargylpalladium systems are readily available towards attack from a wide range of nucleophiles. The palladium atom acts as a key leaving group which upon dissociation reforms to the correct oxidation state to regenerate the catalyst. The attack of nucleophiles on allylpalladium species has come in recent decades to be known as the Tsuji-Trost reaction (Scheme 11).

1.1.2.1 The Catalytic Cycle

The generally accepted mechanism of the Tsuji-Trost reaction (Scheme 12) first proceeds by the association of palladium to the olefin. Oxidative addition and release of a leaving group then occurs to form a η³ palladium species. This species can then be reactive towards nucleophile. Depending on the nature of the ligand employed, this can proceed by an ionic or a less reactive neutral complex.
The addition of the nucleophile can proceed in two different ways depending on whether it is a “hard” or “soft” nucleophile. Soft nucleophiles directly attack the allylic carbon which reduces the palladium back to Pd(0); this dissociates readily for the next cycle. Hard nucleophiles tend to attack palladium; the palladium then undergoes reductive elimination to afford the product and Pd(0).

![Scheme 12]

The earliest report of this type of transformation with a carbon nucleophile was published by Tsuji in 1965. Tsuji reported the additions of electrophilic allyl groups from allylpalladium chloride (9) to the enolate forms of ethyl malonate and ethyl acetoacetate proceeded smoothly at room temperature (Scheme 13). These reactions made use of stoichiometric amounts of palladium.

![Scheme 13]

In 1970, Atkins and co-workers reported palladium catalysed allyl transfer for a selection of allylic alcohols, esters and amines. This report was a follow up to a side reaction reported in a previous paper. Allylic alcohols were effectively used as allyl transfer reagents on acetyl acetone with catalyst loadings of 0.5 mol%. Amine reagents such as allyl diethylamine and allyl esters in the presence of tertiary amines were also reacted effectively. The example shown in Scheme 14 suggests the presence of a common π-allyl intermediate for the reaction of both starting materials.
Trost’s investigation of steroid synthesis published in 1976 showed an “overall stereospecific $\text{S}_\text{N}2$ displacement” of allylic acetates with “overall retention of stereochemistry” in these reactions (Scheme 15).\textsuperscript{14,15} This was explained by the occurrence of 2 inversions during the process of the catalytic cycle; the palladium catalyst first attacks from the least hindered face of the olefin (anti-attack) and subsequently the attacking nucleophile adds to the opposite face to the palladium.

\textbf{1.1.2.2 Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation}

Palladium catalysed decarboxylative allylic alkylation (also known as the Tsuji Allylation Reaction) was pioneered by Tsuji in the 1980’s. This useful transformation has the potential to create tertiary and quaternary chiral centres in the $\alpha$-position to a carbonyl. This reaction has been shown to be viable for a range of substrates including allyl enol carbonates,\textsuperscript{16} silyl enol ethers,\textsuperscript{17} allyl $\beta$-ketoesters\textsuperscript{18} and enol acetates\textsuperscript{19} (Scheme 16).
The first examples of the asymmetric Tsuji allylation were published in 2004 by Stoltz and co-workers. After screening a number of chiral ligands using substrate 17, it was discovered that the t-Bu-PHOX ligand (22) afforded the best results. This ligand gave consistently high enantiomeric excesses (79 - 92%) for a range of differently substituted cyclic allyl enol carbonates (Scheme 17).
In 2005, Trost reported similar transformations using a selection of his own ligands. For example, ligand 23 was proven to be the best ligand screened with consistently high enantioselectivities for all substrates (76 - 99% ee). Excellent enantioselectivity was also achieved in the formation of tertiary stereocentres (Scheme 18).

![Scheme 18]

In cases where the formation of more than one enol isomer is possible a mixture of products is obtained. To solve this problem the Stoltz group employed allyl-β-ketoesters to undergo the same transformation as the enol carbonates. These substrates afford the desired enolate regiospecifically in the α-position to the CO₂ leaving group. This variant of the Tsuji allylation has a broad substrate scope. Good yields and high enantioselectivity can be achieved in the presence of acidic functional groups (e.g. nitriles, esters), steric bulk and heteroatoms (Scheme 19). Using this catalyst system yields and enantioselectivity were almost identical to those of products from allyl enol carbonates.

![Scheme 19]
1.2 Ligands in Palladium Catalysed Cross Couplings

1.2.1 Phosphine ligands

Phosphine ligands have been employed in Heck chemistry since its development in the late 1970s. A milestone was reached in the early 1980s by Spencer who showed that the arylation of olefins with activated aryl bromides can be achieved effectively with low catalyst loading and high turnover numbers if carried out in polar aprotic solvents such as DMF and using sodium acetate as a base.\textsuperscript{22} \(\text{P(o-Tol)}_3\) was the ligand favoured for these reactions and since then has remained a favourite ligand for this type of chemistry (Scheme 20).

\begin{center}
\includegraphics[scale=0.5]{Scheme_20}
\end{center}

Scheme 20

Spencer’s work became the basis for further improvements in Heck reaction protocols. His conditions were also tested for Heck reactions of activated aryl chlorides with olefins in 1984. The best results for this were achieved using \(\text{PPh}_3\) and \(\text{P(o-Tol)}_3\) although with modest yields, the best result is shown in Scheme 21.\textsuperscript{23}

\begin{center}
\includegraphics[scale=0.5]{Scheme_21}
\end{center}

Scheme 21

By the late nineties there had been some success in the area of palladium couplings with aryl chlorides.\textsuperscript{24} Probably the most versatile method was published in 1999 by Littke and Fu.\textsuperscript{25} By using tributylphosphine as a ligand and \(\text{CsCO}_3\) as base, yields of up to 84\% were achieved in the Heck couplings of electron neutral and electron rich aryl chlorides (Scheme 22). It was found that other electron rich alkyl and aryl ligands displayed no catalytic activity.
In 2001, this procedure was updated by Littke and Fu to use Cy₂NMe as the base.\textsuperscript{26} Under these conditions the Heck coupling of activated aryl chlorides was achieved at room temperature with yields of up to 87%. Although the coupling of unactivated aryl chlorides still required elevated temperatures, the scope of olefin reactivity was significantly diversified (Scheme 23).

In 2006, Ackermann reported a range of air stable diaminophosphine oxide and diaminophosphine chloride precatalysts that efficiently catalyse a range of transition metal reactions.\textsuperscript{27} Diaminophosphine oxides were found to effectively catalyse the Suzuki reaction with deactivated aryl chlorides under relatively mild conditions (Scheme 24).

These catalysts proved ineffective for Buchwald-Hartwig aminations but their precursors, diaminophosphine chlorides, were shown without precedent to be good precatalysts for Buchwald-Hartwig (Scheme 25), Suzuki, Kumada and α-enolate arylation reactions.\textsuperscript{28}
During NMR investigations it was discovered that in the reaction of diaminophosphine chloride 35 with NaO\text{tBu} led to the formation of diaminooxophine 37. When this is coordinated with Pd(dba)$_2$ is believed to form the active catalytic species.

\[
\text{Scheme 25}
\]

1.2.2 \textit{N}-Heterocyclic Carbenes

Over the last 20 years, \textit{N}-heterocyclic carbenes (NHCs) have emerged as a major new alternative to phosphines as ligands for metal mediated catalysis.\textsuperscript{29} The main functionality of these molecules is a highly reactive divalent carbon atom bearing a lone pair which is stabilized on both sides by nitrogen atoms. These molecules are strong sigma-donors in the same manner as traditional 2 electron donors (phosphines, amines etc.). Some general and related examples of these molecules are shown in Figure 1.

[Diagram of NHC structures]

The stabilizing effect of the nitrogen atoms can be attributed to pi-donation into the out of plane p-orbital and also to the sigma electronegativity effect of the nitrogens (Figure 2).\textsuperscript{30} NHCs are usually stored and handled in the form of imidazolium salts.
which have a long shelf life and are air and moisture stable. Treatment of the corresponding imidazolium salt with base affords the desired carbene in situ.

![Figure 2](image)

**Scheme 26**

NHCs can also be isolated. The first example of this was in 1991 when Arduengo published the crystal structure of an adamantyl substituted NHC 39 (Scheme 26). Decreased reactivity due to steric bulk would have been a major factor in the isolation of this particular compound but it was discovered in later years that large steric bulk is not absolutely necessary to isolate NHCs.

A method of deprotonating imidazolium salts in liquid ammonia using NaH or KNH₂ was developed by Herrmann. The addition of liquid ammonia to THF allows for carbene formation within minutes at temperatures below -30°C. Earlier methods had relied on heating under reflux for up to 24 hours which precluded the isolation of temperature sensitive carbenes. Examples of isolated carbenes are shown in Figure 3.

![Figure 3](image)

There are a selection of reliable routes to synthesize imidazolium salts which allow for a wide range of structurally diverse carbenes to be obtained. Scheme 27 shows the
straightforward one pot synthesis using glyoxal, 2 equivalents of primary amine, formaldehyde and a brønsted acid to produce a symmetrical imidazolium salt. Scheme 28 shows modified routes for the synthesis of an imidazolium salt with differently substituted nitrogen atoms.

\[
\begin{align*}
\text{O} &= \text{O} + R-\text{NH}_2 + \text{H}_2\text{C}=\text{O} + \text{HX} \\
&\quad \rightarrow R-N^+\text{N}^-\text{N}^+R
\end{align*}
\]

Scheme 27

\[
\begin{align*}
\text{O} &= \text{O} + R_1-\text{NH}_2 + \text{NH}_2\text{Cl} + \text{H}_2\text{C}=\text{O} + (\text{H}_3\text{PO}_4) \\
&\quad \rightarrow R_1-N^+\text{N}^-\text{N}^+R_2 + \text{K}^+ + \text{H}_2\text{O} + R_1\text{X} + \text{KX}
\end{align*}
\]

Scheme 28

A harsher but often effective route involves the treatment of thioureas with potassium (Scheme 29) to afford an NHC. The bisamine precursor of the thiourea can be readily synthesised by a double Buchwald-hartwig coupling to 1,2-dibromobenzene or by the successive coupling of two different amines. Another alternative involves the treatment of the bisamine with triethylorthoformate.

\[
\begin{align*}
\text{R}_1-\text{NH} &\quad \xrightarrow{\text{Cl}_2\text{CS} \cdot 2 \text{HCl}} \quad \text{R}_1-\text{N}^-\text{S}^-\text{N}^+R_2 \\
&\quad \xrightarrow{+2 \text{K}} \quad \text{R}_1-\text{N}^-\text{N}^-\text{N}^+R_2
\end{align*}
\]

Scheme 29

A notable preparation involves the vacuum thermolysis of a methoxy derivative. Scheme 30 shows the preparation of 1,3,4-triphenyl-4,5-dihydro-lH-1,2,4-triazol-5-ylidene (40) which was the first commercially available carbene.
NHCs have been shown to bind with practically every transition metal in multiple oxidation states. Metal centres are both stabilised and activated by NHCs due to their specific coordination chemistry. Over the past two decades this competitive field has yielded many successes especially in the area of homogenous catalysis.\textsuperscript{29}

![NHC complexes 41 and 42](image)

The first catalytic results of NHCs were published by Herrmann in 1995.\textsuperscript{38} This report describes the formation of highly stable palladium carbene complexes 41 and 42 followed by their effective use as catalysts for the Heck reaction. A complex formed \textit{in situ} in the reaction mixture was also tested. Catalyst loadings could be lowered to the order of $10^{-3}$ mol\% in the case of aryl bromides (Scheme 31) and 0.1-1 mol\% in the case of aryl chlorides (Scheme 32) to achieve full conversions.

![Scheme 31](image)

![Scheme 32](image)

In 1999 McGuinness and Cavell reported the synthesis of a range of monodentate NHC-palladium complexes with pendant ketone, ester and pyridyl functionalities.\textsuperscript{39} Complex 46 showed the best activity, achieving TONs of up to $1.7 \times 10^6$ for the Heck
reaction of 4-bromoacetophenone and butyl acrylate and a TON of $1.1 \times 10^5$ for the Suzuki reaction of 4-bromoacetophenone and phenylboronic acid.

![Image of Pd complex](image.png)

1.3 Ligands in the Asymmetric Heck Reaction

Compared to extensive studies of the reactivity of ligand-palladium complexes, successful examples of asymmetric palladium catalysed reactions have been limited. The most commonly used ligands are BINAP, its derivatives and phosphinooxazoline (PHOX) ligands.

Pioneering work on asymmetric intermolecular Heck reactions was published in 1991 by Hayashi and co-workers.\textsuperscript{40} Hayashi discovered that high enantioselectivities could be achieved in the reaction of aryl triflates and 2,3-dihydrofuran (47) using (R)-BINAP as a ligand (Scheme 33).\textsuperscript{32-33} The same reaction using aryl iodides had been shown to afford racemic products. This has been rationalised by the ability of the triflate to act as a leaving group allowing the catalyst to form a cationic species. When iodide is used it is believed that the ligand must partially dissociate to allow olefin coordination, leading to a loss in enantioselectivity.

![Scheme 33](image.png)

BINAP has since proven itself to be useful in a multitude of intermolecular couplings and intramolecular cyclisations beyond the scope of this work. It is the dominating ligand in literature reviews on this subject owing to its reliability and versatility on a wide range of substrates.
Phosphinoxazole (PHOX) ligands have also shown their ability to induce high enantiomeric excesses. PHOX ligands have shown one major advantage over BINAP ligands in that they appear to suppress double bond migration. In 1996, Pfaltz and co-workers were the first to show the effectiveness of PHOX by achieving enantiomeric excesses of up to 99% for Heck reactions of vinyl triflates and olefins with little or no double bond migration observed (Scheme 34).\(^4\) The t-Bu-PHOX ligand 22 gave the best enantioselectivity and activity in these reactions.

\[
\text{Scheme 34}
\]

### 1.4 Sulfur Containing Catalyst Systems

Sulfur containing catalyst systems can be considered an area of catalysis which is still underdeveloped. Although there is a significant body of literature pertaining to sulfur containing ligands, phosphorous and nitrogen containing ligands have a clear lead in terms of literature volume and general usage.

The inherent chirality and binding ability of sulfur makes it an attractive target for incorporation into ligands. In many cases, sulfur is used in conjunction with one or more other donor atoms.\(^4\) Often thioethers and sulfoxides are used as pendant stereodirecting groups to direct binding to the desired side of the main donor atom. Thioureas have also seen a surge in interest in recent years as both organocatalysts and ligands in transition metal catalysed chemistry.

#### 1.4.1 Chiral Sulfoxides

Chiral sulfoxides have been used in asymmetric synthesis in two ways. They have been used extensively as chiral auxiliaries, especially in cycloaddition reactions and conjugate additions.\(^5\) They have also found uses as external ligands used in conjunction with lewis acids and transition metal catalysts.\(^6\)
For most sulfoxides, pyramidal inversion (and therefore loss of chirality) does not occur at a significant rate until temperatures of around 200 °C are reached.\textsuperscript{47} For some examples such as benzyl (130 – 150°C) and allyl sulfoxides (50 – 70°C) the temperature of thermal stereomutation occurs at lower temperatures.

There are a range of synthetic methods available to prepare enantiopure chiral sulfoxides in both forms. These include asymmetric oxidation of non-symmetrical sulfides,\textsuperscript{48} optical resolution, resolution by chiral chromatography and the nucleophilic addition of substrates to optically pure chiral sulfinates such as the Anderson procedure.\textsuperscript{49}

\begin{center}
\begin{align*}
\text{S-49} & \xrightarrow{\text{Et-MgI}} \text{S-p-Tol} \\
\text{(S)-49} & \xrightarrow{\text{Et-MgI}} \text{(R)-50}
\end{align*}
\end{center}

Scheme 35

The commonly used Anderson procedure makes use of commercially available chiral menthyl \( p \)-toluenesulfinyl and reacts it with an appropriate organometallic reagent (Scheme 35). Upon displacement of the menthyl leaving group, complete inversion of stereochemistry at the sulfur atom occurs.\textsuperscript{50} This technique can be used to make a large variety of alkyl and aryl sulfoxides with a range of organometallic nucleophiles (e.g. Grignard reagents).

\subsection*{1.4.1.1 Metal-Sulfoxide Bonding}

Since sulfoxides are polarised with a net positive charge on the sulfur atom, transition metals can bind to either the sulfur or the oxygen. Molecular orbital calculations and X-ray spectroscopy have indicated that the sulfoxide structure is a resonance hybrid of three canonical forms (Figure 4). The first two forms are largely predominant.\textsuperscript{46}

\begin{center}
\begin{figure}
\begin{align*}
\text{R-S-R} & \xrightarrow{\text{O}} \text{R-S-O} \\
\text{R-S-R} & \xrightarrow{\text{O}} \text{R-S-O} \\
\text{R-S-R} & \xrightarrow{\text{O}} \text{R-S-O}
\end{align*}
\end{figure}
\end{center}

Theoretically, sulfur-binding should be preferred by “soft” metals according to Hard-Soft-Acid-Base theory; although the hardness or softness of a metal can be affected by the nature of coordinated ligands. The presence of \( \pi \)-electron acceptors to withdraw electron density from a metal centre can also cause a metal to become “harder” and
hence more prone to oxygen binding. Overall there is a delicate balance of electronic and steric factors governing binding mode.

In considering the periodic table it has been observed that there is a general predominance of metal-oxygen bonding for sulfoxides. Soft metals such as Ag(I), Cd(II) and Hg(II) also show a predominance of oxygen binding. This is thought to be because of the lesser $\pi$-bonding abilities of these metals. Metal-sulfur bonding is favoured in $d^6$ and $d^8$ transition metal complexes due to greater $\pi$-back bonding contributions.\textsuperscript{51}

The bonding mode can usually be determined by $^1$H-NMR and IR spectroscopy. In NMR spectroscopy a much larger downfield shift is observed in $\alpha$-protons when sulfur-bonded compared to a very small shift when oxygen-bound. A greater shift is also observed in IR spectroscopy when sulfur binding takes place.

1.4.1.2 Chiral Sulfoxides in Catalytic Asymmetric Hydrogenation Reactions

Chiral sulfoxide ligands have seen some success in the field of asymmetric hydrogenation. The first attempts were reported in 1976 by James and co-workers using (+)-methyl $p$-tolyl sulfoxide as a ligand in ruthenium and rhodium catalysed reductions of olefins.\textsuperscript{52} In a subsequent report, inspired by the use of diop (8) by Kangan and Dang, James and McMillan developed three chiral sulfoxide ligands which they named dios (51), ddios (52) and bdios (53) (Scheme 36).\textsuperscript{53}

![Scheme 36](image)

Although these ligands were obtained as mixtures of up to three diastereomers, a moderate degree of asymmetric induction was achieved. An ee of just over 25% was
achieved in the reduction of itaconic acid to methyl succinic acid (54) using 2.6 mol% of RuCl$_2$(dios)(ddios) under 44 psi of H$_2$ (Scheme 37).

Scheme 37

The use of amino sulfoxide (56) by Kvintovics, James and Heil achieved some more promising results when applied to the asymmetric transfer hydrogenation of unsymmetrical ketones (Scheme 38). Even though the ligand 56 was once again racemic at the sulfur atom an impressive 75% ee was obtained. There has been no study to investigate each diastereomer individually by these groups.

Scheme 38

Using a similar transformation, van Leeuwen’s group compared the effectiveness of a mixture of diastereomers of a chiral sulfoxide ligand against each diastereomer separately (Scheme 39). A chiral co-operative effect was clearly demonstrated between the sulfoxide and the amino acid derived stereogenic centre of their ligand. While the mixture of diastereomers gave an ee of 35%, ligand 57 gave a 65% ee compared to ligand 58 which gave 27% ee.$^{54}$

Scheme 39
1.4.1.3 Chiral sulfoxides in Lewis Acid Promoted Diels-Alder Cycloadditions

In 2001 the Ellman group designed a chiral bis(sulfinyl)imidoamidine (siam) ligand which has provided excellent catalytic activity and asymmetric induction for lewis acid catalysed Diels-Alder cycloadditions (Scheme 40). The ligand 59 is thought to provide such high enantioselectivities because of its unique binding mode. A crystal structure of the copper complex shows a rare M$_2$L$_4$ quadruple stranded helicate. This was not present for another similar ligand 60 which displayed good catalytic activity but poor ee.$^{55}$

\[
\text{Scheme 40}
\]

In the same year, the Hiroi group also investigated the same reaction using chiral sulfoxides bridged by a benzene ring to a chiral oxazoline. In their investigation it was concluded that substituents on both the chiral oxazoline and the chiral sulfoxide were important for asymmetric induction as to change either group resulted in a loss of ee. Ligand 62 provided the best results. The choice of lewis acid was also important; MgI$_2$ provided significantly higher ee than any other lewis acid tested under the conditions (Scheme 41).$^{56}$

\[
\text{Scheme 41}
\]
1.4.1.4 Chiral Sulfoxides in Asymmetric Catalytic Allylic Substitution Reactions

The Williams group has shown chiral sulfoxides bridged to oxazolines to be highly efficient ligands in the asymmetric allylic addition of dimethyl malonate (63) to 1,3-diphenyl-1-propenyl-3-acetate (64) (Scheme 42). Ligands employed and results are shown in Table 1.57

\[
\text{MeO} \quad \text{O} \quad \text{OMe} + \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} + \quad \text{Ph} \quad \text{Ph} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me}
\]

\[\text{Scheme 42}\]

Once again it was shown that there is a relationship between the two chiral centres, the comparison of the two diastereomers 66 and 67 shows a significant difference in both catalytic activity and asymmetric induction. Interestingly ligands 68 and 69 also gave moderate enantioselectivities, these are the first examples of chiral sulfoxides independently controlling the enantioselectivity of a palladium catalysed allylic substitution.

Similar levels of enantioselectivity to compound 66 were observed from equivalent sulfides, the author suggests that the stereochemistry of the sulfides can switch to the preferred configuration upon binding to palladium. No catalytic activity was observed from the equivalent sulfones, which implies that binding is required at the sulfur atom in these reactions.

**Table 1: Performance of chiral sulfoxide ligands in the asymmetric allylation of dimethyl malonate**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>55</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>49</td>
<td>60</td>
</tr>
</tbody>
</table>
1.4.2 Thioureas as Ligands

Thioureas have been reported as ligands for Ru-, Rh-, Ir- and Pd-catalysed reactions. In 1997 Lemaire and co-workers first reported the asymmetric transfer hydrogenation of prochiral ketones using chiral thiourea derived catalysts achieving enantiomeric excesses of up to 94% (Scheme 43).

Scheme 43

Since 2000, there have been a number of reports from the Yang group describing a selection of carbonylative annihilations to afford variously substituted benzofurans and flavones. In a report from 2005 they describe the synthesis of a triple ring component of micrandilactone A (73) wherein two of the key steps are a Co-thiourea Pausen-Khand reaction followed by a Pd-thiourea carboylative annulation (Scheme 44).

Scheme 44

Thiourea 72 was first reported in 2004 when it was applied to the Heck and Suzuki coupling of arenediazonium salts. Reactions were stirred for 4 hours with no added base under aerobic conditions and moderate to good yields were obtained (Scheme
The best results were obtained with strongly electron withdrawing aryl-NO$_2$ groups on the arenediazonium salt.

\[
\begin{align*}
\text{Ar-N}_2\text{BF}_4 & + \quad \begin{array}{c}
\text{R} \\
\text{or} \\
\text{or}
\end{array} \\
\text{Ar}^{+}-\text{B(OH)}_2 & \quad \xrightarrow[72 \ (1 \text{ mol\%})]{\text{Pd(OAc)}_2 \ (1 \text{ mol\%}),} \\
\text{MeOH, 4 h, r.t.} & \quad \rightarrow \\
\text{R} = \text{Ar}, \text{COOME} & \quad \text{26-98\% yield}
\end{align*}
\]

Scheme 45

Dan Yang soon after reported the use of sterically bulky thioureas as air and moisture-stable ligands for Pd-catalysed Heck reactions of aryl halides (Scheme 46). These catalysts achieved TONs of up to 500,000 for the reaction of iodobenzene and methyl acrylate. The Heck reaction of 2-nitrochlorobenzene and styrene was driven to completion using molten Bu$_4$NBr as an ionic solvent in the presence of 1 mol\% Pd-thiourea catalyst.

\[
\begin{align*}
\text{Ar-X} & + \quad \begin{array}{c}
\text{R} \\
\text{or}
\end{array} \\
& \quad \xrightarrow[\text{Pd(dba)$_2$, 74}]{\text{Base, } >100^\circ \text{C}} \\
& \quad \rightarrow \\
\text{X} = \text{I, Br, Cl} & \quad \text{R} = \text{Ph, CO$_2$Me, CO$_2$Bu}
\end{align*}
\]

Scheme 46

1.5 Investigations into the Nature of Palladium Catalysts and the Effect of Additives

When a catalyst system is initially investigated, studies should be performed in order to properly identify the active species. In many cases, the nature of the active species is not clearly established. This is especially important in palladium catalysis, as the ligand-metal species in certain cases may merely be acting as a precatalyst for heterogeneous Pd(0) nanoparticles.

In 1982, Crabtree published guidelines on how to distinguish between homogenous and heterogeneous catalysts. Dibenzo[a,e]octatetraene (75) was used as a selective poison for homogenous catalysts. This is a rigid “tub-shaped” molecule which binds strongly to platinum group metal complexes and not to their metal surfaces. This was used in conjunction with the “mercury drop test” in which an excess of mercury is used to selectively poison heterogenous catalysts.
In 2003, De Vries and co-workers compared the reaction rates of a PCP pincer catalyst 76 against that of ligand free Pd(OAc)$_2$ at low concentrations. This pincer catalyst was shown to perform at a very similar rate to that of Pd(OAc)$_2$ for the Heck reaction of butyl acrylate and bromobenzene. Further ES-MS experiments also confirmed the lack of any phosphine bound palladium in the reaction mixture that was supposedly catalysed by the palladacycle. This led the authors to conclude that both reactions were catalysed by the same ligand free monomeric palladium species.

In the same report investigations were made into the effect of “homeopathic” catalysis in relation to the Heck reaction. That is the phenomenon that leads to higher TOF by lowering the concentration of catalyst in solution. During the Heck reaction of aryl bromides oxidative addition is believed to be the predominant rate determining step, therefore the majority of resting palladium in the cycle is Pd(0) which is liable to form clusters which then precipitate out of solution, eventually ending the reaction. At lower concentrations the rate of oxidative addition can be greater than that of clustering which has a higher rate order. Under the conditions shown in the optimal loading was found to be 0.01-0.1 mol%. Above and below this range reaction rates were impractically slow.

In 2004, Eberhard published a study on the nature of four PCP pincer catalysts in relation to the Heck reaction. A combination of kinetic studies, the mercury drop test, NMR studies and quantitative poisoning experiments were used. All the tests performed indicated that metallic palladium(0) played a significant role as the active catalytic species. More labile catalysts (which degrade easily) are thought to contribute more significantly to this effect.
1.5.1 The Use of Quaternary Ammonium Salts in the Heck Reaction

The beneficial effects of quaternary ammonium salts was first noticed by Jeffery and in further publications the addition of these salts to Heck reactions has been referred to as Jeffery’s conditions. There are a number of beneficial effects gained from these salts which work in conjunction with each other. They act as phase transfer agents which solubilise bases that would normally be sparingly soluble in organic solvents and likewise solubilise organic substrates normally insoluble under aqueous conditions.

Halides, acetate and some other anions can also improve reactivity by interaction with palladium. The formation of a more electron rich anionic palladium species can increase the rates of some steps of the catalytic cycle. Chloride and bromide anions can also enter the coordination sphere of underligated Pd(0) species, helping to prevent clustering. Ion exchange on the palladium species may also increase reactivity. For example exchange of iodide for chloride followed by dissociation may open up a cationic pathway (Scheme 48).1

![Scheme 48]

Overall the effects of tetrabutyl ammonium salts are complex and not entirely understood; no single effect can be attributed in any given reaction. The positive results, however, are undeniable. The most in-depth studies have been performed by Jeffery.70-73 The effect of different salts varies depending on reaction conditions, especially whether water is present and the choice of base employed.

Tetrabutylammonium chloride generally provides the most consistently positive results; the results obtained by use of other salts can be more variable depending on conditions. Under strictly anhydrous conditions tetrabutylammonium hydrogensulfate (generally considered ineffective) can be just as effective. When used in the presence of an inorganic base the presence of water is required to gain any advantage. The effect is lesser when an amine base is used but conditions can be optimised.72
Larock and Babu were the first to use promoter salts in a practical sense beyond model reactions.  

A range of heterocyclic products including indoles, oxindoles (Scheme 49), indolines, quinolines, isoquinilines and isoquinilones were synthesised. All reactions were performed under milder conditions with higher yields than any similar previous reactions and in some cases the products had not been synthesised by palladium catalysed cyclisation before.

\[
\text{Scheme 49}
\]

1.6 The Use of Microwaves in Organic Synthesis

The domestic use of microwaves dates back just over 60 years but it is only in the last 25 years that the effects of microwave irradiation have been exploited in organic synthesis. In 1986 a number of papers were published demonstrating shortened reaction times for some routine organic reactions. In one of these reports, Gedye compared the rates of some simple organic reactions performed by classical means to the rates obtained in a domestic microwave. Each reaction produced comparable or greater yields with hugely increased reaction rates. Gedye also investigated the effect of pressure in the synthesis of 4-cyanophenyl benzyl ether by using different sized sealed reaction vessels and found that the reaction rate was directly proportional to the pressure developed inside the container.

The first commercial microwave specifically designed for chemical synthesis was introduced in 2000. Prior to this, reactions were carried out in domestic microwaves which were not designed to create a homogenous field suitable for synthesis and therefore produced unpredictable results. The introduction of scientific microwaves also allowed greater control and monitoring of temperature and pressure.

There are many effects that take place that contribute to the increased efficiency. These include the ability of the microwaves to heat the entire reaction volume homogenously (as opposed to slow introduction of heat from the surface of the vessel)
and the ability to heat solvents above their normal boiling points (superheating); especially observable with polar media.\textsuperscript{76}

It is also believed that the electromagnetic radiation is stabilising towards polar intermediates and transition states.\textsuperscript{77} This would favour reactions involving such intermediates and may open up polar synthetic routes in otherwise competitive reactions.

A report by Kappe and co-workers in 2009 detailed the effects of using silicon carbide (SiC) reaction vessels under microwave conditions.\textsuperscript{78} SiC is a strongly microwave absorbing, semiconductive ceramic material which when irradiated produces ohmic heat.\textsuperscript{79} Due to the strong microwave absorbing ability of this material, it was hypothesised that it could be used to shield the material contained in the vessel from microwave radiation while heating it, therefore separating thermal and non-thermal heating effects.

This effect was confirmed by comparison of the rate of heating of hexane ($\tan\delta = 0.02$) to that of the strongly absorbing EtOH ($\tan\delta = 0.941$) in different vessels. In a standard Pyrex vessel the rate of heating was seen to correspond to the microwave absorbivity of the solvent. In SiC vessels the heating rates of the solvents were remarkably similar and did not correlate to microwave absorbivity; they appeared to correlate only to specific heat capacity, viscosity and heat transfer coefficients.

The results of a range of reactions were also compared between the two types of vessel. In each case practically identical results were achieved in terms of conversion, purity profile and product yields. This confirms that for the reactions tested only bulk temperature effects are responsible for reaction enhancements. A selection of examples is shown in Scheme 50.
1.6.1 The use of Microwaves in Palladium Catalysed Reactions

As for many areas of synthesis microwave chemistry has lent itself well to palladium catalysis. It has been shown time and again that the use of microwaves not only allows the chemist to drastically shorten reaction times but also allows for significantly lower catalyst loadings to be employed.

The use of aqueous elemental palladium as a catalyst for Heck and Suzuki couplings with ultra low loadings has been reported by Arvela and co-workers. Palladium concentrations of between 50 ppb and 5 ppm were used under microwave conditions. The focus of this work by Arvela was also to investigate the scaling up of microwave reactions to multi gram scale using an automated batch stop flow microwave apparatus. Using this system of automatically pumping reagents in batches into the reaction vessel, quantities of approximately 18 grams of Suzuki coupled product (Scheme 51) and 20 grams of Heck coupled product (Scheme 52) can be achieved in approximately 2½ hours with minimal workup procedure.
Dawood has reported the microwave assisted Suzuki and Heck cross-couplings of aryl chlorides and bromides under aqueous conditions using benzothiazole Pd(II) precatalysts.\textsuperscript{81} Both a homogenous catalyst \textsuperscript{84} and its immobilised form \textsuperscript{85} were employed with excellent results under microwave conditions (Scheme 53).
1.7 The Oxindole Alkaloids

The oxindole core is a structural motif common to a large family of naturally forming alkaloids. This core is naturally derived from tryptamine. The first examples of oxindole alkaloids were extracted from the roots of *Gelsemium sempervirens* (wild yellow jasmine). Since then, many other examples have also been isolated from plants such as *Aspidosperma, Mitragyna, Ourouparia, Rauwolfia* and *Vinca*. Many oxindole alkaloids are characterised by a unique spiro-fused pyrrolidine ring at the 3-position. The architecture of these compounds is often associated with significant biological activity which renders these compounds to be targets of significant synthetic interest. Figure 6 displays some representative examples of oxindole alkaloids.

![.spirotryprostatin B](image1.png) ![strynofoline](image2.png) ![welwistatin](image3.png)

87 spirotryprostatin B 88 strynofoline 89 welwistatin

![horsiline R = MeO](image4.png) ![coerulescine R = H](image5.png) ![alstonisine](image6.png)

90 horsiline R = MeO 91 coerulescine R = H 92 alstonisine

Figure 6

1.7.1 Synthesis of Oxindoles

In this section a selection of methodologies for the synthesis and functionalisation of oxindoles from literature will be reported. This will also include reports related to the induction of stereochemistry at the 3-position. Previous syntheses of esermethole, which is commonly derived from an oxindole intermediate, will also be reported.
1.7.1.1 Synthesis of Oxindoles by Aryne Cyclisation

Some of the earliest investigations of aryne intermediates in heterocyclic synthesis by Hrutford and Bunnett involved the preparation of 3-acetyloxindole (94) from acetoaceto-\textit{o}-chloroanilide (93) (Scheme 54).\textsuperscript{85} This was achieved by treatment of the anilide with potassium amide in liquid ammonia.

![Scheme 54](image)

In a comprehensive study of ring closure via aryne intermediates by Bunnett and co-workers, a selection of secondary and tertiary anilides were screened using this procedure.\textsuperscript{86} In the case of secondary anilides it was discovered that a sufficiently strong electron withdrawing group was required in the $\alpha$-position to increase delocalisation of charge from the deprotonated nitrogen. It was believed that delocalisation of this charge into the anilide ring lowered the ring’s acidity, preventing formation of the aryne. In some cases oxygen could also act as the nucleophile forming a benzoxazole product. The reaction yield of $N$-methyl tertiary anilides also proved to be variable depending on the substrate (Scheme 55).

![Scheme 55](image)

In 1991, Overman reported a method of synthesising 3-acyl-3-alkyloxindoles by treatment of 3-(silyloxy)acryloyl-2'-haloanilides with LDA (Scheme 56).\textsuperscript{87} Having found that the base-promoted cyclisation of 95 did not proceed in preparatively useful amounts, it was reasoned that a silyl ether derivative 96 would provide a more nucleophilic enolate. The cyclisation proceeded in 65% yield; the product 97 could
then be cleanly hydrolised to give the desired 3,3-spirooxindole ketone 98. Reported examples also include substrates of varying ring size and an acyclic substrate.

\[
\begin{align*}
\text{Scheme 56}
\end{align*}
\]

1.7.1.2 Synthesis of Oxindoles by Enolate Arylation

A report by Hartwig and co-workers published in 2001 details improved palladium catalysts for the synthesis of oxindoles by amide α-arylation. Some of the best results achieved employed Pd(OAc)\(_2\) as the palladium source and P(Cy)\(_3\) as the ligand. Notable examples include the cyclisation of aryl chloride substrates (Scheme 57) and also the combined intra- and intermolecular Pd-catalysed arylation of amides (Scheme 58).

\[
\begin{align*}
\text{Scheme 57}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 58}
\end{align*}
\]
More recently, Marsden and co-workers has reported the use of a similar catalyst system for the synthesis of 3-alkoxy-3-aryloxindoles.\textsuperscript{89} By using microwave irradiation reaction times were cut to only ten minutes (Scheme 59).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.8\textwidth]{scheme59.png}};
\end{tikzpicture}
\end{center}

Scheme 59

Later that year, the Marsden and Kündig published a communication on the enantioselective syntheses of 3-alkoxy- and 3-amino-oxindoles in high yield and high ee by taking advantage of chiral-N-heterocyclic carbene ligands.\textsuperscript{90} The best performing ligand was a new ligand \textbf{104} shown in Scheme 60.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.8\textwidth]{scheme60.png}};
\end{tikzpicture}
\end{center}

Scheme 60

The Marsden group has also reported another effective palladium-carbene catalyst system which has been shown to catalyse cyclisation to quaternary-3-aminooxindoles with only 0.1 mol% catalyst loading.\textsuperscript{91} This is the lowest catalyst loading used to effectively form oxindoles to date (Scheme 61).
In 2010, the Dorta group reported the highly chemo- and enantioselective synthesis of 3-allyl-3-aryl oxindoles by means of a direct palladium-catalysed α-arylation of amides.\textsuperscript{92} This was achieved by the introduction of a new bulky NHC-palladium catalyst 108. This catalyst provided excellent reactivity at room temperature while also affording the desired products with high enantioselectivity (Scheme 62). As opposed to other catalysts screened, this catalyst afforded only trace amounts of the competing Heck cyclisation products.
1.7.1.3 Synthesis of Oxindoles using the Heck Reaction

Having reported one of the first enantioselective intramolecular Heck reactions in 1989, the Overman group maintained a significant focus on the use of the Heck reaction for the synthesis of quaternary stereocentres. The synthesis of oxindoles as possible precursors to alkaloid natural products has constituted a major component of this work.\(^93\)

During exploratory investigations published in 1998, Overman and co-workers discovered that spirooxindoles can be synthesised with good enantioselectivity by the same enantiomer of a chiral diphosphine ligand depending on the choice of HI scavenger. In the case of substrate 109 the use of Ag\(_3\)PO\(_4\) as an additive yielded the (S)-spirooxindole in 71\% ee. The use of the amine base PMP yielded the (R)-enantiomer in 66\% ee (Scheme 63).\(^94\) This phenomenon has for the most part been limited to anilides, with little or no stereoselectivity observed in the absence of the amide carbonyl.

In 2000, Overman and Rosen were able to apply these conditions to the synthesis of spyrotryprostatin B (87) in a tandem Heck-\(\eta^3\)-allylpalladium capture process.\(^95\) By inducing a stereocontrolled Heck reaction in substrate 111 it was possible to generate a \(\eta^3\)-allylpalladium intermediate 112. Subsequent nucleophilic attack of the proximal nitrogen should proceed to form the correct diastereomer of the product as a result of the induced configuration of the intermediate (Scheme 64).
In practice it was possible to synthesise the frameworks for 18-epi-spirotryprostatin B (115) and 3-epi-spirotryprostatin B (117) from substrate 113 in 6:1 d.r. by employing opposite enantiomers of BINAP (Scheme 65).

It was believed that the (E)-isomer of the diene would afford the correct configuration to produce spirotryprostatin B but it was found that 18-epi-spirotryprostatin B (109) was once again formed due to rapid isomerisation of the double bond. After extensive screening, it was found that by using (o-tol)_3P as a ligand in THF that this isomerisation could be avoided. However, due to lack of stereocontrol, chromatographic separation of the two isomers 87 and 121 was required (Scheme 66).
In 2002, Grigg and co-workers reported the synthesis of spiro-oxindoles by means of a bimetallic [Pd(0)/Ag(I)] catalytic intramolecular Heck-1,3-dipolar cycloaddition cascade reaction.\textsuperscript{96} The methodology first employs an intramolecular Heck reaction which generates oxindole \textit{123 in situ}. This compound is known to be somewhat unstable,\textsuperscript{97} but the mild conditions employed and also the removal of the product by the cascade reaction counteracts this problem. The subsequent Ag(I) catalysed 1,3-dipolar cycloaddition of an imine (which is converted to an azomethine ylide by the catalyst) leads to spiro-oxindole formation with excellent regioselectivity and good stereoselectivity. (Scheme 67)

Scheme 66

\textbf{1.7.1.4 Copper mediated Synthesis of Oxindoles}

In 2009, the Taylor group first reported a novel copper mediated synthesis of oxindoles.\textsuperscript{98} Although initially investigations were aimed at a Pd(II) catalysed route, it was discovered that Cu(OAc)$_2$.H$_2$O (which was originally thought to act as an oxidant to regenerate Pd(II)) was actually the main contributor to the reaction. A variety of EWG containing oxindoles were synthesised in high yield.
In an extension of this report, similar reaction products were treated with acid to afford a range of singly substituted 3-alkyl oxindoles (Scheme 69).\(^9\)

\[
\begin{align*}
\text{Scheme 68} & \\
\text{In 2010, more efficient conditions were described. It was discovered that by refluxing the reaction mixture in mesitylene under aerobic conditions that excellent yields could also be achieved using only 5 mol\% of Cu(OAc)\(_2\).H\(_2\)O without additional base. (Scheme 70)}^{10}
\end{align*}
\]

1.7.1.5 Induction of Stereochemistry in Oxindoles by O/C Acyl Migration

The Fu group has been pursuing the development of chiral DMAP and 4-(pyrrolidino)pyridine (PPY) derivatives and their application in enantioselective nucleophile catalysed transformations. One report from 2003 describes the catalytic enantioselective synthesis of oxindoles and benzofuranones that bear a quaternary stereocentre at the 3 position.\(^10\) This was achieved by means of the ferrocenyl PPY derivative 132 catalysed rearrangement of O-acylated compounds to form a C-acylated compound (Scheme 71). This was the first enantioselective report of such a transformation.
In 2005, the Vedejs group published a report on “enantioselective TADMAP catalysed carboxyl migration reactions for the synthesis of stereogenic quaternary carbon”. In a similar transformation to that of Fu, Vedejs employed a more accessible DMAP derived catalyst 134 to achieve high enantioselectivities for oxindoles and a range of other synthetically useful products. (Scheme 72)

In 2009, the Richards group also reported moderately good results for the formation of oxindoles containing a quaternary stereogenic centre by catalytic O/C-carboxyl rearrangement. Rearrangement was achieved by employing a cobalt metallocene-pyrrolidinopyridine catalyst 137. (Scheme 73)
1.7.1.6 Oxidative Rearrangement to Oxindoles

N-bromosuccinimide has been shown to facilitate the oxidative rearrangement of tetrahydro-β-carbolines to oxindoles. Other oxidants such as osmium tetroxide, lead tetraacetate and sodium tungstate have also been used for the same transformation but NBS has proven to be a more popular choice.

In 1994, Borshberg and co-workers developed this technique to prepare (-)-horsfiline for the first time (Scheme 74). Substrates were prepared by performing a Pictet-Spengler reaction on L-tryptophan derivatives combined with the appropriate aldehyde. It was hoped that the chiral centre derived from L-tryptophan would be the main contributor to diastereoselectivity but it was found that results could be highly divergent depending on the nature of substitution on the piperidine nitrogen atom.

Scheme 74
Using similar techniques, Danishefsky and co-workers have also reported the spirorearrangement of tetrahydro-β-carbolines to oxindoles as a key step in their total synthesis of spirotryprostatin A (142) (Scheme 75).

\[ \text{Spiro}[\text{pyrrolidine}-3,3'-'\text{oxindole}] \]

\[ \text{(Scheme 75)} \]

1.7.1.7 Dipolar cycloaddition reactions of Oxindoles

Grigg and co-workers were the first to use a 1,3-dipolar cycloaddition to achieve the spiro[pyrrolidine-3,3'-oxindole] skeleton.\(^{108}\) This reaction, reported as “decarboxylative transamination”, takes advantage of the formation of azomethine ylides by the combination of α,α-disubstituted amino acids and carbonyl compounds. The reaction of azomethine ylides with oxindolin-3-ylidienes allows the spiro[pyrrolidine-3,3'-oxindole] motif to be achieved (Scheme 76). Alternatively, amino acids can be reacted with isatin to form an ylide which can in turn be reacted with a dipolarophile (Scheme 77).

\[ \text{Scheme 76} \]
The Williams group has employed this methodology in their total synthesis of spirotryprostatin B. Using this approach they were able to synthesise both enantiomers and also prepare analogues of the natural product. The spirooxindole core was constructed by combining morpholine 145, oxindoylideneacetate 146 and aldehyde 147. The product 148 was formed as a single diastereomer in 82% yield (Scheme 78).
1.7.1.8 Alkylation of Oxindoles by Nitroolefination

Assymetric nitroolefination has been proven to be a useful tool in the synthesis of chiral spirooxindoles. This technique was first reported by Fuji in 1986 wherein it was shown that enolates can react with chiral nitro-enamines to afford chiral quaternary stereocentres with high enantioselectivity.\(^{110}\) This addition-elimination process was later effectively employed in the synthesis of (\(-\))-horsfiline \(90\) (Scheme 79)\(^{111}\) and spyrotryprostatin B \(87\) (Scheme 80).

\[\text{Scheme 79}\]

1.7.2 Syntheses of Esermethole

The hexahydropyrrolo[2,3-b]indoline ring system is found in a number of indole alkaloids. These alkaloids are associated with strong biological properties. Alkaloids such as phenserine (154) and its derivatives have proven themselves to be potent in the treatment of Alzheimer’s disease.\(^{112}\) Notably the structurally related physostigmine (155) is commercially available and is effective for a selection of other clinical uses.\(^{113-115}\)
Esermethole (156) is an important precursor to these compounds and thus there has been much interest in its synthesis. Effective introduction of the quaternary stereocentre at the c3-a position remains a common focus among published reports. In the vast majority of reported syntheses stereochemistry is induced at the 3- position of an oxindole; this is then manipulated further to form the correct ring system.

The Douglas group have developed a palladium catalysed asymmetric cyanoamidation which can enantioselectively afford oxindoles bearing a quaternary stereocentre. The resulting pendant nitrile group is highly versatile and synthetic utility of these products was highlighted by the synthesis of (+)-horsline, (-)-coerulesine and (-)-esermethole (Scheme 81).
Valoti and co-workers devised a synthesis involving the asymmetric alkylation of racemic oxindoles by employing chiral alkylating agents. A chloroacetyl derivative of 1-phenylethylamine 160 was reacted with oxindole 161 under basic conditions to afford the correct diastereomer (162) as the major product. The minor diastereomer 163 was easily separated by chromatography. Cleavage of the chiral auxiliary by hydrogenation followed by treatment with LiAlH₄ afforded (−)-esermethole in > 99% ee (Scheme 82).

Scheme 82
Another synthesis of both enantiomers of esermethole by Valoti and co-workers relies on the chemical resolution of racemic primary amine-bearing oxindole 1. This is achieved by treating the hydrochloride salt of the racemate with KOH and optically pure tartaric acid in order to precipitate the desired enantiomer as the tartrate salt. Once the free amine has been isolated only two further steps are required to afford either enantiomer of esermethole in greater than 99% ee. (Scheme 83)

The Overman group developed a dialkylation of an enantiopure tartrate derived ditriflate 168 in order to induce chirality at the 3 position of oxindoles. It was expected that upon reacting oxindole enolates with 168 that a particular C₂ diastereomer would be obtained as the major product. Using a variety of differently substituted oxindoles, conditions were investigated and optimised to obtain this diastereomer in the highest yield. Recrystallisation of the mixture of major and minor diastereomers afforded the desired pure diastereomer in good yield.
For the synthesis of esermethole the synthesis began with oxindole 167. The desired dialkylation product 169 was afforded with a d.r. of 89:11 against undesired diastereomers. The purified product was then treated with p-TSA to form a vicinal diol. Subsequent treatment with NaIO₄ resulted in an oxidative cleavage to form aldehyde 170 with an enantiomeric excess of over 99%. Condensation of the aldehyde with methylamine and treatment with LiAlH₄ afforded (−)-esermethole 156 in excellent yield. Esermethyl was then converted to (−)-phenserine 154 in two further steps (Scheme 84).
The Overman group also achieved the synthesis of compound 170 by means of the asymmetric Heck reaction.\textsuperscript{119, 120} By applying the conditions shown in Scheme 85 it was possible to cyclise substrate 171. Hydrolysis of the silyl enol ether 172 afforded 170 in 84% overall yield and 95% ee. A single recrystallisation afforded the enantiopure product. Conditions shown in Scheme 84 were once again used to convert 170 into (-)-esermethole.

Scheme 85
Chapter 2: Results and Discussion

There are a wide number of reports utilising a 1,3-nitrogen skeleton as a basis for catalyst/ligand design; for example, diaminophosphines (Section 1.2.1) \(N\)-heterocyclic carbenes (Section 1.2.2), and thioureas (Section 1.4.2). Indeed, 1,3-amines and imines have themselves been reported as ligands and catalysts. Traditionally, phosphine ligands have been used to stabilise reactive palladium intermediates, and excellent results have been reported for Pd-catalysed Mizoroki–Heck reactions. The air-sensitivity of these types of ligands, however, precludes their use in a variety of synthetic applications. Therefore, the development of phosphine-free palladium catalysis is a topic of enormous interest, with thioureas being amongst the most effective systems to date.

![Thiadiazolidines and Thiadiazolidine Oxides](image)

There are very few reports regarding the synthesis of structurally related thiadiazolidines \(173\) or thiadiazolidine oxides \(174\). The majority of reports regarding thiadiazolidine 1,1-dioxides (\(175\)) relate to their pharmacological properties.\(^{121, 122}\) The zwitterion \(176\) has been used in a Mitsunobu-type reaction\(^{123}\) and \(177\) has been proposed in connection with Oppolzers sultam model.\(^{124-127}\) Thiadiazolidine 1,1-dioxides have also been reported as useful polar aprotic solvents\(^{128}\) and as key intermediates for the synthesis of constrained peptides.\(^{129-131}\)

We were particularly attracted to the thiadiazolidine oxides (\(174\)) as we postulated that they may be interesting and useful ligands for metal-catalysed reactions. The creation of a chiral centre at the sulfur atom was also an appealing target. If the sulfur atom were to bind directly to metal this would theoretically lead to increased chiral information being projected and possibly lead to high enantioselectivity in catalytic reactions.
2.1 Investigation of thdiazolidine and related compounds as ligands

2.1.1 Initial investigations

Work began by testing the hypothesis that thdiazolidine-1-oxides can be used as ligands in palladium mediated processes. This began with the preparation of mesityl derived thdiazolidine oxide \textbf{180}. It was prepared quite easily in two steps. Mesityl amine and glyoxal were stirred without solvent to form a bright yellow bis-imine which was subsequently reduced to the bis-amine \textbf{178} using sodium borohydride in ethanol. The bis-amine was added to a solution of triethylamine/ether and treated with thionyl chloride to afford the thdiazolidine 1-oxide \textbf{179} in excellent yield (Scheme 86). The structure was confirmed by X-ray crystallography (Figure 8).

Experimentation began by screening a range of palladium sources using the Heck reaction of iodoanisole and styrene as the test system (Table 2). Each source afforded excellent yields confirming the hypothesis that this class of compound may be a viable ligand for palladium catalysis. Since very little difference was observed between the
effectiveness of each palladium source, \( \text{Pd}_2(\text{dba})_3 \) was chosen as the standard palladium source due to availability. The reactions were carried out by stirring the ligand with the palladium source in DMF for an hour, followed by addition of base and the reagents with subsequent microwave irradiation.

**Table 2: Palladium screening**

<table>
<thead>
<tr>
<th>Entry</th>
<th>“Pd Source”</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Pd(dba)}_2 )</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Pd}_2(\text{dba})_3 )</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Pd(OAc)}_2 )</td>
<td>95</td>
</tr>
</tbody>
</table>

For convenience, stock catalyst solutions were prepared. Initially when the \( \text{Pd}_2(\text{dba})_3 \)-ligand solutions were prepared they would take on a dark red colour. At this stage the solutions displayed no catalytic activity. After a sufficient amount of stirring they would gradually change to a bright yellow colour to show that it is in the active form. When making larger stock solutions it was observed that the activation times could be significantly longer with significant amounts of palladium black precipitating in the process. It was found that the activation times could be improved by exposing as much of the surface area of the solution to air as possible while stirring vigorously. The Pd black could simply be filtered from the solution or allowed to settle to the bottom of the container while the solution is syringed from the surface. It was later discovered that by doubling the number equivalents of ligand that Pd black precipitate could be eliminated from the stock solution.

A significant advantage to the use of these thiaiazolidine 1-oxide systems is that the ligand/palladium complex has proven itself to be extremely air and moisture stable in solution. Stock solutions of the complex can be left exposed to air on a bench for weeks and still retain all of their activity. This is in contrast to a range of commonly
used phosphine ligands which must be prepared and used under highly inert conditions. Also it is worth noting that although these compounds contain sulfur they are odourless.

Experiments to optimise the microwave reaction conditions showed that Heck reactions could be effectively carried to completion at 150°C within 10 minutes of irradiation (Table 3). Good yields were obtainable within 1 minute at 200°C but it was decided to run further reactions for 10 minutes at 200°C for convenience and reliability.

Table 3: Optimisation of microwave conditions for Heck reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>10</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>10</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>1</td>
<td>85</td>
</tr>
</tbody>
</table>

Although the vast majority of reactions were carried out under microwave irradiation, it was also confirmed that these reactions can take place under more conventional thermal conditions. The Heck reaction of butyl acrylate and iodobenzene achieved completion within 2 hours using standard reflux conditions (Scheme 87).
Using the optimised microwave conditions, a variety of substituted aryl iodides and olefins were screened. The reaction proved tolerant to both electron donating and electron withdrawing groups located on both the aryl iodide and a range of styrenes (Scheme 88). The use of methyl acrylate as one of the substrates reacted unreliably giving varying yields each time it was reacted with iodobenzene. One possible reason for this is the ability for the acrylate to polymerise with itself hindering the desired reaction.

Scheme 88
Attention was turned towards the effectiveness of the ligand system over a range of catalyst loadings. The Heck reaction of 4-iodoanisole and styrene was chosen so that conversions could be calculated by $^1$H NMR comparison of the starting material methoxy peak with that of the product. Experiments have shown that the system was quite effective at extremely low catalyst loadings, for loadings as low as 0.0002 mol% the reaction times could be extended to give conversions >95%.

Table 4: Catalyst loading study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (mol%)</th>
<th>Lig, (mol%)</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$2 \times 10^{-1}$</td>
<td>$4 \times 10^{-1}$</td>
<td>10</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>$2 \times 10^{-2}$</td>
<td>$4 \times 10^{-2}$</td>
<td>10</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>$2 \times 10^{-3}$</td>
<td>$4 \times 10^{-3}$</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>$2 \times 10^{-3}$</td>
<td>$4 \times 10^{-3}$</td>
<td>30</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>$2 \times 10^{-4}$</td>
<td>$4 \times 10^{-4}$</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>$2 \times 10^{-4}$</td>
<td>$4 \times 10^{-4}$</td>
<td>60</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>$2 \times 10^{-5}$</td>
<td>$4 \times 10^{-5}$</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>$2 \times 10^{-5}$</td>
<td>$4 \times 10^{-5}$</td>
<td>10 + 30</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>$2 \times 10^{-5}$</td>
<td>$4 \times 10^{-5}$</td>
<td>10 + 30 + 30</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>$2 \times 10^{-5}$</td>
<td>$4 \times 10^{-5}$</td>
<td>60</td>
<td>18</td>
</tr>
</tbody>
</table>
Following the work on aryl iodides, Heck reactions were attempted using aryl bromides as substrates (Table 5). The conditions used for aryl iodides were found to be unsuitable for aryl bromides. The solvent was changed from DMF to N-methylpyrrolidinone (NMP) and sodium acetate was used as the base. Some reactions performed at 200 °C were prone to excess pressure build-up inside the sealed vials used for irradiation. In these cases, the reaction temperatures were reduced to 160 °C. Pd(dba)$_2$ was used as the palladium source due to availability and reaction times were extended to 30 minutes.

Over the course of the initial experiments with the Heck reactions of aryl bromides, only two were ever safely brought to 200 °C without problems; namely the reactions of bromobenzene with styrene (Table 5, entry 1) and butyl acrylate (Table 5, entries 4 and 5). Any attempts to bring reactions involving substituted aryl bromides, substituted styrenes or methyl acrylate to 200 °C in the microwave would result in shattering of the vial. Lowering of the temperature to below 170 °C would prevent shattering of the vial but would also result in loss of yield.

In order to push the reaction temperatures up to a level where clean conversions could take place, reactions were attempted with 10-20 mL microwave vials instead of the 2-5 mL vials that were previously used. This was in order to see if the extra headspace would lessen the pressure build up preventing the desired temperatures from being reached. Bromobenzene and styrene were successfully reacted for 30 min. to give a complete yield as before. Unfortunately though, once extra the substituents were placed on either of the aryl rings, the reactions would explode as before. The nature of the explosions was sudden and often with no observed pressure rise by the pressure gauge of the microwave.
Table 5: Heck reactions of aryl bromides

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image2.png" alt="Structure" /></td>
<td>181</td>
<td>200</td>
<td>30</td>
<td>99</td>
</tr>
<tr>
<td>2*</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image3.png" alt="Structure" /></td>
<td>183</td>
<td>160</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>3*</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image4.png" alt="Structure" /></td>
<td>31</td>
<td>160</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image5.png" alt="Structure" /></td>
<td>77</td>
<td>200</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image6.png" alt="Structure" /></td>
<td>77</td>
<td>200</td>
<td>180</td>
<td>28</td>
</tr>
<tr>
<td>6*</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image7.png" alt="Structure" /></td>
<td>1</td>
<td>160</td>
<td>30</td>
<td>N.R.</td>
</tr>
<tr>
<td>7*</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image8.png" alt="Structure" /></td>
<td>187</td>
<td>160</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>8*</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image9.png" alt="Structure" /></td>
<td>184</td>
<td>160</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

* Reaction exploded at temperatures above 180°C
Heck reactions using aryl bromides were attempted using conventional heating. In these cases, temperature exceeding 180°C would result in a complex mixture of products. Keeping temperatures below 150°C was sufficient to achieve crude yields consisting only of the expected product and its starting materials. Unfortunately the yields were still low. (Table 6: entries 2 & 3)

Table 6: Heck reactions performed using conventional heating

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F (\text{Ph}^{+})</td>
<td>(\text{PhCl}^{+})</td>
<td>184</td>
<td>200</td>
<td>c.m.</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph}^{+})</td>
<td>(\text{PhCl}^{+})</td>
<td>183</td>
<td>140</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{MeO-Ph}^{+})</td>
<td>(\text{MePh}^{+})</td>
<td>187</td>
<td>140</td>
<td>18%</td>
</tr>
</tbody>
</table>
A theory was put forward that the explosive nature of some of the reactions with aryl bromides in the microwave may have been due to superheating of undissolved sodium acetate in the reaction mixture. In order to test this theory a small amount of tetrabutylammonium bromide (TBAB) was added to the reaction of 1-bromo-4-flourobenzene and 4-chlorostyrene, a reaction that was known to be explosive under the optimal conditions. The logic being that the TBAB would act as a phase transfer agent preventing the suspected superheating of small undissolved particles. The reaction proceeded smoothly to completion without incident (Scheme 89).

The addition of TBAB to other previously explosive reactions also allowed them to proceed smoothly at 200°C (Scheme 89). The synthesis of various stilbene products with both electron donating and withdrawing groups was now possible in excellent yields. The addition of TBAB also made it possible to increase the yield of the reaction of bromobenzene and butyl acrylate to 73%. During these experiments 8 equivalents of ligand (relative to palladium) was believed to be the optimum amount required. It was later found out that the effect of this change was negligible in NMP, so in subsequent experiments only 4 equivalents were used.
Low catalyst loading experiments were then carried out using loadings of 0.0001 mol% of palladium. Moderately good yields were once again achieved for the synthesis of trans-4-methoxystilbene (Table 7). Yields could be improved somewhat by extending reaction times but we were unable to push the reaction to completion under these conditions (Table 7, entry 3).

![Chemical reaction diagram]

Table 7: Catalyst loading study using aryl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>74</td>
</tr>
</tbody>
</table>

Attempts to react aryl chlorides under similar conditions were made but unfortunately they were all unsuccessful (Table 8). Despite the ability of TBAB to encourage palladium catalysed reactions (See section 1.5.1), no effect was observed even after employing a large excess.
Table 8: Attempted Heck reactions of aryl chlorides

\[
\begin{align*}
R^-Cl + \text{R}^1 & \rightarrow \text{R}^-\text{R}^1 \\
Pd(\text{dba})_2, \text{TBAB}, \\
    \text{NaOAc, DMF, mw,} & \\
    30 \text{ min, } 200 \degree C
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Pd (mol%)</th>
<th>TBAB (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>0.5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>0.5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

It was decided not to spend too much time trying to optimise the conditions for these reactions. Adjustments to the ligand structure itself may lead to better conversions in the reactions that had not worked very well. We therefore set about investigating the steric and electronic effects of the substituents attached to the nitrogen atoms in an attempt to better understand the nature of the catalyst system.
2.1.2 Further ligand Synthesis

The commercial availability of some $N,N'$-substituted ethylenediamines allowed for simple preparation of phenyl- and benzyl- substituted ligands (188,189) in a single step by treatment with thionyl chloride and triethylamine. (Scheme 90)

$$\text{Ar} - \text{N} - \text{N} - \text{Ar} \xrightarrow{\text{SOCl}_2, \text{NEt}_3, \text{Et}_2\text{O}, 18 \text{ h}, 0 \degree \text{C} - \text{r.t.}} \text{Ar} - \overset{\text{O}^*}{\text{N}} - \overset{\text{N}^*}{\text{S}} - \text{Ar}$$

188 yield = 33%
189 yield = 59%
190 yield = 0%

Scheme 90

The preparation of an $o$-tolyl substituted thiaadiazolidine oxide (190) however would not proceed under the same solvent conditions as previously employed, the use of dichloromethane instead of diethyl ether as solvent is required for the thionyl chloride addition to be successful (Scheme 91). Also, for unknown reasons the stability of this compound is lower than the others, if left at room temperature it can visually be seen to revert back to its purple bis-amine precursor (191) over the period of a few days (Scheme 92).

$$\text{H} - \text{N} - \text{N} - \text{H} \xrightarrow{\text{SOCl}_2, \text{NEt}_3, \text{CH}_2\text{Cl}_2, 18 \text{ h}, 0 \degree \text{C} - \text{r.t.}} \text{O}^* \text{N} - \overset{\text{S}^*}{\text{N}} - \text{Ar}$$

191
190 yield = 46%

Scheme 91

$$\text{H} - \text{N} - \text{N} - \text{H} \xrightarrow{\text{SOCl}_2, \text{NEt}_3, \text{CH}_2\text{Cl}_2} \text{O}^* \text{N} - \overset{\text{S}^*}{\text{N}} - \text{Ar} \xrightarrow{\text{r.t. in air}} \text{H} - \text{N} - \text{N} - \text{H}$$

191
190

Scheme 92
A (2,6-diisopropylphenyl)-substituted ligand 194 was prepared using a similar route to the original mesityl substituted ligand, differing only in the choice of reducing agent to convert the bis-imine 192 to its bis-amine counterpart 193. As NaBH₄ proved ineffective, LiAlH₄ was used instead (Scheme 93). This compound was highly crystalline and an X-ray structure was obtained (Figure 9). The (4-methoxyphenyl)-analogue 196 was synthesised in the same manner as the original mesityl substituted ligand (Scheme 94).

Scheme 93

Figure 9
In some cases the preparation of substituted bis-amine precursors proved difficult. Sometimes isolatable bis-imines would not be formed on reaction of certain primary amines with glyoxal. A method of bypassing the imine formation stage was discovered by adding 2 equivalents of benzotriazole (relative to glyoxal) to the reaction. This resulted in the benzotriazole adduct shown in Scheme 95. If successfully formed this adduct could easily be filtered and reduced using sodium borohydride to produce the corresponding bis-amine.

NMR data on these adducts proved impossible to decipher due to the number of isomers formed. However, on reduction the desired bis-amine could be cleanly obtained. Two thiadiazolidine 1-oxides that otherwise could not be synthesised using the original method were prepared by these means, \( p \)-tolyl- \( 199 \) (Scheme 96) and \( p \)-chloro-substituted \( 200 \) (Scheme 97).
In an attempt to simplify the preparation of the diisopropylphenyl derivative (194) and eliminate the need for the use of LiAlH₄ as a reducing agent during its synthesis, the benzotriazole method was also tested. Unfortunately this was unsuccessful. Only the bis-imine product 192 was recovered (Scheme 98), which still required the use of LiAlH₄ to give the corresponding bis-amine 193. It is believed that the steric bulk prevents the formation of the benzotriazole adduct.

The p-chlorophenyl derivative has also been seen to be unstable when stored at room temperature, degrading within a matter a days to its bis-amine precursor. The unfavourability of electron withdrawing groups as aromatic substituents on these structures has been shown by the failure to produce any other ligands with electron withdrawing groups acting on the nitrogen atoms. The syntheses of the p-nitrile and p-nitro analogues were also attempted but failed (201, 202). This unfavourability mainly extends to the ability to produce the bis-amine precursors. This is probably due to the lower reactivity of the primary amine starting materials due to the electron density being withdrawn from the nitrogen, thus hindering the desired reaction with glyoxal.

Synthesis of N,N’-(tert-butyl)ethylenediamine was also unsuccessful. Although literature procedures have reported ~70% yields for this compound, mainly oligomeric products were obtained (Scheme 99).133, 134
A possible alternative route was investigated by reacting thionyl chloride directly with primary amines, which would then be followed by thiazolidine ring closure using dibromoethane. Unfortunately this proved fruitless, as the reaction of 4-nitroaniline with thionyl chloride at low temperature (Scheme 100) gave an unstable product. This product was seen as new peaks which appeared to correlate to the protons of a para-aromatic in the $^1$H NMR spectrum. Further analysis of this material was not possible due to its poor stability. Isolation of this material and trapping using dibromoethane was unsuccessful (Scheme 101).

The reaction of thionyl chloride with ethylenediamine to produce the unsubstituted thiazolidine-1-oxide 203 was also attempted without success (Scheme 102).

### 2.2 Reactivity

Two different Heck reactions were used as test reactions for the comparison of the ligands. Stock solutions of each ligand were prepared and also a control solution containing only the palladium source. The control solution was treated in the same
manner as the ligand solutions, using bench solvent and stirred openly in air to maintain consistency. Different stock solutions took on different colours, varying from yellow, to red and dark brown. Surprisingly the control solution also changed colour from the initial red to a bright yellow.

The reaction of bromobenzene and butyl acrylate afforded good yields but for two of the ligands screened (Scheme 103). The \( p \)-chlorophenyl- (200) and benzyl- (189) substituted ligands performed very well with yields >90%. Surprisingly, the control solution also afforded a moderate yield of 49%. At first glance it might appear that ligands with less electron density in the thiadiazolidine ring are more reactive.

![Scheme 103](image)

However, when the reaction of 4-bromoanisole and butyl acrylate was screened the general reactivity of the catalysts decreased (Scheme 104). Once again, the reaction performed in the absence of ligand has proven to be surprisingly effective;
outperforming the majority of the ligand containing reactions. It is believed that the solvent used, N-methylpyrrolidinone (NMP), may also have the ability to coordinate as a ligand, also suggested by the colour change of the control stock solution.

Otherwise, the majority of conversions were disappointing. If the solvent is playing a larger role in these reactions than anticipated, different conditions will have to be employed to obtain a valid comparison. As it stands, no correlation has been observed in terms of steric bulk or electronics of the N-substituents towards reactivity of the catalysts.

However, upon increasing the concentration of palladium, solutions containing ligands provide better results than those without (Scheme 105). This result suggests decreased stability of the ligand-free catalyst at higher concentrations. This is consistent with the theory of “homeopathic” catalysis discussed in section 1.5.

Scheme 104
2.3 Investigations into the Nature of the Catalyst System

In order to exclude any stabilising effect in other solvents, solvent screening was performed for ligand 188 catalyst solutions and “blank” palladium catalyst solutions with no added ligand. 188 was chosen due to the fact that its activation (i.e. when the catalyst solution changes colour from red to yellow) appears to occur much quicker in NMP and DMF than any of the other ligands. A selection of commonly used solvents was tested as shown in Table 9.

Table 9: Solvent screening

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion without ligand (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Toluene</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The results show that this catalyst system and the blanks give negligible catalytic activity in other commonly used solvents. When DMF and NMP are used however, catalytic activity was significant (See section 2.1.1). This suggests that the amide moiety of these solvents is playing quite a significant role in stabilising the palladium source in solution.

A number of publications have described catalytic results from ligand free or unlikely ligand sources while using NMP as a solvent without attributing any effect to the solvent itself.\textsuperscript{135-138, 65} In many cases catalyst loadings described are below 0.1 mol% and at a concentration where, according to De Vries, the “homeopathic effect” is
believed to be most effective.\textsuperscript{68} It should be noted that De Vries’ investigations employed NMP as solvent without mention of others.

Although ligands in these publications do indeed have individual merit, the effect of the solvent combined with the “homeopathic effect” may have been underestimated. In this work, catalyst loadings have been pushed to extreme lows by incorporation of the heating effect of microwave irradiation (Table 4 and Table 10).

NMP-metal complexes have been isolated in the past. These include complexes of copper, iron, zinc and tin.\textsuperscript{139-142} This prompts a more in-depth look into the effect of NMP and the possibility of NMP-palladium coordination.

In order to test whether we have been dealing with a homogenous catalyst system it was decided to employ the “mercury drop” test. When the reaction of iodobenzene and butyl acrylate was tested under conventional reflux conditions identical results were obtained with and without mercury present in the reaction (Scheme 106). Since the catalyst was not affected it can be concluded that only homogenous catalysis is taking place in these reactions, this was also true in the absence of ligand. The mercury test was not performed under microwave conditions for safety reasons.

\begin{equation}
\text{PhI} + \text{CH}_2=\text{CHCOOBu} \xrightarrow{\text{Pd(db)} \text{a}_2 (0.1 \text{ mol\%}), \text{NMP, NaOAc, 18 h, } \Delta} \text{PhCH=CHCOOBu}
\end{equation}

\textbf{Scheme 106}

In an investigation into whether NMP could bind as a ligand in its own right, sub-stoichiometric amounts of NMP were added to reactions in toluene and THF. No reaction occurred with these low levels of NMP. (Scheme 107)

\begin{equation}
\text{PhBr} + \text{CH}_2=\text{CHCOOBu} \xrightarrow{\text{NMP (1 mol\%), } \text{Pd(db)} \text{a}_2 (0.1 \text{ mol\%}), \text{toluene or THF, NaOAc, 200 }^\circ\text{C, 30 min, } \text{mw}} \text{PhCH=CHCOOBu}
\end{equation}

\textbf{Scheme 107}

If Pd(db)a\textsubscript{2} was dissolved in NMP, the excess solvent could be removed by Kugelröhrr distillation. This would yield a bright yellow solid. Unfortunately this material proved
difficult to characterise. $^1$H NMR spectroscopy gave the appearance of NMP in a number of different forms, showing what appeared to be a number of distinct methyl group singlets among the multiplet signal of the methylenes. Only trace amounts of dibenzylideneacetone (dba) remained in the sample.

The material was also analysed by UV-vis spectroscopy. The observed absorption for the free NMP carbonyl was 220 nm; a similar carbonyl absorption was also observed for the yellow solid but at a slightly different wavelength of 214nm. This indicates that the NMP carbonyl is in a different electronic environment in the presence of palladium, suggesting that a complex of some sort has been formed. All attempts to grow a crystal for X-ray analysis were unsuccessful.

Precipitation of an NMP complex by the displacement of PhCN from palladium was also attempted. Pd(PhCN)$_2$Cl$_2$ was stirred in dichloromethane with 10 equivalents of NMP to no avail. It was also stirred in a solution of neat NMP without any sign of precipitate.

Attempts were also made to obtain a palladium complex involving mesityl derived ligand 178. By stirring the compound at room temperature with Pd(PhCN)$_2$Cl$_2$ in dichloromethane a bright yellow precipitate was obtained. Once again this material proved difficult to characterise. $^1$H NMR spectroscopy indicated that a new substance had been obtained that did not contain benzonitrile. (See Appendix B)

![Scheme 108](image)

The presence of two distinct aromatic singlets in the proton NMR suggests that free rotation of the mesityl- group has been halted. This implies that palladium has bound to one face of the molecule. Analysis by COSY shows that these peaks belong to the same molecule; they are also coupled to three other signals which correspond to the methyl groups of the aromatic ring. The methylene peaks could not be distinctly identified by $^1$H NMR but a corresponding signal could be clearly seen by $^{13}$C DEPT135. It is not clear however whether the S-O moiety has remained intact.
MS analysis gave its main accurate mass signals at 771.2978 and 911.1619; this molecular weight could not be given a reasonable molecular formula by the MS computer or by the author. It is without doubt that from the isotope pattern obtained that palladium is present in the material. Attempts to obtain a crystal for X-ray analysis were unsuccessful.

178 was also subjected to the equivalent platinum complex Pt(PhCN)₂Cl₂; in this case no new material was formed and starting material was recovered (Scheme 109).

2.4 General Reactivity of Thiadiazolidine 1-oxides

In order to test the general reactivity of thiadiazolidine 1-oxides, the mesityl derived compound 178 was subjected to nucleophiles. Firstly, 178 was treated with Grignard reagents. Under reflux with commercially available reagent 205 no reaction occurred. Only the intact thiadiazolidine 1-oxide was recovered after work-up. 178 was also treated with phenylmagnesium bromide to once again afford starting material showing that these compounds are resilient to nucleophilic attack (Scheme 110).

178 was also treated with electrophillic reagents. Treatment with electrophiles caused the ring to open and affording the bis-amine precursor 177. This was the case when 178 was heated to reflux in the presence of benzyl bromide, dimethylsulfate and acid. When o-Tolyl thiadiazolidine 1-oxide 190 was treated with methyl triflate, ring opening occurred and subsequently both nitrogen atoms were methylated to afford compound 206 (Scheme 111).
178 was then treated with a selection of metal complexes that were on hand. Conditions involved stirring 178 with 1 equivalent of metal complex in dichloromethane at room temperature overnight. Nickel(II) chloride was unreactive towards the compound with a return of intact starting material. Treatment with ZnBr₂ on the other hand resulted in approximately 50% of the compound degrading to its bisamine counterpart.

Treatment with copper(II) chloride produced much different results. After stirring, a green precipitate was filtered from solution. ¹H NMR spectroscopy suggests the presence of a new complex. Three sharp peaks corresponding to the methyl groups are present and peaks corresponding to the methylenes of the thia diazolidine ring are present approximately 0.5 ppm further upfield from those of the free ligand. Also, the aromatic hydrogens have been split into two distinct environments suggesting that copper is occupying one face of the molecule.

This preliminary result would suggest that it is possible for copper to ligate to this type of molecule, opening the possibility of developing thia diazolidine 1-oxides for use in copper-mediated chemistry. This avenue has not been pursued for the time being but it may prove worthwhile to investigate in the future.

2.5 Synthesis of Chiral Ligands

The next logical step was to synthesise enantiomerically pure ligands based on the thia diazolidine-1-oxide core. In addition to the stereo-directing effects of the surrounding molecule, it was hoped that by introducing different substituents to each of the nitrogen atoms that asymmetry would be induced at the sulfur atom, thus creating a chiral centre at sulfur (Figure 10). If a single diastereoisomer were obtained as a ligand, this would theoretically lead to increased chiral information being projected closer to any bonded metal if sulfur binding takes place.
In each case the ligands have been synthesised from mostly inexpensive, simple materials in relatively few steps. In common with previous ligands, each was derived by the reaction of thionyl chloride with a bis-amine. The synthesis of compound 208 was chosen first due to its short synthetic pathway and easily available starting materials. This scaffold has also been reported in the synthesis of an analogous NHC.\textsuperscript{143,144} The bis-amine precursor 207 was prepared by the Buchwald-Hartwig coupling of two equivalents of (S)-α-methyl benzylamine with 1,2-dibromobenzene. This was then treated with thionyl chloride to afford C\textsubscript{2}-symmetric 208 (Scheme 112). It was possible to crystallise this compound and obtain an X-ray crystal structure (Figure 11).

\begin{center}
\textbf{Scheme 112}
\end{center}

\begin{center}
\textbf{Figure 10}
\end{center}

\begin{center}
\textbf{Figure 11}
\end{center}
The second chiral molecule that was synthesized began with the coupling of ethylchloroacetate and phenylglycinol under basic conditions to afford 209. The amide moiety was then converted to the imino ether 210 using trimethyloxonium tetrafluoroborate. Addition of phenylhydrazine hydrochloride afforded the bis-amine precursor 211 which was suitable for treatment with thionyl chloride to afford the intended target molecule 212 (Scheme 113). ¹H NMR analysis suggested that this compound was a single diastereomer. An X-ray crystal structure was obtained (Figure 12) which confirmed that the compound was a single diastereomer and that the oxygen bound to the sulfur is in an anti-position to the phenyl group on the morpholine ring system. This scaffold was chosen because related NHC compounds have achieved good enantioselectivities in literature for the Stetter reaction.¹⁴⁶-¹⁴⁸
For the same reason, a similar compound 216 was also synthesised using (1S, 2R)-(-)-
cis-1-amino-2-indanol as the starting material. This compound also appeared to be a
single diastereomer by $^1$H NMR however a crystal of this compound was not obtained
for X-ray analysis. Its synthesis is shown in Scheme 114.

The next molecule to be synthesised was a thiaadiazol-3-one 1-oxide 220. This was
chosen because of the inexpensive starting materials involved and also because the
structure is related to the secondary amine organocatalysts of MacMillan.\textsuperscript{149-151} The
first step was the esterification of phenylalanine to afford 217. This was followed by
conversion of the ester moiety to a secondary amide using methylamine. The primary
amine was then protected with a $p$-methoxybenzyl group and subsequent treatment of
the bis-amine 218 with thionyl chloride resulted in the final product 220 in four simple
steps (Scheme 115). An X-ray structure could not be obtained for this compound since
it was an oil, however it did appear to be a single diastereomer by $^1$H NMR
spectroscopy.
In order to obtain a similar compound with a more complex substituent at the amide nitrogen (in this case a chiral \( \alpha \)-methyl benzyl group), a different synthetic approach had to be taken. In order to employ amide coupling reagents a direct PMB protection of phenylalanine was attempted; this resulted in a hygroscopic insoluble product 221 which was unsuitable for any further synthesis. An alternative route to this molecule was also attempted resulting in the same insoluble compound (Scheme 116). Instead, a Boc-protection was performed which proceeded in near quantitative yield. The Boc-protected phenylalanine was then subjected to an EDCI coupling with \( \alpha \)-methylbenzylamine to afford 223. A poor 13% yield was obtained. The Boc-protected bisamine 223 was then treated with thionyl chloride and triethylamine in an attempt to obtain compound 224, but no reaction occurred and starting material was recovered.
(Scheme 117). This result suggests that electron rich amines are required for insertion of the SO moiety.

\[
\begin{align*}
\text{Ph}_{\text{NH}} \text{O} & \quad \xrightarrow{\text{Boc}_2\text{O, }1\text{M NaOH}} \quad \xrightarrow{\text{1,4-dioxane, 2 h, r.t.}} \quad \text{Ph}_{\text{HN}} \text{Boc} \\
\text{OA} & \quad \text{OH} & \quad \text{OH} & \quad \text{222 Yield} = 99% \\
\end{align*}
\]

The Boc group was then removed in order to be replaced with the more electron rich PMB protecting group. This compound 226 could then be treated with thionyl chloride to achieve the desired target molecule 227 (Scheme 118).

\[
\begin{align*}
\text{Ph}_{\text{NH}} \text{N}^{-} \text{Me} \text{O} & \quad \xrightarrow{\text{SOCl}_2, \text{NEt}_3, \text{CH}_2\text{Cl}_2, 18 \text{ h, r.t.}} \quad \text{Ph}_{\text{HN}} \text{Me} \\
\text{Boc} & \quad \text{224} & \quad \text{223 Yield} = 13% \\
\end{align*}
\]

The Boc group was then removed in order to be replaced with the more electron rich PMB protecting group. This compound 226 could then be treated with thionyl chloride to achieve the desired target molecule 227 (Scheme 118).

\[
\begin{align*}
\text{Ph}_{\text{HN}} \text{N}^{-} \text{Me} \text{O} & \quad \xrightarrow{TFA, \text{CH}_2\text{Cl}_2, 1 \text{ h, r.t.}} \quad \xrightarrow{i) \text{p-Anisaldehyde, } \text{EtOH, 2 h, r.t.} \quad \text{ii) } \text{NaBH}_4, 2 \text{ h, r.t.}} \quad \text{Ph}_{\text{HN}} \text{Me} \\
\text{Boc} & \quad \text{223} & \quad \text{225 Yield} = 92% \\
\end{align*}
\]

Since the yield for this synthesis was poor, alternative reagents were investigated. Replacement of EDCI with DCC improved the yield of the amide coupling to 76%.
However, the urea-by-product obtained from the reaction of DCC proved extremely difficult to separate from the product.

An amide coupling method developed by the Katritsky group was also investigated. This involved the treatment of Boc-protected phenylalanine with triethylamine and mesityl benzotriazole 228, to form 229 (Scheme 120). This could then be treated with α-methylbenzylamine in THF to achieve formation of the desired amide bond. The preparation of BtMs is shown in Scheme 119. When the synthesis of 229 was attempted, it was found that the chiral centre in phenylalanine had racemised on treatment with mesityl benzotriazole (αD = 0). The racemic compound was treated with (S)-α-methylbenzylamine in order to confirm that two diastereomers of 230 would be formed. It was clearly seen by 1H NMR that a 1:1 mixture had been obtained despite the literature claim that racemisation does not occur.

![Scheme 119](image)

Scheme 119

![Scheme 120](image)

Scheme 120

It was possible to synthesise compound 232 by simple PMB protection of phenylalanol followed by the standard treatment with thionyl chloride (Scheme 121). Interestingly, a 2:1 mixture of diastereomers was clearly observed. Distinct peaks for the protons of the benzyl group were observed for both diastereomers. This is evidence that if two diastereomers of this type of compound are present they can be observed by 1H NMR.
After synthesis of compound 234 by means of a double Buchwald-Hartwig reaction, an attempt was also made to synthesis compound 235 (Scheme 122). Unfortunately, although a crude product was obtained, it was found to be unstable and could not be purified by column chromatography. It is possible that the configuration of the nitrogen atoms in a trans-position is unsuitable for ring closure. It is also conceivable that instability is due to the same reasons as for the o-tolyl substituted compound 190 since both compounds have a single ortho-substituent on each aromatic ring.

2.5.1.1 Reactivity

Being the most readily available, compound 220 was used as a ligand in one of the previously employed test reactions (Section 2.2). By achieving a conversion of 63% (Scheme 123), this catalyst displayed greater reactivity than all the previous reactions (Scheme 104). It was noted that this ligand has a similar amide functionality to that of...
NMP but also contains extra potential binding sites; combined these may play a role in its higher activity.

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{Ph} \quad + \quad \text{MeO} \\
\text{Br} & \quad + \quad \text{Ph} \quad + \quad \text{MeO} \\
\text{Br} & \quad + \quad \text{Ph} \quad + \quad \text{MeO}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{Br} & \quad \text{O} \\
\text{Br} & \quad \text{O}
\end{align*}
\]

Scheme 123

Since previous experiments with very low catalyst loadings had shown a significant increase in catalytic efficiency (Table 4), an aliquot of the catalyst solution was diluted to give a catalyst loading of \(10^{-4}\) mol% and subjected to the same reaction conditions. Table 10 shows that the conversion increased from 63% to 77%. A similar result was observed when the control solution was diluted to the same loading, increasing the conversion from 55% to 77%. This observation once again highlights the danger of underestimating the effect of “homeopathic catalysis” in NMP (See sections 1.5 and 2.3).

Table 10: Heck reactions performed with low catalyt loading

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ligand</td>
<td>78%</td>
</tr>
<tr>
<td>Ligand (0.0004 mol%), Pd(dba)_2 (0.0001 mol%), NMP, NaOAc, 200 °C, mw, 30 min</td>
<td>77%</td>
</tr>
</tbody>
</table>
2.5.2 Asymmetric Heck Reactions

Selected catalyst systems were then tested in Heck reactions with alkenes that would form chiral products (Table 11). The alkenes 2,3-dihydrofuran and 1-phenylcyclohexene were both tested in reactions with 4-bromoanisole but none of the catalysts tested succeeded to drive any of these reactions even to obtain a racemic product. In each case starting material was recovered after irradiation for 30 minutes at 200 °C.

2.6 Synthesis of Oxindoles

2.6.1 Synthesis of Oxindoles using the Asymmetric Heck Reaction

A number of substrates were synthesised to investigate the effectiveness of our catalyst systems in intramolecular Heck cyclisations. 1-Cyclohexene carboxylic acid was treated with thionyl chloride to convert it to an acid chloride so that it could be coupled with 2-iodoaniline under basic conditions, the amide was then methylated to achieve the desired substrate 239. The same methodology was used to synthesise the analogous bromo-substrate 240 (Scheme 124).

A substrate derived from tiglic acid was also prepared in a similar manner (242) (Scheme 125).
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Catalyst Loading</th>
<th>Aryl Halide</th>
<th>Alkene</th>
<th>Solvent</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ligand</td>
<td>0.1</td>
<td>MeO</td>
<td>Ph</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
<tr>
<td>No Ligand</td>
<td>0.0001</td>
<td>MeO</td>
<td>Ph</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>0.1</td>
<td>MeO</td>
<td>O</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>0.1</td>
<td>MeO</td>
<td>O</td>
<td>DMF</td>
<td>NEt₃</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>0.1</td>
<td>MeO</td>
<td>O</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>0.1</td>
<td>MeO</td>
<td>O</td>
<td>NMP</td>
<td>/TBAB</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>0.0001</td>
<td>MeO</td>
<td>O</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td>0.1</td>
<td>MeO</td>
<td>O</td>
<td>NMP</td>
<td>NaOAc</td>
</tr>
</tbody>
</table>
1-cyclohexene carboxylic acid (236) was initially bought from a commercial source; but due to cost, it was decided to synthesise it in the lab from inexpensive materials when more was required. The first attempt at this involved the hydrocyanation of cyclohexanone with the intention of hydrolysing the nitrile and dehydration under acidic conditions. Unfortunately, only removal of the TMS group was achieved (Scheme 126). Cyclohexanone cyanohydrin 243 proved itself to be remarkably stable to repeated treatment with a range of strong acids. In each attempt neither dehydration nor hydrolysis of the nitrile was achieved and 243 was recovered in each case.

Scheme 126

Acidic Conditions:  
- TFA, CHCl₃, 2h, 0 °C - r.t.  
- Conc. HCl, 4h, Δ  
- H₂SO₄, H₂O, 4h, Δ  
- H₃PO₄, 4h, Δ

It was however possible to synthesise 1-cyclohexene carboxylic acid by the bromination of inexpensive cyclohexane carboxylic acid in the 2-position followed by treatment with methanolic KOH (Scheme 127). When this method was used the product 236 was obtained as a crude oil with an estimated 50% purity. All attempts at purification were unsuccessful. It was however still possible to react the crude material using the same methodology in Scheme 124 and purify at a later step.

Scheme 127

Compound 239 was the first to be subjected to Heck conditions (Table 12). Ligand 220 was used because of its availability, proven reactivity, and chirality. The reaction was found to proceed under milder conditions than those used for the unsuccessful
intermolecular asymmetric Heck reactions. The reaction could achieve conversions at temperatures as low as 150 °C.

Table 12: Asymmetric intramolecular Heck reactions of substrate 233

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>245:246</th>
<th>e.e. of 245 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(\text{PMBN-S}^+)(\text{O}^-)</td>
<td>200</td>
<td>&gt;99</td>
<td>2:3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>93</td>
<td>1:3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>125</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No Ligand</td>
<td>200</td>
<td>&gt;99</td>
<td>1:2</td>
<td>-</td>
</tr>
</tbody>
</table>

At 200 °C the products formed were practically racemic but when the temperature was lowered to 150 °C an enantiomeric excess of 12% was observed for compound 245. This excess could only be observed in product 245 as the enantiomers of product 246 could not be readily separated by chiral HPLC.

The reaction could also be performed with the previous symmetric ligands and also proceeded well in the absence of ligand to produce the racemic products. The ratio of the products was found to differ slightly depending on what ligand and temperature...
was used. When the bromo-substrate was subjected to similar Heck conditions no reaction was observed after 30 minutes of irradiation at 200 °C (Scheme 128). The substrate derived from tiglic acid reacted readily but only negligible enantiomeric excesses were achieved.

Table 13: Asymmetric intramolecular Heck reactions of substrate 242

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150</td>
<td>94</td>
<td>&lt; 2</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>87</td>
<td>&lt; 3</td>
</tr>
</tbody>
</table>

The other chiral ligands were then tested under the same reaction conditions as used in Table 12. Unfortunately, none of them were successful in inducing any significant level of asymmetry.
2.6.2 Attempted synthesis of Oxindoles by $\alpha$-Enolate Arylation

Attention was turned to the use of thiadiazoline 1-oxide catalyst systems in the cyclisation of acetanilides into oxindoles. A number of attempts were made using both bromo- and iodo- substituted acetanilides (250, 251) to form oxindole 242 by palladium catalysed enolate arylation but none were successful. The conditions used are shown below in Table 14. Scheme 130 illustrates the synthesis of the substrates.

Table 14: Attempted $\alpha$-enolate arylation reactions

<table>
<thead>
<tr>
<th>$X=$</th>
<th>Ligand</th>
<th>Pd Loading (mol %)</th>
<th>Solvent</th>
<th>Mw settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td><img src="image1" alt="Br Ligand" /></td>
<td>0.5</td>
<td>NMP</td>
<td>30 min, 120 °C</td>
</tr>
<tr>
<td>Br</td>
<td><img src="image2" alt="Br Ligand" /></td>
<td>5</td>
<td>NMP</td>
<td>30 min, 120 °C</td>
</tr>
<tr>
<td>Br</td>
<td><img src="image3" alt="Br Ligand" /></td>
<td>5</td>
<td>Dioxane</td>
<td>30 min, 120 °C</td>
</tr>
<tr>
<td>Br</td>
<td><img src="image4" alt="Br Ligand" /></td>
<td>5</td>
<td>Toluene</td>
<td>30 min, 120 °C</td>
</tr>
<tr>
<td>Br</td>
<td><img src="image5" alt="Br Ligand" /></td>
<td>2.5</td>
<td>Toluene</td>
<td>30 min, 140 °C</td>
</tr>
<tr>
<td>I</td>
<td><img src="image6" alt="I Ligand" /></td>
<td>0.1</td>
<td>NMP</td>
<td>30 min, 200 °C</td>
</tr>
</tbody>
</table>
2.6.3 Synthesis of Oxindoles using Aryne Intermediates

Alternative to the use of palladium mediated chemistry to form oxindoles, chloro-substituted anilides were employed in attempts to cyclise oxindoles using benzyne chemistry. Work within the group has shown that an ortho-chloroacetanilide will cyclise in the presence of lithium diisopropylamine (LDA) to afford oxindole 248 (Scheme 131). It was hoped to develop this technique by using a 3,4-dichloro-analogue to facilitate the formation of a second benzyne by charge transfer. This benzyne would theoretically then react further to allow the synthesis of a more structurally complex oxindole. In the examples attempted below, furan was used in the hope of trapping the second benzyne by means of a Diels-Alder reaction (Scheme 132).
The 3,4-dichlorophenyl)acetanilide (253) was synthesised in a similar manner as the previous acetanilide (Scheme 133). On treating 253 with LDA and furan, no cyclisation occurred and only a complex mixture of products was obtained (Scheme 134).

A substrate (256) was then synthesised with two extra methyl groups to provide extra steric bulk in the hope that this would provide a cleaner reaction. (Scheme 135)

The anticipated cyclisation did not occur either but instead two products were isolated (Scheme 136). One is believed to be a dimer formed by two benzynes undergoing a [2+2] cycloaddition reaction (258). The other is the result of cleavage between the nitrogen atom and the carbonyl of the starting material (259).
The formation of dimer 258 indicates that benzyne formation does occur, but indicates that the aryne is more reactive towards another benzyne than the enolate in the molecule. This may be due to electronic effects caused by the chlorine in the 4-position, since dimerisation is not observed when there is one chlorine in the ortho-position of the ring. An alternative explanation is that the enolate is not formed at all using this substrate and that the benzyne is the only reactive part of the molecule which leads to dimerisation.

The synthesis of another substrate containing a phenyl ring and a methoxy-group in the amide α-position is illustrated in Scheme 137. It begins with the conversion of mandelic acid to its methyl ester counterpart 260. The free hydroxyl is then methylated using iodomethane. The ester is then hydrolysed and carboxylic acid 262 is coupled to 2-chloroaniline using EDCI. A final methyl group is added to protect the nitrogen and to afford the desired substrate 264. This substrate was synthesised with only an ortho-chlorine to see whether cyclisation could be achieved before attempting the tandem cyclisation.

\[
\begin{align*}
\text{Ph} \text{COOH} & \quad \xrightarrow{\text{MeOH, AcCl, } 2 \text{ h}, \Delta} \quad \text{Ph} \text{COOMe} & \quad \xrightarrow{\text{MeI, NaH, THF, } 18 \text{ h, r.t.}} \quad \text{Ph} \text{COOMe} \\
\text{Ph} \text{CON} \text{Me} & \quad \xrightarrow{\text{NaH, THF, } 18 \text{ h, r.t.}} \quad \text{Ph} \text{CON} \text{Me} & \quad \xrightarrow{i) \text{ SOCl}_2, 50^\circ\text{C, } 2 \text{ h}, \text{ ii) 2-chloroaniline, } \text{NET}_3, \text{ CH}_2\text{Cl}_2} \quad \text{Ph} \text{COOMe} \\
\text{264 yield} = 40\% & \quad \text{(over 2 steps)} & \quad \text{263} & \quad \text{262 yield} = 69\%
\end{align*}
\]

Scheme 137
Cyclisation of this substrate was also unsuccessful, affording a complex mixture. It is believed that the bulky enolate formed on treatment with base is not reactive enough to undergo the desired cyclisation cleanly (Scheme 138).

![Scheme 138](image)

The use of triisopropropylsilyl- (TIPS) protected β-keto-\(\sigma\)-chloroanilides was investigated as a possible route to functionalised oxindoles. These substrates provide a pre-formed more nucleophilic enolate which has been shown in literature to undergo this type of cyclisation quite well. An example provided by Overman was first repeated to afford oxindole 266 in 49% yield (Scheme 139), the literature yield was 53%.

![Scheme 139](image)

The synthesis of the substrate 265 is shown in Scheme 140. It begins with the methylation of ethyl acetoacetate, this is followed by base hydrolysis and EDCI coupling with 2-chloroaniline to afford 268. TIPS protection of the β-keto anilide is then followed by another methylation to afford the substrate 265. This synthesis does not always proceed smoothly as there can be a significant loss of yield during the hydrolysis and EDCI coupling steps. This is attributed to the instability of the unprotected β-keto-acid and also the low reactivity of 2-chloroaniline as a nucleophile.
The next step was to attempt the cyclisation again using different electrophiles to introduce functionality at the 4-position of the oxindole. The electrophiles were added after stirring the starting material with LDA for 2 hours and were allowed to react while attaining room temperature overnight. The reaction was then quenched with water and worked up as before.

When anisaldehyde was used to quench the reaction cyclisation of the product was observed but only to give the same oxindole 266 as before. Surprisingly, approximately 40% of the excess anisaldehyde was found to have been reduced to \( p \)-methoxybenzyl alcohol (270). The reaction was also attempted using dibromoethane and in this case no cyclisation was observed. It was however discovered in the \( ^1 \text{H} \) NMR spectrum that triisopropylsilane, a reducing agent, was somehow being generated in the reaction.
This explains the unexpected reduction of anisaldehyde but indicates that the TIPS protecting group is not suitable for this chemistry.

![Scheme 142]

Although other trialkylsilyl- groups may provide adequate protection, it was decided not to continue with this chemistry. Considering the fact that the TIPS group is already considered a robust protecting group, the synthesis of the desired substrates was too unreliable and time consuming to proceed.

2.7 Investigations into the Synthesis of Esermethole

2.7.1 Investigation of the Decarboxylative Asymmetric Allylic Alkylation Reaction

The synthesis of esermethole was attempted in order to highlight the synthetic utility of the palladium catalysed decarboxylative asymmetric allylic alkylation (DAAA) reaction in natural product synthesis. Scheme 143 displays the anticipated key stereodirecting step, after which literature procedures can be employed to synthesise esermethole.

![Scheme 143]

A model compound (275) was first used to test the viability of the reaction. This compound was selected due its immediate availability and also due to the fact that if high enantioselectivity could be achieved the methodology could also prove to be a useful method to synthesise unnatural chiral amino acids. In the presence of Pd(dba)$_2$
and triphenylphosphine the reaction proceeded in a matter of minutes to form the desired product 275 in the racemic form (Scheme 144).

\[ \text{Scheme 144} \]

A number of ligands were then tested to see whether asymmetry could be induced in the product (Table 15). The reaction was first attempted with ligand 220 in an NMP solution, the reaction did not proceed at room temperature, but did afford a racemic product in good yield when heated to 85 °C for 24 hours (Entries 1 & 2). This was also the case with no added ligand (Entry 3). More traditional phosphines ligands were required to catalyse the reaction at room temperature. Out of 3 available ligands (Figure 13) the only one to provide any significant ee was ligand 23 with 21%. (Entry 6) This was not high enough to proceed with amino acid synthesis but justified the screening of substrates for the functionalisation of oxindoles.

**Table 15: Ligand screening for decarboxylative asymmetric allylic alkylation reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>220</td>
<td>NMP</td>
<td>r.t.</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>220</td>
<td>NMP</td>
<td>85</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>NMP</td>
<td>85</td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-276</td>
<td>THF</td>
<td>r.t.</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>(S)-22</td>
<td>THF</td>
<td>r.t.</td>
<td>86</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-23</td>
<td>THF</td>
<td>r.t.</td>
<td>&gt;99</td>
<td>21</td>
</tr>
</tbody>
</table>
It was then decided to attempt the reaction on a simple oxindole motif. Synthesis of the substrate began with the Boc- protection of commercially available 3-methyl oxindole. 277 was then treated with allyl chloroformate under basic conditions to afford the substrate 278 (Scheme 145). This was not the intended substrate as it was expected that the allyl chloroformate would be attacked by the oxygen atom of the carbonyl rather than the enolate carbon. Since the reaction of both substrates should afford the same product it was seen as an equally acceptable result.

The reaction to obtain the racemic product 279 proceeded also smoothly in a matter of minutes. However, it was found that the separation of enantiomers by chiral HPLC was difficult. In order to achieve complete separation the Boc- protecting group had to be removed under acidic conditions (Scheme 146).

When the selection of chiral ligands was screened under similar conditions it was found that reaction rates became significantly slower. A standard reaction time of 24 hours was used to obtain a comparison. Ligands 276 and 22 gave high conversions.
while ligand 22 showed lower reactivity. Enantioselectivity was poor; the best result was achieved by ligand 23 at 26% ee. Nevertheless, this was seen as a reasonable start for a reaction that may be quite substrate dependent. It was decided to synthesise the correct substrate for the synthesis of esermethole on this basis.

Table 16: Ligand screening for decarboxylative asymmetric allylic alkylation reaction to form an oxindole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-276</td>
<td>90</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>2</td>
<td>(S)-22</td>
<td>63</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-23</td>
<td>89</td>
<td>26</td>
</tr>
</tbody>
</table>

It was discovered that in order for allyl chloroformate the react with an oxindole in the presence of triethylamine that an electron withdrawing group is required at the amide nitrogen. This was proven by the attempted synthesis of substrate 284 (Scheme 147). Compound 283 failed to react under these conditions, prompting an alternative synthetic pathway for the synthesis of esermethole without the excessive addition and replacement of a Boc group.
2.7.2 Synthesis of Esermethole

The synthesis of esermethole began with the methylation of \( p \)-anisole. This was achieved by the treatment of \( p \)-anisole with ethyl chloroformate under basic conditions. \( \text{285} \) was then reduced with LiAlH\(_4\) to afford the singly methylated product \( \text{286} \) which is also commercially available (Scheme 148).

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
& \quad \text{Ethyl chloroformate} \quad \overset{(i-\text{Pr})_2\text{NET}, \text{DMAP}, \text{THF}, 30 \text{ min}, 0^\circ \text{C}}{\longrightarrow} \\
& \quad \text{MeO} \quad \text{O} \\
& \quad \text{N} \quad \text{OEt} \\
\text{285 yield} & \quad 90\% \\
& \quad \downarrow \text{LiAlH}_4, \text{THF}, 18 \text{ h}, \Delta \\
& \quad \text{MeO} \quad \text{N} \quad \text{Me} \\
& \quad \text{H} \\
\text{286 yield} & \quad 23\%
\end{align*}
\]

Scheme 148

The next step was to perform a Mukaiyama coupling with monoallyl malonate (\( \text{288} \)). Monoallyl malonate was prepared by treatment of Meldrum’s acid (\( \text{287} \)) with allyl alcohol (Scheme 149). \( \text{290} \) was subsequently methylated with methyl iodide in the presence of potassium tert-butoxide to afford \( \text{291} \) (Scheme 150).

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{C} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{287} \quad \text{Allyl alcohol} \quad 18 \text{ h}, \Delta \\
& \quad \text{HO} \quad \text{C} \\
& \quad \text{O} \\
& \quad \text{C} \\
& \quad \text{O} \\
& \quad \text{H} \\
\text{288 yield} & \quad 44\%
\end{align*}
\]

Scheme 149

\[
\begin{align*}
\text{MeO} & \quad \text{NH} \quad \text{Me} \\
& \quad \text{Monoallyl malonate, 289} \\
& \quad \text{NEt}_3, \text{CH}_2\text{Cl}_2, 1 \text{ h}, \text{r.t.} \\
& \quad \text{MeO} \quad \text{N} \quad \text{OC} \\
& \quad \text{O} \\
& \quad \text{C} \\
& \quad \text{O} \\
& \quad \text{Me} \\
\text{290 yield} & \quad 66\%
\end{align*}
\]

Scheme 150
The next step of the synthesis was to cyclise 291 in order to form an oxindole. This was achieved by treatment with Cu(OAc)$_2$.H$_2$O under basic conditions. Compound 293 was formed as a side product in this reaction. In literature reports of this methodology there have been no reports of such a side product. It is believed that it is formed as a result of the reaction of molecular oxygen during a radical reaction mechanism. The reaction was attempted under nitrogen atmosphere but a complex mixture was formed and neither product was obtained.

The reaction of the substrate once again proceeded quickly and in excellent yield when triphenylphosphine was used as a ligand (Scheme 152).

When chiral ligands were screened ligand 23 was once again the only one to provide a significant ee. A moderate result of 43% was obtained at room temperature. An ee of 46% was achieved by lowering the temperature to -78 °C; this shows that the ee could not be significantly raised by lowering the temperature.
Table 17: Ligand screening for decarboxylative asymmetric allylic alkylation reaction of esermethole precursor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R,R))-276</td>
<td>91</td>
<td>&lt;2</td>
</tr>
<tr>
<td>2</td>
<td>((S))-22</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>((R,R))-23</td>
<td>&gt;99</td>
<td>43</td>
</tr>
<tr>
<td>4*</td>
<td>((R,R))-23</td>
<td>50</td>
<td>46</td>
</tr>
</tbody>
</table>

*Performed at -78 °C for 6 hours

Since a moderate enantiomeric excess had been achieved it was decided to see whether the addition of bulky N-protecting groups could drive asymmetric induction up further. A Boc- group was added to \(p\)-anisole but it was discovered that compound 295 was unreactive towards the Mukaiyama coupling (Scheme 153).

![Scheme 153](image)

It was however possible to perform the coupling with a more electron rich PMB-protecting group. It was possible to apply the same conditions as in the previous synthesis up until the copper mediated cyclisation to afford an oxindole. Synthesis of 301 was completely unsuccessful affording a complex mixture of products (Scheme 154).
An alternative route to 301 was also attempted. This involved the synthesis of indole 303 by a modified Bishler indole synthesis.\textsuperscript{153} This would be followed by oxidation using HCl and DMSO to form oxindole 304. This could then be treated with allyl chloroformate and triethylamine to give the desired substrate 301. Unfortunately this synthesis failed at the first step. In what should have been a “one-pot” procedure to form an indole, the intermediate 302 was isolated in 50% yield. Despite repeated treatment with different batches of zinc chloride, cyclisation was not achieved.
The synthesis of racemic esermethole was attempted with compound 294. The methodology was obtained from a literature source. The first of three steps was to perform an ozonolysis converting the allyl moiety into an aldehyde, a reductive amination with methylvamine and LiAlH₄ would then be performed to afford the natural product. Unfortunately, due to equipment malfunction and time constraints, the ozonolysis could not be completed. (Scheme 156)

![Scheme 156](image)

The oxidation step could be achieved with OsO₄ as described in a report by Zhang and co-workers (Scheme 157).

![Scheme 157](image)

### 2.8 Sulfur Monoxide Transfer

#### 2.8.1 Background

The trapping of sulfur monoxide from chemical sources is an area of chemistry which has received some attention due its applications in the synthesis of thiophenes. Episulfoxides can be thermally degraded to generate sulfur monoxide and the corresponding olefin. In the 1960s, studies into the synthesis and degradation of ethylene episulfoxide (306) sparked an interest in the possible applications of generated sulfur monoxide in organic reactions.

The first such organic reaction was the thermal degradation of ethylene episulfoxide in the presence of dienes in 1967 by Dodson and co-worker. Dodson was able to synthesise a range of simple cyclic sulfoxides albeit in poor yields (21-40%). A later report by Dodson also investigated the degradation of ethylene episulfoxide in the
presence of trienes.\textsuperscript{159} \textit{Trans}-3,4-diphenylhexa-1,3,5-triene (307) was reacted with sulfur monoxide to form 2,7-dihydro-4,5-diphenylthiopin-1-oxide (308) in 35\% yield (Scheme 158). The observed isomerisation around the \textit{trans}- double bond demonstrated that the sulfur monoxide generated was reacting in a non-concerted mechanism with the hexatriene. This indicates that the sulfur monoxide reacts in the triplet state over the less favourable singlet state.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {$\text{O}$};
\node at (0.5,0) {Ph};
\node at (0.5,0.5) {Ph};
\node at (1,0) {$\text{Ph}$};
\node at (1,0.5) {Ph};
\node at (1.5,0) {S};
\node at (1.5,0.5) {O};
\node at (2,0) {$\Delta$};
\node at (-1.25,0) {$306$};
\node at (1.25,0) {$307$};
\node at (2.5,0) {$308$ yield = 35\%$};
\end{tikzpicture}
\end{center}

\textbf{Scheme 158}

A study by Saito has also indicated that sulfur monoxide generated by the degredation of ethylene episulfoxide is produced in the triplet state.\textsuperscript{160} He analysed the degredation by microwave spectroscopy and was unable to observe any singlet state sulfur monoxide. A study by Lemal and Chao also indicated that trapping with dienes proceeds by a biradical intermediate suggesting triplet state reactivity of sulfur monoxide.\textsuperscript{161}

More recent work from the last two decades has focused on the development of more efficient systems for the trapping of sulfur monoxide. In 1997 Harpp and co-worker developed effective precursors for sulfur monoxide formation in adamantylideneadamantanethiirane-1-oxide (309) and bicycle[3.3.1]-nonylidenebicyclo[3.3.1]nonanethiirane-1-oxide (310).\textsuperscript{162,163}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {309};
\node at (2,0) {310};
\end{tikzpicture}
\end{center}

The best results for sulfur monoxide release and its trapping were achieved by refluxing episulfoxide 309 in toluene at 110°C with 2,3-dimethyl-1,3-butadiene (305) affording the corresponding sulfoxide 312 in 82\% isolated yield (Scheme 159). Reactions run at the same temperature in xylene and decane provided a lower yield of 68\%. The yield diminished further on refluxing in xylene to 35\%. The reaction did
not proceed in more polar solvents. Slightly lower but comparable yields were obtained with episulfoxide 310.

![Scheme 159](image)

Work by Grainger and co-workers in 2001 utilised a cyclic trisulfide-2-oxide 308 heated in the presence of various dienes to form cyclic unsaturated sulfoxides in good to excellent yields. An excess of diene was required to obtain high yields. In each example reported the disulfide 316 was recovered in near quantitative yields. Scheme 160 shows the synthesis of thioperillene (317), a constituent of hop and rose oil. The reaction of 314 with piperine (318) afforded the novel thiophene 319 which was isolated directly from the reaction mixture. (Scheme 161)

![Scheme 160](image)
In 2003 Nakayama and co-workers reported that the Diels-Alder reaction of 3,4-di-
tert-butylthiophene-1-oxide (320) with dimethylacetenedicarboxylate (DMAD) affords dimethyl 4,5-di-tert-butylidipthalate (322) in high yield at room temperature (Scheme 162).\textsuperscript{165} Extrusion of sulfur monoxide from 321 leading to rearomatization was considered the probable mechanistic explanation for this.

In 2007 the Nakayama group published another report detailing chemical trapping experiments of the sulfur monoxide generated from the same reaction.\textsuperscript{166} They were able to trap the extruded sulfur monoxide using a range of simple dienes (Yields 27-76\%) isolating the phthalate 322 in all cases in over 80\% yield. In the case of cyclic dienes, they observed stereospecific product formation where the S=O group is \textit{anti} to the resulting double bond. Addition of S=O was also achieved with alkynes but in significantly lower yields (5-20\%).

Excess sulfur monoxide in these reactions was found to produce elemental sulfur, sulfur dioxide and disulfur dioxide. The latter was seen to undergo a Diels-Alder reaction with 3,4-di-tert-butylthiophene-1-oxide to produce 323. This would then
undergo a 1,2-rearrangement to form 324 and on heating this could be converted to form compound 325 by extrusion of sulfur dioxide. (Scheme 163)

The writers concluded that the behaviour of sulfur monoxide produced under these conditions resembles that of singlet state SO because of its capability to add to alkenes and alkynes. This differs from sulfur monoxide produced by other sources such as thirane oxides wherein the sulfur monoxide produced is believed to be in the triplet state.

### 2.8.2 Investigations into Sulfur Monoxide Transfer

It was hypothesised that the more instable thiadiazolidines may provide a viable source of *in situ* sulfur monoxide for reaction with dienes. If successful, the products of these reactions could be subjected to Pummerer conditions to afford thiophenes. The first experiment attempted was the reflux of isoprene with the *p*-chlorophenyl substituted thiadiazolidine 200 (Scheme 164), which is the least stable of all thiadiazolidine 1-oxides succesfully synthesised.

The only material left on evaporation of all volatile material (including isoprene) was a 1:1 mixture of the starting thiadiazolidine 1-oxide and its bis-amine counterpart 198. No evidence of any sulfur monoxide transfer was visible (Scheme 165).
The same reactants were placed in a sealed tube and subjected to microwave irradiation for 30 minutes. It was hoped that sulfur monoxide would react more readily when contained within the sealed vessel but unfortunately this was not the case. The bis-amine 198 achieved 50% conversion while a new unknown compound achieved 14% conversion (Scheme 166).

This new compound correlated to new peaks in the aromatic region of the $^1$H NMR spectrum. These new peaks appeared to be those of a para-substituted aromatic but did not match any compound previously isolated. It was hypothesised that the thiadiazolidine 1-oxide had lost the S-O moiety to form compound 326.

In an attempt to verify this by obtaining a purer sample of the compound, 200 was dissolved in toluene and irradiated for 1 hour without any other reactants present. In this case, there was 62% conversion to the bis-amine 198 and 22% conversion to the same unidentified material (The remaining 16% consisted of starting material). However this compound proved unstable to chromatography and could not be isolated.

In 1999, Simpkins reported the synthesis of episulfoxides by employing Rh$_2$(OAc)$_4$ as a catalyst to effect SO transfer from *trans*-stilbene episulfoxide to norbornene (327) or
norboradiene. The reported conditions were tested but exchanging thiadiazolidine 1-oxide 200 for trans-stilbene episulfoxide (Scheme 167). Once again, no SO transfer product was obtained. The bis-amine 198 achieved a conversion of 58% with the remaining mass consisting of starting material.

![Scheme 167]

Having previously seen that ZnBr₂ encourages degradation of thiadiazolidine 1-oxides (Section 2.4), this was also tested as an additive in SO transfer reactions. Although full degradation did occur under these conditions at room temperature, no SO transfer was achieved (Scheme 168).

![Scheme 168]

The slightly more stable o-tolyl thiadiazolidine ligand 190 was also subjected to the same conditions as the p-chlorophenyl derivative. 50% conversion to its bis-amine counterpart 191 was obtained when subjected to the conditions in Scheme 165. No new compound was observed under microwave conditions and no reaction whatsoever was seen in the presence of Rh₂(OAc)₄ and norbornene at room temperature. Full degradation was also observed in the presence of ZnBr₂. No SO capture was achieved in any case.

### 2.9 Conclusion

Initial investigations into the use of a thiadiazolidine 1-oxide as an air-stable phosphines-free ligand for palladium mediated chemistry showed great promise. A range of styrene and α,β-unsaturated esters were synthesised in high yield by means of the Heck reaction of aryl iodides. When Heck reactions were attempted using aryl
bromides and chlorides it became clear that the catalyst system was not as versatile and reactive as initially anticipated.

Synthesis of a range of thiadiazolidine 1-oxide analogues was undertaken in order to better understand the nature of the system. It was found that synthesis of this type of compound was mainly limited to those with electron donating substituents. When the catalytic reactivity of these compounds was compared the results were disappointing. No correlation was found between reactivity and structure. It was also found that the “blank” catalyst solution containing no added ligand achieved surprisingly high conversions for the test reactions.

The reactivity of the “blank” catalyst solution raised questions as to the effect of the solvent NMP in palladium-mediated chemistry. It is believed that NMP has a weak stabilising effect on palladium at low concentration contributing to what has been reported as the “homeopathic effect”. This allows for good catalyst reactivity at ultra low concentrations without the need for added ligands. It is also believed that the use of microwave heating allows for even lower concentrations of palladium to be effectively employed in reactions.

Attempts were made to isolate both NMP-palladium and thiadiazolidine 1-oxide-palladium complexes. Although promising bright yellow material was obtained in each case, definitive characterisation could not be completed.

The general reactivity of thidiazolidine 1-oxides was tested to discover that they are resilient to nucleophilic attack but are susceptible to ring opening and loss of SO in the presence of electrophiles. There is also some evidence to suggest that these compounds ligate to copper leaving open an avenue of investigation for copper-mediated chemistry.

A selection of chiral compounds of related structure were also synthesised including the first reported enantiomerically pure thidiazol-3-one 1-oxide and thiatriaza-indene 3-oxide systems chiral at the sulfur atom.

Results for the asymmetric Heck reaction were also disappointing. Intermolecular Heck reactions were completely unsuccessful. The intramolecular Heck reaction to form oxindoles proceeded much more readily but enantiomeric excesses were for the
most part negligible. In a single case an ee of 12% was recorded. Attempts to cyclise oxindoles using α-enolate arylation were also completely unsuccessful.

At this stage it was clear that the thiaadiazolidine 1-oxides and related compounds synthesised would not afford palladium catalysts of enough value to be considered for general use.

We investigated the use of the palladium catalysed decarboxylative asymmetric allylic alkylation reaction for the functionalisation of oxindoles with the intention of synthesising esermethole. We relied on more traditional phosphines ligands in order to induce asymmetry in this key reaction but these were not as high as anticipated. The Phe-TROST ligand which has an excellent track record with this type of transformation provided the best result at 46%. The development of a new formal synthesis of esermethole was outlined consisting of 8 steps from commercially available material.

Finally, the loss of SO led us to believe that more unstable thiaadiazolidine 1-oxides may be suitable for in situ sulfur monoxide transfer, a useful step in the preparation of thiophenes. Unfortunately, although release of SO could be instigated no SO capture was achieved in the target molecules.
Chapter 3: Experimental

Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at $\lambda=589$ nm, corresponding to the sodium line, (D), at the temperatures indicated. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used.

The reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, under a nitrogen atmosphere unless otherwise stated. Dry reaction solvents were obtained commercially, except light petroleum (b.p. 40-60 °C) which was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulphate or chloride. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran (THF), was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical.

All $N$-protected amino acids were either purchased commercially or produced from known literature procedures.\textsuperscript{168,169}

Enantiomeric excesses were determined by Chiral High Performance Liquid Chromatography, (Chiral HPLC). The chiral column used for the determination of enantiomeric excesses (ee), of non-racemic mixtures by chiral HPLC, was Eurocel 01 (Chiracel OD equivalent) attached to a Gilson instrument, with the ultra-violet absorption detector set at 254 nm and was controlled by the Clarity software package. Both solvents used to gain measurements (hexane and isopropanol), were of HPLC grade.
Synthesis of N,N'-dimesitylethlenediamine (178)\(^{170}\)

![Chemical structure](image)

Mesityl amine (5.0 g, 37.0 mmol) was added to a stirred solution of glyoxal (2.68 g, 18.5 mmol 40% solu. in H\(_2\)O) after 30 minutes a bright yellow solid precipitated (bis-imine). Dichloromethane (50 mL) was added to dissolve the mixture followed by ethanol (50 mL) this was then followed by portion-wise addition of sodium borohydride (5.6 g, 148.0 mmol). The reaction was left to stir overnight at room temperature and the colourless solution quenched by addition of conc. hydrochloric acid (0.5 mL) quickly followed by the addition of water (50 mL). The ethanol was evaporated under reduced pressure, and the aqueous solution was extracted with ethyl acetate (3 x 50 mL) and dried with MgSO\(_4\). Evaporation of the organics under reduced pressure afforded product as a colourless oil which was used directly in the next step (5.1 g, 17.2 mmol, 93%). \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 2.23 (6H, s), 2.28 (12H, s), 3.15 (4H, s), 6.82-6.83 (4H, m); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 18.4 (4 x CH\(_3\)), 20.6 (2 x CH\(_3\)), 49.2 (2 x CH\(_2\)), 129.2 (4 x Ar.), 129.8 (quat.), 131.5 (quat.), 143.4 (quat.).

Synthesis of 2,5-Dimesityl-1,2,5-thiadiazolidine-1-oxide (179)

![Chemical structure](image)

A solution of N,N'-dimesitylthane-1,2-diamine (5.0 g, 16.9 mmol) in diethyl ether (100 mL) and triethylamine (5.2 mL, 37.2 mmol) was treated with thionyl chloride (1.2 mL, 16.9 mmol) by dropwise addition at 0 °C and stirred for 12 h whilst attaining ambient temperature. Filtration of the triethylamine hydrochloride and evaporation under reduced pressure afforded the thiadiazolidine-1-oxide. Recrystallisation from dichloromethane/diethyl ether afforded colourless crystals (4.8 g, 14.0 mmol, 83%). m.p. 133-135 °C; \(\nu_{\text{max}}(\text{film}) /\text{cm}^{-1}\) 3462, 2917, 2865, 1607, 1481, 1375, 1241, 1123, 851, 735; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 2.29 (6H, s), 2.45 (12H, m), 3.59-3.63 (2H, m), 4.22-4.25 (2H, m), 6.93 (4H, s); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\), 60 °C) 18.9 (4 x CH\(_3\)), 20.7 (2 x CH\(_3\)), 51.4 (2 x CH\(_2\)), 129.5 (4 x Ar.), 134.4 (quat.), 137.6 (quat.), 138.6 (quat.).
139.0 (quat.); m/z 342.1764; C_{20}H_{26}N_{2}SO (M+) requires 342.1766; found C, 70.23; H, 7.44; N, 8.01. C_{20}H_{26}N_{2}SO requires C, 70.14; H, 7.65; N, 8.18 %.

**Synthesis of 2,5-diphenyl-1,2,5-thiadiazolidine-1-oxide (188)**

![Chemical Structure of 2,5-diphenyl-1,2,5-thiadiazolidine-1-oxide](image)

1,2-Dianiloethane (3.0 g, 14.1 mmol) was dissolved in diethyl ether (100 mL) at 0°C followed by addition of triethylamine (4.29 mL, 30.8 mmol). Thionyl chloride (1.02 mL, 14.1 mmol) was then slowly added. After addition of the thionyl chloride the resulting mixture was brought back to room temperature and allowed to stir for 18 hours. The mixture was then filtered to remove the resulting triethylamine salt and the cake washed with ether. The ether was then washed with water (3 x 80 mL) and the solvent was evaporated under reduced pressure to afford the crude product. Recrystallisation in ether afforded a tan coloured solid (1.2 g, 4.7 mmol, 33%). m.p. 159-161°C; υ_{max} (film) /cm^{-1} 1595, 1127, 745, 688; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 3.89-3.98 (2H, m), 4.18-4.28 (2H, m), 7.08 (2H, t, J = 12 Hz), 7.17 (4H, d, J = 10 Hz) 7.36 (4H, t, J = 8 Hz); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) 47.4 (2 x CH\textsubscript{2}), 117.4 (Ar.), 123.0 (Ar.), 129.5 (Ar.), 141.3 (2 x quat.); m/z 259.0909 C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}SO (M+H) requires 259.0905.

**Synthesis of 2,5-dibenzyl-1,2,5-thiadiazolidine-1-oxide (189)**

![Chemical Structure of 2,5-dibenzyl-1,2,5-thiadiazolidine-1-oxide](image)

N,N\textsuperscript{-}Dibenzylethlenediamine (2.94 mL, 12.5 mmol) was dissolved in diethyl ether (100 mL) at 0 °C followed by addition of triethylamine (3.81 mL, 27.4 mmol). Thionyl chloride (0.90 mL, 12.5 mmol) was then slowly added. After addition of the thionyl chloride the resulting mixture was brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water (3 x 80 mL) and the combined organic phases were dried and evaporated under reduced pressure to afford a light brown oil which crystallised over time. (2.1 g, 7.3 mmol, 59%) m.p. 62-65°C; υ_{max} (film) /cm^{-1} 3028, 2865, 1652, 1494, 1455, 1362, 1311, 1107, 930, 698; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 3.09-3.18 (2H, m), 3.35-3.44 (2H, m), 4.05
(2H, d, J = 14 Hz), 4.25 (2H, d, J = 14) 7.22-7.36 (10H, m); $^{13}$C-NMR (100MHz, CDCl$_3$) 49.9, 52.3, 127.8, 128.4, 136.5; m/z 287.1221 C$_{16}$H$_{18}$N$_2$SO (M+H) requires 287.1218.

**Synthesis of 2,5-di(orthotolyl)-1,2,5-thiadiazolidine-1-oxide (190)**

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{SOCl$_2$} \\
\text{NET$_3$, CH$_2$Cl$_2$} \\
18 \text{ h, 0°C - r.t.} \\
\end{array}
\]

$N,N'$-Di(o-tolyl)ethylenediamine (1.5 g, 6.2 mmol) was dissolved in dichloromethane (100 mL) at 0°C followed by addition of triethylamine (0.87 mL, 13.7 mmol). Thionyl chloride (0.45 mL, 6.2 mmol) was then slowly added. After addition of the thionyl chloride the resulting mixture was brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water and the combined ether layers dried and evaporated under reduced pressure. Recrystallisation in ether afforded a tan coloured solid (0.82 g, 2.8 mmol, 46%) $\nu_{\text{max}}$(film) /cm$^{-1}$ 3019, 2950, 2868, 1598, 1580, 1488, 1458, 1246, 1192, 1126, 1045, 977, 908, 840, 787, 761, 721, 656, 610; $^1$H-NMR (400 MHz, CDCl$_3$) 2.43 (6H, s), 3.64-3.67 (2H, m), 4.22-4.26 (2H, m), 7.14-7.25 (6H, m), 7.31-7.33 (2H, m); $^{13}$C-NMR (100 MHz, CDCl$_3$) 18.6 (2 x CH$_3$), 51.7 (2 x CH$_2$), 126.4 (2 x Ar.), 127.0 (2 x Ar.), 127.1 (2 x Ar.), 131.2 (2 x Ar.), 136.4 (2 x quat.), 139.6 (2 xquat.); Compound unstable, could not obtain accurate mass.

**Synthesis of N,N'-(ethane-1,2-diylidene)bis(2,6-diisopropylaniline) (192)**

\[
\begin{array}{c}
\text{iPr} \\
\text{NH}_2 \\
\text{H} \\
\text{O} \rightarrow \text{CO} \\
\text{HCO$_2$H} \\
\text{MeOH} \\
1 \text{ h, r.t.} \\
\end{array}
\]

2,6-Diisopropylaniline (3 mL, 24.0 mmol) and glyoxal (1.74 g, 12.0 mmol, 60% w/w in aqueous solution) were dissolved in methanol (40 mL). A few drops of formic acid were added and the resulting solution was allowed to stir at room temperature for 1 hour. The precipitate was filtered over vacuum and washed with methanol to afford a bright yellow solid (0.95 g, 2.5 mmol, 21%); $\nu_{\text{max}}$(film) /cm$^{-1}$ 3060, 2960, 2869, 1626, 1455, 1431, 1360, 1174, 1042, 921, 817, 793, 757; $^1$H-NMR (400 MHz, CDCl$_3$) 1.23 (24H, d, J = 6.8 Hz), 2.97 (4H, sep) 7.21 (6H, m), 8.13 (2H, s); $^{13}$C-NMR (100 MHz,
Synthesis of N,N'-bis(2,6-diisopropylphenyl)ethylenediamine (193)

N,N’-(ethane-1,2-diyliidene)bis(2,6-diisopropylaniline) (0.95 g, 2.5 mmol) was placed in a three necked round bottomed flask and dissolved in dry THF (50 mL) under a nitrogen atmosphere. 2M LiAlH₄ in THF solution (1.5 mL) was carefully added via syringe and allowed to stir at room temperature for 3 hours by which time the solution had become white. The reaction was quenched with aqueous sodium potassium tartrate and the organics were extracted with dichloromethane (3 x 40 mL). Solvent was removed under reduced pressure to afford a white solid (0.62 g, 1.63 mmol, 65%); ν<sub>max</sub>(film) /cm<sup>-1</sup> 3367, 2957, 2864, 1587, 1456, 1441, 1383, 1330, 1248, 1230, 1196, 1111, 1084, 944, 909, 798, 752; <sup>1</sup>H-NMR (400 MHz, CDCl₃) 1.26 (24H, d, J = 6.8 Hz), 3.16 (4H, s), 3.36 (4H, sep, J = 6.8 Hz), 7.07 (6H, m); <sup>13</sup>C-NMR (100 MHz, CDCl₃) 24.2 (8 x CH₃), 27.7 (4 x CH), 52.3 (2 x CH₂), 123.6 (4 x Ar.), 123.8 (2 x Ar.), 142.4 (4 x quat.), 143.3 (2 x quat.).

Synthesis of 2,5-di(2,6-diisopropylphenyl)-1,2,5-thiadiazolidine-1-oxide (194)

N,N’-bis(2,6-diisopropylphenyl)ethylenediamine (0.62 g, 1.6 mmol) was dissolved in dichloromethane (50 mL) at 0°C followed by addition of triethylamine (0.59 mL, 4.2 mmol). Thionyl chloride (0.14 mL, 1.6 mmol) was then slowly added. The resulting mixture was then brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water (3 x 50 mL) and the organic phase were evaporated under reduced pressure to afford the crude product. Recrystallisation from ether afforded a white solid (0.42 g, 1.0 mmol, 60%); m.p. 185-188 °C; ν<sub>max</sub>(film) /cm<sup>-1</sup> 2958, 2864, 1607, 1584, 1444, 1323, 1263, 1208, 1183, 1129, 1063, 805, 734; <sup>1</sup>H-NMR (400 MHz, CDCl₃) 1.25-1.29 (24H, m), 3.41 (2H, sep., J = 6.8 Hz).
Hz), 3.63-3.67 (2H, m), 3.81 (2H, sep., J = 6.8 Hz), 4.19-4.23 (2H, m), 7.19 (1H, d, J = 1.6 Hz), 7.21 (1H, d, J = 1.6 Hz), 7.23 (1H, d, J = 2 Hz), 7.25 (1H, d, J = 1.6 Hz), 7.33 (2H, t, J = 7.6 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 24.3 (CH$_3$), 24.7 (CH$_3$), 24.9 (CH$_3$), 25.1 (CH$_3$), 28.5 (2 x CH), 28.8 (2 x CH), 54.3 (2 x CH$_2$), 123.9 (2 x Ar.), 124.6 (2 x Ar.), 128.8 (2 x Ar.), 134.2 (2 x quat.), 149.2 (2 x quat.), 151.1 (2 x quat.); m/z 427.2775; C$_{26}$H$_{38}$N$_2$SO (M+H) requires 427.2783.

**Synthesis of N,N’-di(4-methoxyphenyl)ethylenediamine (195)$^{170}$**

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{MeO} & \quad + \quad \overset{\text{i}) \quad \text{HCO}_2\text{H}, \text{MeOH, 1 h, r.t.}}{\text{O} \quad \text{CH} & \quad \text{O} \\
\text{MeO} & \quad \overset{\text{ii}) \quad \text{NaBH}_4, \text{MeOH/CH}_2\text{Cl}_2}{\text{NH} & \quad \text{N} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

$p$-Anisidine (3.0 g, 24.4 mmol) and glyoxal (1.77 g, 12.2 mmol, 40 % aq. solution) were stirred in methanol (40 mL) in the presence of a few drops of formic acid. After 1 hour the resulting bright yellow bis-imine precipitate was filtered and dried by vacuum filtration (2.82 g, 10.6 mmol, 87%). The bis-imine (1.0 g, 3.7 mmol) was dissolved in dichloromethane (30 mL) and MeOH (30 mL), NaBH$_4$ was gradually added until the solution became colourless. The reaction was quenched with conc. HCl (0.5 mL) and water (50 mL). The organics were extracted with dichloromethane (3 x 60 mL) and dried with MgSO$_4$. The solvent was evaporated under reduced pressure to afford a tan coloured solid (0.82g, 3.03 mmol, 82%); $^1$H NMR (400 MHz CDCl$_3$) 3.39 (4H, s) 3.75 (6H, s) 6.63 (4H, d, J = 9.2 Hz) 6.79 (4H, d, J = 8.8Hz) $^{13}$C NMR (100 MHz CDCl$_3$) 44.5 (2 x CH$_2$), 55.8 (2 x OCH$_3$), 114.6 (Ar.), 114.9 (Ar.), 142.2 (quat.), 152.5 (quat.).

**Synthesis of 2,5-di(4-methoxyphenyl)-1,2,5-thiadiazolidine-1-oxide (196)**

\[
\begin{align*}
\text{MeO} & \quad \overset{\text{SOCl}_2, \text{NEt}_3, \text{Et}_2\text{O, 18 h, 0°C - r.t.}}{\text{N} & \quad \text{N} \\
\end{align*}
\]

A solution of N,N’-di(4-methoxyphenyl)ethylenediamine (0.22 g, 0.8 mmol) in diethyl ether (30 mL) and triethylamine (0.24 mL, 1.8 mmol) was treated with thionyl chloride (0.57 mL, 0.8 mmol) by dropwise addition at 0 °C and stirred for 18 hours whilst attaining ambient temperature. Filtration of triethylamine hydrochloride and evaporation under reduced pressure afforded the thidiazolidine-1-oxide as a tan
coloured solid (0.23 g, 0.7 mmol, 92%); m.p. 149-151 ºC; νmax(film) /cm⁻¹ 2947, 1514, 1452, 1245, 1125, 1028, 823; ¹H-NMR (400 MHz, CDCl₃) 3.80 (6H, s), 3.83-3.86 (2H, m) 4.16-4.19 (2H, m), 6.91 (4H, d, J = 8.8 Hz), 7.14 (4H, d, J = 9.2) ¹³C NMR (100MHz CDCl₃) 48.7 (2 x CH₂), 55.6 (2 x OCH₃), 114.9 (Ar.), 120.5 (Ar.), 134.5 (quat.), 156.3 (quat.); m/z 318.1043; C₁₆H₁₈N₂SO₃ (M+) requires 318.1038.

Synthesis of N,N’-bis(p-tolyl)ethylenediamine (197)

\[ \text{p-Toluidine (4.0 g, 37.3 mmol) and benzotriazole (4.40 g, 37.3 mmol) were dissolved} \]
\[ \text{in ethanol (80 mL) and stirred at room temperature for 10 minutes. Glyoxal (1.80 g,} \]
\[ \text{18.6 mmol, 60% w/w aqueous) was then added and stirring was continued for 18} \]
\[ \text{hours. The formed precipitate was then filtered over vacuum to afford the} \]
\[ \text{benzotriazole adduct as a white solid (5.09 g, 10.7 mmol, 58%). The solid was then} \]
\[ \text{dissolved in tetrahydrofuran (80 mL). Sodium borohydride (1.20 g, 32.1 mmol) was} \]
\[ \text{added to the flask and stirred at room temperature for 18 hours. The solution was} \]
\[ \text{diluted with ethyl acetate (50 mL), then washed with water (50 mL) and 2M} \]
\[ \text{potassium hydroxide (50 mL). The formed precipitate was filtered off. The filtrate was} \]
\[ \text{dried over MgSO₄ and the solvent was removed to afford a pale yellow solid. (1.35 g,} \]
\[ \text{5.6 mmol, 30%); ¹H-NMR (400 MHz, CDCl₃) 2.23 (6H, s), 3.32 (4H, s), 3.70-4.60} \]
\[ \text{(2H, br), 6.55 (4H, d, J = 8.4 Hz), 6.98 (4H, d, J = 8.4 Hz); ¹³C-NMR (100 MHz,} \]
\[ \text{CDCl₃) 20.5 (2 x CH₃), 43.7 (2 x CH₂), 115.4 (4 x Ar), 127.3 (2 x quat.), 129.8 (4 x} \]
\[ \text{Ar), 145.8 (2 x quat).} \]

Synthesis of N,N’-bis(p-chlorophenyl)ethylenediamine (198)

\[ \text{4-Chloroaniline (4.71 g, 36.9 mmol) and benzotriazole (4.30 g, 36.9 mmol) were} \]
\[ \text{dissolved in ethanol (80 mL) and stirred at room temperature for 10 minutes. Glyoxal} \]
\[ \text{(1.7 g, 18.5 mmol, 60% w/w aqueous) was then added and stirring was continued for} \]
18 hours. The formed precipitate was then filtered over vacuum to afford the benzotriazole adduct as a white solid (5.21 g, 10.1 mmol, 55%). The solid was then dissolved in tetrahydrofuran (80 mL). Sodium borohydride (1.60 g, 42.3 mmol) was added to the flask and stirred at room temperature for 18 hours. The solution was diluted with ethyl acetate (50 mL), then washed with water (50 mL) and 2M sodium hydroxide (50 mL). The organic phase was dried over MgSO₄ and the solvent was removed to afford a white solid. (2.04 g, 7.3 mmol, 39%); ¹H-NMR (400 MHz, CDCl₃) 3.31 (4H, s), 3.60 – 3.90 (2H, bs), 6.53 (4H, d, J = 8.8 Hz), 7.12 (4H, d, J = 8.8 Hz); ¹³C-NMR (100 MHz, CDCl₃) 43.3 (2 x CH₂), 114.1 (4 x Ar.), 122.4 (2 x quat.), 128.9 (4 x Ar.), 146.2 (4 x Ar.).

**Synthesis of 2,5-di(p-tolyl)-1,2,5-thiadiazolidine-1-oxide (199)**

![Synthesis reaction](image)

N,N’-bis(p-tolyl)ethylenediamine (1.35 g, 5.6 mmol) was dissolved in diethyl ether (50 mL) at 0°C followed by addition of triethylamine (1.71 mL, 12.3 mmol). Thionyl chloride (0.41 mL, 5.6 mmol) was then slowly added. The resulting mixture was then brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water (3 x 50 mL) and the combined organic phases were evaporated under reduced pressure to afford the crude product. Recrystallisation in ether afforded a tan coloured solid (0.86 g, 3.0 mmol, 54%); m.p. 146-148 ºC; ν_max(film) / cm⁻¹ 2865, 2447, 1616, 1511, 1457, 1255, 1127, 1074, 901, 807, 748; ¹H-NMR (400 MHz, CDCl₃) 2.29 (6H, s), 3.81-3.85 (2H, m), 4.12-4.15 (2H, m), 7.05 (4H, d, J = 8.4 Hz), 7.14 (4H, d, J = 8 Hz); ¹³C-NMR (100 MHz, CDCl₃) 20.7 (2 x CH₃), 47.7 (2 x CH₂), 118.0 (4 x Ar.), 130.2 (4 x Ar.), 132.7 (2 x quat.), 138.9 (2 x quat.).

**Synthesis of 2,5-di(4-chlorophenyl)-1,2,5-thiadiazolidine-1-oxide (200)**

![Synthesis reaction](image)

N,N’-bis(p-chlorophenyl)ethylenediamine (2.12 g, 7.6 mmol) was dissolved in diethyl ether (50 mL) at 0°C followed by addition of triethylamine (2.31 mL, 16.6 mmol).
Thionyl chloride (0.55 mL, 7.6 mmol) was then slowly added. The resulting mixture was then brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water (3 x 50 mL) and the combined organic phases were evaporated under reduced pressure to afford the crude product. Recrystallisation in ether afforded a pale green solid (1.76 g, 5.4 mmol, 72%); m.p. 85-87 °C; \( \nu_{\text{max}}(\text{film}) \, \text{cm}^{-1} \) 2873, 1593, 1490, 1261, 1124, 1095, 814, 721, 611; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 3.76 - 3.83 (2H, m), 4.04 - 4.10 (2H, m), 7.03 (4H, d, \( J = 8.8 \, \text{Hz} \)), 7.28 (4H, d, \( J = 8.8 \, \text{Hz} \)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 47.6 (2 x CH\(_2\)), 118.7 (4 x Ar.), 128.9 (2 x quat.), 129.8 (4 x Ar.), 139.7 (2 x quat.); Compound unstable, could not obtain accurate mass.

General procedure for microwave Heck reaction using aryl iodides

\[
\begin{align*}
\text{R}^+\text{I} &\quad + \quad \text{179 (0.4 mol\%)} \quad \text{Pd}_2(\text{dba})_3 (0.1 \, \text{mol\%}, \text{DMF, NEt}_3, \text{mw, 200°C, 10 min.}) &\quad \rightarrow &\quad \text{R}^\cdot\text{R'}
\end{align*}
\]

Pd\(_2\)(dba\(_3\)) (2.3 mg, 0.0025 mmol) and 179 (0.01 mmol) were stirred in dimethylformamide (0.5 mL) for 1 h at room temperature. Aryl iodide (2.5 mmol, substrate/catalyst ratio = 1000:1), olefin (2.5 mmol) and triethylamine (0.42 mL, 3.0 mmol) were then added. The vial was crimped and heated at 200°C under microwave irradiation for 10 minutes. After the indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure. The product was isolated by flash chromatography.

General procedure for Heck reaction using conventional reflux conditions

\[
\begin{align*}
\text{R}^+\text{X} &\quad + \quad \text{179 (0.4 mol\%)} \quad \text{"Pd source" (0.1 mol\%), DMF or NMP, Base, \Delta} &\quad \rightarrow &\quad \text{R}^\cdot\text{R'}
\end{align*}
\]

Palladium source (0.0025 mmol) and 179 (0.01 mmol) were stirred in the chosen solvent (3 mL) for 1 h at room temperature. Aryl halide (2.5 mmol, substrate/catalyst ratio = 1000:1), olefin (2.5 mmol) and base (3.0 mmol) were then added. The reaction mixture was then heated under reflux. After the indicated time, the solution was diluted with ethyl acetate (30 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure. The product was isolated by flash chromatography.
General procedure for microwave Heck reaction using aryl bromides

\[
\text{Pd(dba)}_2 \ (1.5 \text{ mg, } 0.0025 \text{ mmol}) \text{ and } \textbf{179} \ (0.01 \text{ mmol}) \text{ were stirred in NMP (0.5 mL) for 1 h at rt. Aryl bromide (2.5 mmol, substrate/catalyst ratio = 1000:1), olefin (3.8 mmol) and sodium acetate (0.33g, 3.8 mmol) were then added. The flask was crimped and heated at 200°C under microwave irradiation for 30 minutes. The solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure. The product was isolated by flash chromatography.}
\]

Revised procedure for microwave Heck reaction using aryl bromides

\[
\text{Pd(dba)}_2 \ (1.5 \text{ mg, 0.0025 mmol}), \textbf{179} \ (0.02 \text{ mmol}), \text{ tetrabutylammonium bromide (1 mmol) and sodium acetate (0.33g, 3.8 mmol) were stirred in NMP (1.5 mL) for 1 hour at room temperature. Aryl bromide (2.5 mmol, substrate/catalyst ratio = 1000:1) and olefin (2.5 mmol) were then added. The flask was crimped and heated at 200°C under microwave irradiation for 30 minutes. The solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure. The product isolated by flash chromatography.}
\]

Synthesis of Methyl-trans-cinnamate (1)\textsuperscript{171}

Prepared according to general procedure for Heck reaction using aryl iodides from iodobenzene and methyl acrylate; \(v_{\text{max}}\) (film) /cm\(^{-1}\) 2922, 2838, 1600, 1511, 1462, 1254, 1165, 1112, 1030, 834; \(^1\text{H-NMR} (400 MHz \text{ CDCl}_3)\) 3.81 (3H, s), 6.46 (1H, d, \(J = 16.0 \text{ Hz}\)), 7.38-7.44 (3H, m) 7.52-7.56 (2H, m), 7.80 (1H, d, \(J = 16.0 \text{ Hz}\)) \(^{13}\text{C-NMR} (100 MHz, \text{ CDCl}_3)\) 51.8 (OCH\(_3\)), 117.3 (=CH), 128.4 (2 x Ar.), 128.9 (2 x Ar.), 130.7 (Ar.), 134.1 (quat.), 147.1 (=CH), 172.2 (quat.).
Synthesis of Trans-4-methoxystilbene (31)\textsuperscript{172}

Prepared according to general procedure for Heck reaction using aryl iodides from 4-iodoanisole and styrene; \( \nu_{\text{max}} \text{(film)} / \text{cm}^{-1} \) 2961, 2836, 1602, 1514, 1254, 1112, 1031, 966, 827, 812, 750, 689; \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \) 7.64–7.52 (m, 4H), 7.45–7.40 (m, 3H), 7.33 (d, \( J = 12.1 \text{ Hz} \), 1H), 7.10 (d, \( J = 12.1 \text{ Hz} \), 1H), 6.98 (d, \( J = 8.2 \text{ Hz} \), 2H), 3.88 (s, 3H). \(^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)} \) 55.3 (OCH\textsubscript{3}), 116.3 (2 x Ar.), 126.2 (2 x Ar.), 126.6 (=CH), 127.2 (=CH), 127.7 (2 x Ar.), 128.1 (Ar.), 128.6 (2 x Ar.), 130.1 (quat.), 137.6 (quat.), 159.3 (quat.).

Synthesis of \textit{n}-Butyl-trans-cinnamate (77)\textsuperscript{172}

Prepared according to general procedure for Heck reaction using aryl iodides from iodobenzene and butyl acrylate; \( \nu_{\text{max}} \text{(film)} / \text{cm}^{-1} \) 3061, 3028, 2959, 2933, 2873, 1713, 1638, 1449, 1310, 1280, 1172, 980, 768, 699; \(^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \) 0.84 (3H, t, \( J = 7.4 \text{ Hz} \)), 1.27-1.38 (2H, m), 1.55-1.62 (2H, m), 4.1 (2H, t, \( J = 6.8 \)), 6.31 (1H, d, \( J = 16.0 \text{ Hz} \)), 7.24-7.28 (3H, m), 7.37-7.43 (2H, m), 7.6 (1H, d, \( J = 16.0 \text{ Hz} \)) \(^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)} \) 13.7 (CH\textsubscript{3}), 19.1 (CH\textsubscript{2}), 30.6 (CH\textsubscript{2}), 64.0 (CH\textsubscript{2}), 117.5 (=CH), 128.4 (2 x Ar.), 129.0 (2 x Ar.), 130.3 (Ar.), 134.5 (quat.), 144.5 (=CH), 166.2 (quat.).

Synthesis of Trans-4-methylstilbene (180)\textsuperscript{172}

Prepared according to general procedure for Heck reaction using aryl iodides from 4-iodotoluene and styrene; \( \nu_{\text{max}} \text{(film)} / \text{cm}^{-1} \) 3025, 2924, 1655, 1601, 1448, 1265, 1109, 966, 808, 737, 701; \(^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \) 2.34 (3H, s) 7.02 (2H, d \( J = 2.8 \text{ Hz} \)) 7.13 (2H, d, \( J = 8.0 \text{ Hz} \)) 7.22 (1 H, t, \( J = 6.0 \text{ Hz} \)) 7.33 (2H, t, \( J = 7.6 \text{ Hz} \)) 7.39 (2H, d,
Synthesis of Trans-stilbene (181)\textsuperscript{172}

\[ \text{Ph}_2 + \text{Ph} \xrightarrow{179 (0.4 \text{ mol} \%)} \text{Pd}_2(dba)_3 (0.1 \text{ mol} \%, \text{DMF, NEt}_3, \text{mw, 200°C, 10 min.}) \]

Prepared according to general procedure for Heck reaction using aryl iodides from iodobenzene and styrene; \( \nu_{\text{max}} \) (film) /cm\(^{-1}\) 3077, 3020, 1597, 1495, 1108, 1072, 962, 764, 692; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 7.09 (2H, s), 7.23 (2H, t, \( J = 8.0 \) Hz), 7.33 (4H, t, \( J = 8.4 \) Hz), 7.50 (4H, m) \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 126.7 (2 x =CH), 127.7 (2 x Ar.), 128.4 (4 x Ar.), 128.9 (4 x Ar.), 137.3 (2 x quat.).

Synthesis of Trans-4-flourostilbene (182)\textsuperscript{173}

\[ \text{Ph}_2 + \text{Ph} \xrightarrow{179 (0.4 \text{ mol} \%)} \text{Pd}_2(dba)_3 (0.1 \text{ mol} \%, \text{DMF, NEt}_3, \text{mw, 200°C, 10 min.}) \]

Prepared according to general procedure for Heck reaction using aryl iodides from 1-iodo-4-flourobenzene and 4-chlorostyrene; \( \nu_{\text{max}} \) (film) /cm\(^{-1}\) 3025, 2921, 1513, 1494, 1448, 1265, 1109, 969, 808, 738, 706, 690; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 6.90-7.03 (4H, m), 7.15-7.32 (4H, m), 7.37-7.45 (3H, m) \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 115.5 (=CH), 115.7 (=CH), 126.4 (2 x Ar.), 127.5 (2 x Ar.), 127.9 (2 x Ar.), 128.0 (Ar.), 128.7 (2 x Ar.), 137.1 (quat.), 161.1 (quat.), 163.6 (quat.).

Synthesis of Trans-4-chlorostilbene (183)\textsuperscript{173}

\[ \text{Ph}_2 + \text{Ph} \xrightarrow{179 (0.4 \text{ mol} \%)} \text{Pd}_2(dba)_3 (0.1 \text{ mol} \%, \text{DMF, NEt}_3, \text{mw, 200°C, 10 min.}) \]

Prepared according to general procedure for Heck reaction using aryl iodides from iodobenzene and 4-chlorostyrene; \( \nu_{\text{max}} \) (film) /cm\(^{-1}\) 3079, 3019, 2919, 1591, 1448, 1405, 1112, 966, 817, 751, 690; \(^1\)H-NMR (400 MHz CDCl\(_3\)) 7.06 (2H, d, \( J = 2.8 \) Hz), 7.25-7.30 (5H, m), 7.44 (2H, d, \( J = 8.8 \) Hz), 7.51 (2H, d, \( J = 7.2 \) \(^{13}\)C-NMR (100
Synthesis of 1-Chloro-3-[(E)-2-(4-fluorophenyl)vinyl]benzene (184) 

\[
\begin{align*}
\text{F} & \quad + \quad \text{Cl} \\
\text{H} & \quad \quad \text{H}
\end{align*}
\]

Prepared according to general procedure for Heck reaction using aryl iodides from 1-iodo-4-fluorobenzene and 4-chlorostyrene; \( \nu_{\text{max}}(\text{film}) / \text{cm}^{-1} \) 3051, 2924, 1657, 1600, 1508, 1417, 1232, 1097, 968, 834; \(^1\)H-NMR (400 MHz CDCl\(_3\)) \(6.98 (1H, d, J = 16.4)\) 7.04-7.09 (3H, m), 7.35 (2H, d, \( J = 8.8\)), 7.44 (2H, d, \( J = 8.4\)), 7.47-7.51 (2H, m); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 115.6 (=CH), 115.8 (=CH), 127.1 (2 x Ar.), 127.2 (2 x Ar.), 127.6 (2 x Ar.), 128.1 (2 x Ar.), 133.1 (quat.), 133.2 (quat.), 135.7 (quat.), 163.7 (quat.).

Synthesis of 1-Fluoro-3-[(E)-2-(4-methoxyphenyl)vinyl]benzene (185) 

\[
\begin{align*}
\text{F} & \quad + \quad \text{OCH}_3 \\
\text{H} & \quad \quad \text{H}
\end{align*}
\]

Prepared according to general procedure for Heck reaction using aryl iodides from 1-iodo-4-fluorobenzene and 4-methoxystyrene; \( \nu_{\text{max}}(\text{film}) / \text{cm}^{-1} \) 2932, 1600, 1508, 1489, 1232, 1098, 968, 834; \(^1\)H-NMR (400 MHz CDCl\(_3\)) 3.84 (3H s) 6.84-6.96 (4H, m), 7.03 (2H, t, \( J = 8.8\)), 7.41-7.47 (4H, m) \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 55.3 (OCH\(_3\)), 114.2 (2 x Ar.) 115.6 (=CH), 115.8 (=CH), 125.4 (2 x Ar.) 127.6 (2 x Ar.), 128.0 (2 x Ar.), 133.2 (quat.), 135.6 (quat.), 161.2 (quat.), 163.7 (quat.).

Synthesis of 1-Chloro-3-[(E)-2-(4-methoxyphenyl)vinyl]benzene (186) 

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{Cl} \\
\text{H} & \quad \quad \text{H}
\end{align*}
\]

Prepared according to general procedure for Heck reaction using aryl iodides from 4-iodoanisole and 4-chlorostyrene; \( \nu_{\text{max}}(\text{film}) / \text{cm}^{-1} \) 2924, 2843, 1605, 1512, 1489, 1254, 1111, 1032, 832, 737, 615; \(^1\)H-NMR (400 MHz CDCl\(_3\)) 3.84 (3H, s) 6.87-6.94 (3H,
m) 7.03 (2H, d J = 13.2 Hz) 7.31 (2H, d, J = 12.0 Hz) 7.43 (4H, m) 13C-NMR (100 MHz, CDCl₃) 55.3 (OCH₃), 114.2 (2 x Ar.), 125.6 (=CH), 127.4 (2 x Ar.), 127.8 (2 x Ar.), 128.7 (2 x Ar.) 128.8 (=CH), 130.2 (quat.), 132.7 (quat.), 136.2 (quat.), 159.5 (quat.).

**Synthesis of 1-Methoxy-3-[(E)-2-(4-methylphenyl)vinyl]benzene (187)**

\[
\text{MeO} \quad \text{I} \quad + \quad \text{179 (0.8 mol\%)} \\
\text{Pd(dba)₂ (0.1 mol\%), NMP, NaOAc, TBAB, mw, 200 °C, 30 min}
\]

Prepare according to revised general procedure for Heck reaction using aryl bromides from 4-bromoanisole and 4-methylstyrene; νmax(film) /cm⁻¹ 3020, 2935, 2837, 1605, 1512, 1462, 1250, 1177, 1110, 1032, 968, 828, 737; ¹H-NMR (400 MHz CDCl₃) 2.28 (3H, s), 3.75 (3H, s), 6.82 (2H, d, J = 8.8 Hz), 6.87 (1H, d, J = 16.4 Hz), 6.95 (1H, d, J = 16.0 Hz), 7.07 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) 21.2 (CH₃), 55.3 (OCH₃), 114.1 (2 x Ar.), 126.2 (=CH), 126.6 (=CH), 127.2 (2 x Ar.), 127.6 (2 x Ar.), 129.4 (2 x Ar.), 130.4 (quat.), 134.9 (quat.), 137.1 (quat.), 159.2 (quat.).

**Synthesis of N,N’-dimethyl-N,N’-di(o-tolyl)ethylenediamine (206)**

2,5-di(orthotolyl)-1,2,5-thiadiazolidine-1-oxide (0.16 g, 0.56 mmol), was dissolved in toluene (30 mL). Methyl triflate (0.09 mL, 0.56 mmol) was then added and allowed to stir for 18 hours at room temperature. The reaction mixture was then washed with water (2 x 30 mL), dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford the product as an off-white solid (0.058 g, 0.24 mmol, 40%); ¹H-NMR (400 MHz, DMSO) 2.28 (6H, s), 2.92 (6H, s), 3.37 (4H, s), 7.18 (2H, t, J = 7.0 Hz), 7.23-7.31 (4H, m), 7.41 (2H, d, J = 8.0 Hz); ¹³C-NMR (100 MHz, DMSO) 17.4 (2 x CH₃), 44.3 (2 x CH₃), 53.1 (2 x CH₂), 120.2 (2 x Ar.), 126.5 (2 x Ar.), 127.3 (2 x Ar.), 131.5 (2 x quat.), 131.6 (2 x Ar.), 144.8 (2 x quat.).
Synthesis of $N,N'$-bis((S)-1-phenylethyl)benzene-1,2-diamine (207)$^{176}$

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{Ph} \quad \text{NH}_2 \\
& \quad \xrightarrow{\text{Pd}_2(\text{dba})_3, (\pm)-\text{BINAP}} \quad \text{Ph} \quad \text{NH} \quad \text{HN} \quad \text{Ph} \\
& \quad \text{NaO}^+\text{Bu}, \text{Toluene,} \\
& \quad 18 \text{ h, } \Delta
\end{align*}
\]

Into a three-neck round bottomed flask fitted with a reflux condenser and nitrogen bubbler, were dissolved $\text{Pd}_2(\text{dba})_3$ (0.12 g, 0.13 mmol) and (±)-BINAP (0.16 g, 0.26 mmol) in dry toluene (10 mL). The dark red solution was degassed with nitrogen for 10 minutes followed by heating under reflux for 15 minutes in order to activate the catalyst. On cooling, sodium tert-butoxide (0.59 g, 6.2 mmol), 1,2-dibromobenzene (0.40 mL, 3.3 mmol) and (S)-α-methylbenzylamine (1.07 mL, 8.3 mmol) were added to the reaction vessel which was then heated under reflux for another 18 hours. The solution was allowed to cool, diluted with toluene (40 mL) and then washed with brine (3 x 40 mL). The organic phase was dried over MgSO$_4$ and solvent removed under reduced pressure. The crude oil was purified by column chromatography (99:1 Petrol:EtOAc, $R_f = 0.21$) to afford a light brown oil (0.49 g, 1.6 mmol, 47%); $\nu_{\max}$ (film) / cm$^{-1}$ 3407, 1598, 1507, 1255, 740; $^1$H-NMR (400 MHz, CDCl$_3$) 1.59 (6H, d, $J = 6.4$ Hz), 3.71 (2H, bs), 4.52 (2H, q, $J = 6.4$ Hz), 6.41-6.54 (2H, m), 6.55-6.59 (2H, m), 7.24-7.29 (2H, m), 7.31-7.36 (4H, m), 7.39-7.41 (4H, m); $^{13}$C-NMR (100 MHz, CDCl$_3$) 22.7 (2 x CH$_3$), 55.9 (2 x CH), 113.6 (2 x Ar.), 125.9 (2 x Ar.), 126.9 (4 x Ar.), 128.6 (4 x Ar.), 136.3 (2 x Ar.), 145.24 (2 x quat.); $[\alpha]_D = +177.6$ (CHCl$_3$ c 0.9).

Synthesis of 1,3-bis((S)-1-phenylethyl)-1,3-dihydrobenzo [c][1,2,5]thiadiazolidine 1-oxide (208)

N,N'-bis((S)-1-phenylethyl)benzene-1,2-diamine (0.44 g, 1.4 mmol) was dissolved in diethyl ether (60 mL) at 0°C followed by addition of triethylamine (0.39 mL, 2.8 mmol). Thionyl chloride (0.10 mL, 1.4 mmol) was then slowly added. After addition of the thionyl chloride the resulting mixture was brought back to room temperature and allowed to stir for 18 hours. The reaction mixture was then washed with water (60
mL) and brine (60 mL) and the combined organic phases were evaporated under reduced pressure to afford the crude product as a purple oil. The product was purified by column chromatography (15:1 Petrol:EtOAc, Rf = 0.33) to afford a colourless crystalline solid (0.15 g, 0.42 mmol, 30%); νmax(film) /cm⁻¹ 3059, 2973, 2927, 1589, 1485, 1375, 1282, 1127, 1029, 904, 757, 733, 699; ¹H-NMR (400 MHz, CDCl₃) 1.87 (3H, d, J = 7.2 Hz), 1.91 (3H, d, J = 7.2 Hz), 5.10 (1H, q, J = 7.2 Hz), 5.20 (1H, q, J = 7.2 Hz), 6.32 (1H, dd, J = 1.2, 7.6 Hz), 6.51 (1H, dd, J = 1.2, 7.6 Hz), 6.62 (1H, td, J = 1.2, 7.6 Hz), 6.68 (1H, td, J = 1.2, 7.6 Hz), 7.15-7.33 (6H, m), 7.35-7.46 (4H, m); ¹³C-NMR (100 MHz, CDCl₃) 19.5 (CH₃), 20.6 (CH₃), 54.3 (CH), 56.1 (CH), 109.2 (Ar.), 109.6 (Ar.), 119.3 (Ar.), 119.4 (Ar.), 125.4 (2 x Ar.), 126.0 (2 x Ar.), 126.4 (Ar.), 126.9 (Ar.), 127.7 (4 x Ar.), 131.8 (quat.), 131.9 (quat.), 139.7 (quat.), 140.3 (quat.); m/z 362.1458; C₂₂H₂₂N₂O₅ (M⁺) requires 362.1452; [α]D = +83.0 (CHCl₃ c 0.8).

Synthesis of (R)-5-phenylmorholin-3-one (209)¹⁷⁷

(R)-(-)-2-Phenylglycinol (2.03 g, 14.7 mmol) was dissolved in dry tetrahydrofuran (50 mL). Sodium hydride (0.65 g, 16.2 mmol, 60% in mineral oil) was then added and allowed to stir for 20 minutes. Ethyl chloroacetate (1.44 mL, 14.7 mmol) was then added and the reaction mixture was heated under reflux for 18 hours. The yellow solution was then poured into 1M HCL (100 mL) followed by extraction with EtOAc (3 x 60 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was recrystallised in ether to afford a beige solid. (1.58 g, 8.9 mmol, 61%); νmax(film) /cm⁻¹ 3184, 2920, 2856, 1672, 1413, 1342, 1315, 1286, 1124, 1068, 967, 946; ¹H-NMR (400 MHz, CDCl₃) 3.56 (1H, dd, J = 8.4, 12.0 Hz), 4.04 (1H, dd, J = 4.4, 11.6 Hz), 4.21 (1H, d, J = 16.8 Hz), 4.30 (1H, d, J = 16.8 Hz), 4.75 (1H, dd, J = 4.4 Hz), 7.25-7.45 (5H, m); ¹³C-NMR (100 MHz, CDCl₃) 56.6 (CH), 67.7 (CH₂), 70.2 (CH₂), 126.3 (Ar.), 128.6 (Ar.), 129.1 (Ar.), 137.5 (quat.), 169.2 (quat.); [α]D = -71.54 (CHCl₃ c 1.0).
Synthesis of \((R)-5\text{-methoxy-3-phenyl-3,6-dihydro-2H-1,4-oxazine}\) \((210)^{178}\)

\[(R)-5\text{-phenylmorpholin-3-one} \text{(0.55 g, 3.1 mmol)}\] was dissolved in dichloromethane \((30 \text{ mL})\). This solution was added dropwise to a suspension of trimethyloxonium tetrafluoroborate \((0.50 \text{ g, 3.4 mmol})\) in dichloromethane \((30 \text{ mL})\). The reaction mixture changed from a pale red colour on addition to a pale yellow as it was allowed to stir at room temperature for 18 hours. The solution was diluted with dichloromethane \((60 \text{ mL})\) and washed with saturated aqueous NaHCO\(_3\) solution \((60 \text{ mL})\). The organic phase was dried over MgSO\(_4\) and the solvent was removed under reduced pressure. A small amount of Et\(_2\)O was added to the resulting mixture of oil and crystalline solid to allow filtration of the solid material. Removal of solvent from the filtrate afforded a light brown oil \((0.25 \text{ g, 1.3 mmol, 42%})\); \(\nu_{\text{max}}\) (film) /cm\(^{-1}\): 2944, 2845, 1740, 1680, 1451, 1438, 1243, 1124, 1001, 878, 756, 700; \(^1\)H-NMR \((400 \text{ MHz, CDCl}_3\) \(3.21 \text{ (1H, dd, } J = 8.4, 11.6 \text{ Hz}), 3.79 \text{ (3H, s), } 3.98 \text{ (1H, dd, } J = 4.0, 11.2 \text{ Hz)}, 4.06 \text{ (1H, dd, } J = 2.0, 16.4 \text{ Hz}), 4.16 \text{ (1H, dd, } J = 1.6, 16.0 \text{ Hz}), 4.70-4.74 \text{ (1H, m), } 7.23-7.36 \text{ (5H, m)}\); \(^{13}\)C-NMR \((100 \text{ MHz, CDCl}_3\) \(52.3 \text{ (OCH}_3\), 58.0, (CH), 62.3 (CH\(_2\)), 69.4 (CH\(_2\)), 127.0 \text{ (Ar.)}, 127.4 \text{ (Ar.)}, 140.6 \text{ (quat.), } 161.8 \text{ (quat.)}; [\alpha]_D = -197.62 \text{ (CHCl}_3 \text{ c 1.0).}\)

Synthesis of \((R)-3\text{-phenyl-5-(2-phenylhydrazono)morpholine hydrochloride}\) \((211)^{178}\)

Phenylhydrazine hydrochloride \((0.35 \text{ g, 2.5 mmol})\) and \((R)-5\text{-methoxy-3-phenyl-3,6-dihydro-2H-1,4-oxazine} \text{(0.47 g, 2.5 mmol)}\) were dissolved in methanol \((40 \text{ mL})\) and heated under reflux for 3 hours. The solvent was then removed under reduced pressure and the crude red solid was recrystallised in ethanol to afford a colourless crystalline solid. \((0.23 \text{ g, 0.8 mmol, 30%}); \(^1\)H-NMR \((400 \text{ MHz, DMSO}) \(3.85 \text{ (1H, dd, } J = 5.2, 12.4 \text{ Hz}), 4.21 \text{ (1H, dd, } J = 4.4, 12.0 \text{ Hz}), 4.75 \text{ (1H, m), } 4.83 \text{ (1H, d, } J = 16.8 \text{ Hz)}, 4.94 \text{ (1H, d, } J = 16.8 \text{ Hz), 6.88-7.00 (3H, m), 7.25-7.32 (2H, m), 7.33-7.42 (5H, m),\)}}
8.49 (1H, s), 10.58 (1H, s), 11.65 (1H, s); $^{13}$C-NMR (100 MHz, DMSO) 52.8 (CH), 61.6 (CH$_2$), 69.0 (CH$_2$), 113.5 (Ar.), 120.9 (Ar.), 127.1 (Ar.), 128.1 (Ar.), 128.4 (Ar.), 129.0 (Ar.), 138.1 (quat.), 145.9 (quat.), 162.8 (quat.) $[\alpha]_D$ = -99.0 (CHCl$_3$ c 0.8).

**Synthesis of (2R)-4-Diphenyl-2,4,5,7-tetrahydro-6-oxa-3-thia-1,2,3a-triaza-indene (3S)-oxide (212)**

![Reaction Scheme](image)

To a solution of (R)-3-phenyl-5-(2-phenylhydrazono)morpholine hydrochloride (0.32 g, 1.1 mmol) in Et$_2$O (30 mL) was added triethylamine (0.45 mL, 3.2 mmol). The solution was cooled on an ice bath and allowed to stir for 20 minutes. Thionyl chloride (0.08 mL, 1.1 mmol), diluted with Et$_2$O (15 mL), was slowly added to the reaction mixture and allowed to stir for 2 hours while attaining room temperature. The reaction mixture was washed with water and brine. The organic phase was dried over MgSO$_4$ and solvent removed to afford a viscous purple oil. The crude material was purified by column chromatography (9:1 Petrol:EtOAc, Rf = 0.83) to afford a colourless solid (0.26 g, 0.8 mmol, 71%); 1H-NMR (400 MHz, CDCl$_3$) 3.70 (1H, dd, $J$ = 10.4, 12.0 Hz), 4.24 (1H, ddd, $J$ = 0.8, 4.0, 11.6 Hz), 4.61 (1H, d, $J$ = 14.8 Hz), 5.07 (1H, dd, $J$ = 1.2, 15.2 Hz), 5.19 (1H, dd, $J$ = 4.4, 10.0 Hz), 7.12-7.16 (1H, m), 7.33-7.38 (2H, m), 7.42-7.48 (7H, m); m/z 313.0881; C$_{16}$H$_{15}$N$_3$O$_2$S (M+) requires 313.0885; $[\alpha]_D$ = -95.8 (CHCl$_3$ c 0.9).

**Synthesis of (4aS,9aR)-4,4a,9,9a-tetrahydroinden-2,1-b[1,4]oxazin-3(2H)-one (213)**

![Reaction Scheme](image)

To a suspension of sodium hydride (1.33 g, 33.0 mmol, 60% in mineral oil) in dry tetrahydrofuran (80 mL) was added (1S, 2R)-(--)-cis-1-amino-2-indanol (4.0 g, 30.0 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Ethyl chloroacetate (3.20 mL, 30.0 mmol) was then added and the reaction mixture was heated under reflux for 18 hours. The reaction mixture was carefully quenched with
saturated aqueous ammonium chloride (50 mL) followed by extraction with EtOAc (3 x 80 mL). The combined organic layers were dried over MgSO₄ and solvent was removed under reduced pressure to afford a colourless solid. (2.07 g, 10.9 mmol, 37%); v_max(film) / cm⁻¹ 2922, 1671, 1424, 1333, 1107, 740; ¹H-NMR (400 MHz, DMSO) 2.87 (1H, d, J = 16.8 Hz), 3.17 (1H, dd, J = 5.0, 16.6 Hz), 3.84 (1H, d, J = 16.4 Hz), 4.01 (1H, d, J = 16.0 Hz), 4.47 (1H, t, J = 4.6 Hz), 4.68 (1H, t, J = 4.0 Hz), 7.22-7.27 (3H, m), 7.43 (1H, d, J = 5.6 Hz) 8.87 (1H, s); ¹³C-NMR (100 MHz, DMSO) 37.1 (CH₂), 57.6 (CH), 65.8 (CH₂), 123.9 (Ar.), 124.7 (Ar.), 126.6 (Ar.), 127.5 (Ar.), 139.6 (quat.), 142.2 (quat.), 167.4 (quat.); [α]D = +27.6 (MeOH, c 0.9).

**Synthesis of (4aS,9aR)-3-methoxy-2,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazine (214)**

(4aS,9aR)-4,4a,9,9a-Tetrahydroindeno[2,1-b][1,4]oxazin-3(2H)-one (1.0 g, 5.3 mmol) was dissolved in dichloromethane (30 mL). This solution was added dropwise to a suspension of trimethyloxonium tetrafluoroborate (0.86 g, 5.8 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 18 hours. The solution was diluted with more dichloromethane (60 mL) and washed with saturated aqueous NaHCO₃ solution (60 mL). The organic phase was dried over MgSO₄ and solvent was removed under reduced pressure. Removal of solvent from the filtrate afforded a light brown oil which was used in the next step without further purification (0.83 g, 4.1 mmol, 77%); v_max(film) / cm⁻¹ 2922, 1687, 1254, 1110, 740; ¹H-NMR (400 MHz, CDCl₃) 3.08 (1H, d, J = 16.7 Hz), 3.18 (1H, dd, J = 4.8, 16.8 Hz), 3.78 (3H, s), 3.94 (1H, d, J = 16.0 Hz), 3.96 (1H, dd, J = 1.6, 16.0 Hz), 4.29 (1H, t, J = 4.4 Hz), 4.88 (1H, d, J = 4.0 Hz), 7.21-7.28 (3H, m), 7.49 (1H, d, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) 37.6 (CH₂), 52.3 (OCH₃), 61.4 (CH₂), 62.8 (CH), 75.1 (CH), 124.6 (Ar.), 124.9 (Ar.), 126.8 (Ar.), 127.5 (Ar.), 139.1 (quat.), 143.3 (quat.), 161.7 (quat.).
Synthesis of (4aS,9aR,Z)-3-(2-phenylhydrazono)-2,3,4,4a,9,9a-
hexahydroinden[2,1-b][1,4]oxazine hydrochloride (215)

Phenylhydrazine hydrochloride (0.59 g, 4.1 mmol) and (4aS,9aR)-3-methoxy-
2,4a,9,9a-tetrahydroinden[2,1-b][1,4]oxazine (0.83 g, 4.1 mmol) were dissolved in
methanol (40 mL) and heated under reflux for 3 hours. The solvent was then removed
under reduced pressure to afford a crude red solid which was used without further
purification (0.15 g, 3.7 mmol, 90%); \( \nu_{\text{max}}(\text{film}) / \text{cm}^{-1} \) 3206, 2923, 1742, 1662, 1603,
1496, 1236, 1127, 746; 1H-NMR (400 MHz, DMSO) 2.97 (1H, d, \( J = 16.8 \text{ Hz} \)), 3.28
(1H, dd, \( J = 5.0, 17.0 \text{ Hz} \)), 4.68 (1H, d, \( J = 16.8 \text{ Hz} \)), 4.74 (1H, t, \( J = 4.4 \text{ Hz} \)), 4.78
(1H, d, \( J = 16.4 \text{ Hz} \)), 4.90 (1H, t, \( J = 3.2 \text{ Hz} \)), 6.89-6.96 (3H, m), 6.99 (1H, d, \( J = 8.0 \text{ Hz} \)), 7.21-7.34 (5H, m), 7.54 (1H, d, \( J = 6.8 \text{ Hz} \)), 8.64 (1H, s), 11.04 (1H, s); \(^{13}\text{C}-\nNMR (100 MHz, DMSO) 37.0 (CH\(_2\)), 56.1 (CH), 60.2 (CH\(_2\)), 76.7 (CH), 113.7 (2 x
Ar.), 121.0 (Ar.), 124.5 (Ar.), 124.9 (Ar.), 126.8 (Ar.), 128.1 (Ar.), 129.1 (2 x Ar.),
139.8 (quat.), 139.9 (quat.), 145.9 (quat.), 162.3 (quat.); \( [\alpha]_{D} = +41.5 \text{ (MeOH, c 1.1).} \)

Synthesis of (5aR,10bS)-2-phenyl-4,5a,6,10b-tetrahydro-2H-indeno[2,1-
b][1,2,3,5]thiatriazolo[5,4-d][1,4]oxazine (216)

(4aS,9aR,Z)-3-(2-Phenylhydrazono)-2,3,4,4a,9,9a-hexahydroinden[2,1-
b][1,4]oxazine hydrochloride (0.32 g, 1.0 mmol) was dissolved in diethyl ether (50
mL) at 0°C. Triethylamine (0.46 mL, 3.3 mmol) was then added and allowed to stir
for 15 minutes. Thionyl chloride (0.08 mL, 1.0 mmol) was then slowly added. The
resulting mixture was then brought back to room temperature and allowed to stir for a
further 2 hours. The reaction mixture was then washed with water (3 x 40 mL), dried
over MgSO\(_4\), filtered and the solvent was evaporated under reduced pressure to afford
the crude product. The crude materiel was purified by column chromatography to
afford the product as a brown solid (0.25 g, 0.8 mmol, 78%); 1H-NMR (400 MHz,
CDCl₃) 3.23 (1H, d, J = 16.8 Hz), 3.35 (1H, dd, J = 5.2, 16.8 Hz), 4.68 (1H, td, J =
1.3, 4.8 Hz), 4.72 (1H, d, J = 15.6 Hz), 4.86 (1H, d, J = 15.6 Hz), 5.48 (1H, d, J = 4.4
Hz), 7.18 (1H, t, J = 7.4 Hz), 7.29 – 7.35 (3H, m), 7.40 (2H, t, J = 8.0 Hz), 7.46 – 7.59
(3H, m); 13C-NMR (100 MHz, CDCl₃) 37.4 (CH₂), 56.7 (CH), 61.7 (CH₂), 78.6 (CH),
119.4 (2 x Ar.), 124.4 (Ar.), 124.8 (Ar.), 125.3 (Ar.), 127.6 (Ar.), 128.9 (Ar.), 129.6 (2
x Ar.), 139.0 (quat.), 139.4 (quat.), 139.6 (quat.), 140.1 (quat.); [α]D = +38.7 (CHCl₃,
c 1.0).

**Synthesis of (S)-Phenylalanine Methyl Ester Hydrochloride (217)**

![Chemical structure](image)

Methanol (150 mL) was cooled to 0°C in an ice bath. Acetyl chloride (30 mL) was
then added dropwise to the flask. (S)-Phenylalanine (10.0 g, 60.6 mmol) was then
added to the solution and heated under reflux for 2 hours. The flask was then allowed
to cool and solvent removed under reduced pressure to afford a white solid in
quantitative yield; 1H-NMR (400 MHz, D₂O) 3.19 (1H, dd, J = 7.6, 14.8 Hz), 3.31
(1H, dd, J = 5.6, 14.4 Hz), 3.80 (3H, s), 4.39 (1H, dd, J = 6.0, 7.6 Hz), 7.24 (2H, d, J =
7.2 Hz), 7.32-7.41 (3H, m); 13C-NMR (100 MHz, D₂O) 35.5 (CH₂), 53.5 (CH), 54.1
(CH₃), 128.1 (Ar.), 129.2 (2 x Ar.), 129.4 (2 x Ar.), 133.7 (quat.), 170.0 (quat.).

**Synthesis of (S)-phenylalanine N-methyl amide (218)**

![Chemical structure](image)

(S)-Phenylalanine methyl ester hydrochloride (6.0 g, 27.9 mmol) was added to an
ethanolic solution of methylamine (14 mL, 8.0 M). The solution was stirred for 24
hours at room temperature. Solvent was removed under reduced pressure. Diethyl
ether (30 mL) was added to the flask and evaporated several times in order to wash the
product of excess methylamine. The white solid was subsequently washed with
saturated aqueous NaHCO₃ solution and extracted with dichloromethane to afford a
brown oil which would precipitate to a white solid. (3.08 g, 17.3 mmol, 62%) \( ^1 \)H-NMR (400 MHz, CDCl\(_3\)) 2.68 (1H, dd, \( J = 9.2, 13.6 \) Hz), 2.79 (3H, d, \( J = 5.2 \) Hz), 3.28 (1H, dd, \( J = 4.0, 14.0 \) Hz), 3.62 (1H, dd, \( J = 4, 9.2 \) Hz), 7.19-7.32 (5H, m) \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\)) 26.0 (CH\(_3\)), 41.3 (CH\(_2\)), 56.7 (CH), 127.0 (Ar.), 128.9 (2 x Ar.), 129.5 (2 x Ar.), 138.3 (quat.), 175.1 (quat.).

**Synthesis of (S)-2-(4-methoxybenzylamino)-N-methyl-3-phenylpropamide (219)**

(S)-Phenylalanine N-methyl amide (3.07 g, 17.2 mmol) and 4-methoxybenzaldehyde (2.10 mL, 17.2 mmol) were stirred at room temperature in ethanol (100 mL) for 4 hours. Sodium borohydride (1.65 g, 68.8 mmol) was added and the mixture was allowed to stir for a further 24 hours by which time it had become colourless. The reaction was quenched with 2M HCl and extracted with dichloromethane (4 x 60 mL). The combined organics were dried over MgSO\(_4\) and solvent was removed under reduced pressure. The crude material was purified by column chromatography to afford the product a light brown oil (2.61 g, 9.2 mmol, 54%); \( ^1 \)H-NMR (400 MHz, CDCl\(_3\)) 2.70 (1H, dd, \( J = 9.6, 14.0 \) Hz), 2.79 (3H, d, \( J = 4.8 \) Hz), 3.18 (1H, dd, \( J = 4.0, 13.6 \) Hz), 3.36 (1H, dd, \( J = 4, 9.2 \) Hz), 3.45 (1H, d, \( J = 13.2 \) Hz), 3.60 (1H, d, \( J = 12.8 \) Hz), 3.78 (3H, s), 6.77 (2H, d, \( J = 6.8 \) Hz), 6.97 (2H, d, \( J = 8.8 \) Hz), 7.13 (2H, d, \( J = 6.8 \) Hz), 7.19-7.24 (3H, m); \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\)) 25.9 (CH\(_3\)), 39.3 (CH\(_2\)), 51.9 (CH\(_2\)), 55.2 (OCH\(_3\)), 62.9 (CH), 113.8 (2 x Ar.), 126.8 (Ar.), 128.6 (2 x Ar.), 129.0 (2 x Ar.), 129.1 (2 x Ar.), 129.3 (2 x Ar.), 131.1 (quat.), 137.4 (quat.), 158.7 (quat.), 174.3 (quat.).

**Synthesis of (S)-4-benzyl-5-(4-methoxybenzyl)-2-methyl-1,2,5-thiadiazolidin-3-one-1-oxide (220)**

To a solution of (S)-2-(4-methoxybenzylamino)-N-methyl-3-phenylpropamide (2.40 g, 8.1 mmol) in dichloromethane (80 mL) was added triethylamine (2.50 mL, 17.7 mmol). The solution was cooled on an ice bath with stirring. Thionyl chloride (0.59
mL, 8.1 mmol), diluted with dichloromethane (25 mL), was slowly added to the reaction mixture and allowed to stir for 6 hours while attaining room temperature. The reaction mixture was washed with water (40 mL) and brine (40 mL). The organic phase was dried over MgSO4 and solvent was removed under reduced pressure to afford a crude brown oil. This was purified by column chromatography to afford a bright yellow oil (1.32 g, 3.8 mmol, 48%); \( \nu_{\text{max}} \) (film) / cm\(^{-1}\) 2933, 2835, 1711, 1610, 1513, 1454, 1303, 1249, 1148, 1031, 909, 831, 749, 700; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 2.98 (1H, dd, \( J = 9.6, 13.6 \) Hz), 3.06 (3H, s) 3.23-3.31 (1H, m), 3.63 (1H, d, \( J = 14.8 \) Hz), 3.75 (3H, s), 3.82 (1H, dd, \( J = 4.0, 9.6 \) Hz), 4.20 (1H, d, \( J = 14.4 \) Hz) 6.77 (2H, d, \( J = 8.8 \) Hz), 6.83 (2H, d, \( J = 8.4 \) Hz), 7.20-7.35 (5H, m); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) 26.7 (CH\(_3\)), 41.0 (CH\(_2\)), 51.8 (CH\(_2\)), 55.2 (OCH\(_3\)), 62.2 (CH), 114.2 (2 x Ar.), 126.4 (quat.), 127.1 (Ar.), 128.6 (2 x Ar.), 129.6 (2 x Ar.), 129.9 (2 x Ar.), 136.8 (quat.), 159.6 (quat.), 173.7 (quat.); \([\alpha]_D = -87.23 \) (CHCl\(_3\) c 1.1).

**Synthesis of (S)-N-(tert-Butyloxycarbonyl)phenylalanine (222)**

L-Phenylalanine (4.89 g, 29.6 mmol) was dissolved in 1 M aqueous sodium hydroxide solution (80 mL). Di-tert-butyl dicarbonate (7.10 g, 32.5 mmol) was dissolved in 1,4-dioxane (30 mL). The two solutions were combined and stirred for 2 hours at room temperature. The reaction mixture was then acidified to pH 2 with 2 M aqueous hydrochloric acid and the organics were extracted with ethyl acetate (3 x 60 mL). The organic phases were combined and dried over MgSO\(_4\). Solvent was removed under reduced pressure to afford a viscous pale oil (7.32 g, 27.6 mmol, 93%). Spectral data matched literature description.
Synthesis of tert-butyl (S)-1-oxo-3-phenyl-1-((R)-1-phenylethylamino)propan-2-ylcarbamate (223) \(^{152}\)

\[
\begin{align*}
\text{OH} & \quad \text{(R)-(+)\text-\alpha\text{-methylbenzylamine} } \\
& \quad \text{EDCI, NMM, CH}_2\text{Cl}_2, \quad 18 \text{ h, r.t. }
\end{align*}
\]

Boc-phenylalanine (7.32 g, 27.6 mmol) was dissolved in dichloromethane (150 mL) with (R)-(+)\text-\alpha\text{-methylbenzylamine (3.56 mL, 27.6 mmol) and N-methylmorpholine (3.33 mL, 30.3 mmol). EDCI (5.80 g, 30.3 mL) was added portion-wise and allowed to stir at room temperature for 18 hours. The reaction was quenched with 2M HCl (30 mL). The organic phase was separated and washed with brine (50 mL). The organic phase was then washed with saturated aqueous sodium hydrogen carbonate (2 x 50mL). It was then dried over MgSO}_4, filtered and the solvent was removed under reduced pressure to afford a white solid (1.30 g, 3.5 mmol, 13%); \(\nu_{\text{max}}\) (film) /cm\(^{-1}\) 3290, 1651, 1532, 1171, 1020, 734, 697; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.39 (12H, m), 2.99 (2H, d, \(J = 6.8\) Hz), 4.41 (1H, m), 5.05 (1H, m), 5.39 (1H, m), 6.54 (1H, m), 7.15-7.30 (10H, m); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) 28.2 (CH\(_3\)), 38.6 (CH\(_2\)), 48.6 (CH), 79.8 (quat.), 126.1 (2 x Ar.), 126.7 (Ar.), 127.1 (Ar.), 128.3 (2 x Ar.), 128.5 (2 x Ar.), 129.3 (2 x Ar.), 136.7 (quat.), 142.8 (quat.), 170.4 (quat.), 171.1 (quat.).

Synthesis of (S)-2-amino-3-phenyl-N-((R)-1-phenylethyl)propanamide (225) \(^{181}\)

\[
\begin{align*}
\text{OH} & \quad \text{Trifluoroacetic Acid} \\
& \quad \text{CH}_2\text{Cl}_2, \quad 1 \text{ h, r.t. }
\end{align*}
\]

Tert-butyl (S)-1-oxo-3-phenyl-1-((R)-1-phenylethylamino)propan-2-ylcarbamate (2.5 g, 8.15 mmol) was dissolved in dichloromethane (50 mL). Trifluoroacetic acid (4 equiv.) was then added and allowed to stir at room temperature for an hour. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL). The organic phase was dried over MgSO\(_4\), filtered and the solvent was removed under reduced pressure to afford a white solid (2.00 g, 7.5 mmol, 92%); \(\nu_{\text{max}}\) (film) /cm\(^{-1}\) 3065, 1666, 1200, 699; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.34 (3H, d, \(J = 6.8\) Hz), 2.98 (1H, dd, \(J = 8.2, 13.8\) Hz), 3.06 (1H, dd, \(J = 6.2, 13.8\) Hz), 4.40 (1H, m), 4.82 (1H, quint, \(J = 6.8\) Hz), 6.98 (4H, d, \(J = 7.6\) Hz), 7.15-7.25 (6H, m); \(^13\)C-NMR
(100 MHz, CDCl$_3$) 21.1 (CH$_3$), 37.3 (CH$_2$), 50.2 (CH), 55.1 (CH), 125.9 (2 x Ar.), 127.7 (Ar.), 128.1 (Ar.), 128.8 (2 x Ar.), 129.3 (2 x Ar.), 129.3 (2 x Ar.), 132.9 (quat.), 141.6 (quat.), 167.4 (quat.).

Synthesis of (S)-2-(4-methoxybenzylamino)-2-phenyl-N-(R)-1-phenylethyl)propanamide (226)


g~O
\begin{align*}
\text{NH}_2 & \quad \text{N} \\
\text{R} & \quad \text{PMB}
\end{align*}

\[ \text{i) } \text{p-Anisaldehyde, EtOH, 2 h, r.t.} \]
\[ \text{ii) } \text{NaBH}_4, 2 \text{ h, r.t.} \]

(S)-2-amino-3-phenyl-N-((R)-1-phenylethyl)propanamide (0.43 g, 1.1 mmol) was dissolved in ethanol (40 mL). P-anisaldehyde (0.15 mL, 1.2 mmol) was then added to the solution and stirred at room temperature for 2 hours. MgSO$_4$ was then added to the solution and allowed to stir for a further 30 minutes. The mixture was filtered and sodium borohydride (0.80 g, 2.2 mmol) was carefully added to the filtrate with stirring. The reaction mixture was then allowed to stir at room temperature for a further 2 hours. 2M aq. HCl (20 mL) was then carefully added to quench the reaction followed by water (30 mL). Ethanol was removed under reduced pressure and the organics were extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine (60 mL). The organic phase was dried over MgSO$_4$, filtered and solvent removed under reduced pressure. The mixture was diluted with cold ether (10 mL) and the solid material was filtered. Solvent was removed from the filtrate under reduced pressure to afford the product as a pale oil which was used directly in the next step without further purification (0.30 g).

Synthesis of (S)-4-benzyl-5-(4-methoxybenzyl)-2-((R)-1-phenylethyl)-1,2,5-thiadiazolidin-3-one 1-oxide (227)

\[ \text{SOCl}_2 \]
\[ \text{NEt}_3, \text{CH}_2\text{Cl}_2, 18 \text{ h, r.t.} \]

Crude (S)-2-(4-methoxybenzylamino)-2-phenyl-N-(R)-1-phenylethyl)propanamide (0.30 g) was dissolved in dichloromethane (50 mL) at 0°C followed by addition of triethylamine (0.24 mL, 1.7 mmol). Thionyl chloride (0.06 mL, 0.9 mmol) was then slowly added. The resulting mixture was then brought back to room temperature and
allowed to stir for 18 hours. The reaction mixture was then washed with water (3 x 50 mL) and the combined organic phases were evaporated under reduced pressure to afford the crude product. Recrystallisation in ether afforded a white solid (0.19 g, 0.4 mmol, 36% over two steps); $\nu_{\text{max}}$(film) /cm$^{-1}$ 3295, 2922, 1640, 1512, 1246, 1107, 700; $^1$H-NMR (400 MHz, CDCl$_3$) 1.47 (3H, d, $J = 7.2$ Hz), 2.76 (1H, dd, $J = 9.2, 14.0$ Hz), 3.22 (1H, d, $J = 4.2, 13.8$ Hz), 3.37 (1H, dd, $J = 4.4, 9.2$ Hz), 3.42 (1H, $J = 12.8$ Hz), 3.52 (1H, $J = 12.4$ Hz), 3.76 (3H, s), 5.13, (1H, quint, $J = 7.6$ Hz), 6.72 (2H, d, $J = 8.8$ Hz), 6.86 (2H, d, $J = 8.8$ Hz), 7.23-7.37 (10H, m); $^{13}$C-NMR (100 MHz, CDCl$_3$) 21.9 (CH$_3$), 39.2 (CH$_2$), 48.1 (CH$_2$), 52.0 (CH), 55.2 (OCH$_3$), 62.9 (CH), 113.9 (2 x Ar.), 126.1 (2 x Ar.), 126.8 (Ar.), 127.3 (Ar.), 128.7 (2 x Ar.), 128.9 (2 x Ar.), 129.2 (2 x Ar.), 129.4 (2 x Ar.), 137.4 (quat.), 143.3 (quat.), 158.8 (quat.), 172.4 (quat.), 206.9 (quat.); [$\alpha$]$_D$ = -65.6 (CHCl$_3$ c 0.1).

Synthesis of 1-(methylsulfonyl)-1H-benzo[d][1,2,3]triazole (228)$^{182}$

Benzotriazole (11.90 g, 100.0 mmol) was placed in a 500 mL three-necked round bottomed flask under a nitrogen atmosphere. It was then suspended in anhydrous toluene (120 mL) and cooled in an ice bath with stirring. Pyridine (12.30 mL, 120.0 mmol) was added and the resulting solution was stirred for 10 minutes. Methanesulfonylchloride (9.30 mL, 120.0 mmol) was carefully added and the reaction mixture was allowed to stir for 18 hours while attaining room temperature. The mixture was then diluted with ethyl acetate (150 mL), washed with water (100 mL) and then brine (100 mL). The organic phase was dried over MgSO$_4$ and solvent was removed under reduced pressure to afford the product as a white solid (16.50 g, 83.7 mmol, 84%); $\nu_{\text{max}}$(film) /cm$^{-1}$ 3024, 2929, 1378, 1182, 959, 769, 746; $^1$H-NMR (400 MHz, CDCl$_3$) 3.52 (3H, s), 7.54 (1H, t, $J = 7.4$ Hz), 7.68 (1H, t, $J = 7.6$ Hz), 8.02 (1H, d, $J = 8.4$ Hz), 8.16 (1H, d, $J = 8.4$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 42.8 (CH$_3$), 111.9 (Ar.), 120.7 (Ar.), 126.1 (Ar.), 130.5 (Ar.), 131.7 (quat.), 145.3 (quat.).
Synthesis of tert-butyl 1-(1H-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (229)\textsuperscript{152}

(S)-Boc-phenylalanine (15.30 g, 57.7 mmol) and 1-(methylsulfonyl)-1H-benzo[d][1,2,3]triazole (12.51 g, 63.5 mmol) were dissolved in dry tetrahydrofuran (100 mL) under a nitrogen atmosphere. Triethylamine (8.81 mL, 63.5 mmol) was added via syringe and the reaction mixture was heated under reflux for 9 hours. Solvent was then removed under reduced pressure and the product was recrystallised using ethyl acetate/hexanes to afford the racemic product (confirmed by optical rotation) as a white solid (20.5 g, 55.9 mmol, 97%); \textit{v}_{\text{max}}(\text{film})/\text{cm}^{-1} 3363, 2973, 1753, 1684, 1529, 1395, 1171, 1055, 973, 862, 752; \textit{^1}H-NMR (400 MHz, CDCl\textsubscript{3}) 1.41 (9H, s), 3.19 (1H, dd, \textit{J} = 8.6, 12.2 Hz), 3.44 (1H, dd, \textit{J} = 3.6, 10.0 Hz), 5.25 (1H, d, \textit{J} = 6.4 Hz) 6.01 (1H, m), 7.16–7.30 (5H, m), 7.54 (1H, t, \textit{J} = 7.6 Hz), 7.68 (1H, t, \textit{J} = 7.6 Hz), 8.17 (1H, d, \textit{J} = 8.4 Hz), 8.26 (1H, \textit{J} = 8.4 Hz); \textit{^{13}}C-NMR (100 MHz, CDCl\textsubscript{3}) 28.2 (3 x CH\textsubscript{3}), 38.9 (CH\textsubscript{2}), 55.2 (CH), 80.4 (quat.), 114.4 (Ar.), 120.4 (Ar.), 126.5 (Ar.), 127.3 (Ar.), 128.7 (2 x Ar.), 129.3 (2 x Ar.), 130.7 (Ar.), 131.0 (quat.), 135.3 (quat.), 146.1 (quat.), 155.1 (quat.) 171.3 (quat.); [\textit{\alpha}]_D = 0.0 (CHCl\textsubscript{3} c 0.1).

Attempted synthesis of (R)-tert-butyl 1-oxo-3-phenyl-1-(1-phenylethylamino)propan-2-ylcarbamate (230)\textsuperscript{152}

tert-butyl 1-(1H-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (6.50 g, 17.7 mmol) was dissolved in ice cooled dry tetrahydrofuran under a nitrogen atmosphere. (R)-(+)\textendash;\textit{\alpha}-methylbenzylamine (2.25 mL, 17.7 mmol) was then added via syringe and the reaction mixture was allowed to attain room temperature and stirred for 18 hours. The solvent was then removed under reduced pressure and purified by column chromatography (2:1 light petroleum:ethyl acetate, \textit{R}_f = 0.48) to afford a white solid. 1:1 mixture of diastereomers A and B (6.1 g, 16.6 mmol, 94%); \textit{^1}H-NMR (400 MHz, DMSO) 1.26 (A, 3H, d, \textit{J} = 6.8 Hz), 1.31 (9H, s), 1.36 (B, 3H, d, \textit{J} = 7.2 Hz).
Hz), 2.63 – 2.97 (A + B, 4H, m), 4.18 – 4.28 (A, 1H, m), 4.82 – 4.98 (B, 1H, m), 6.85 (A, 1H, dd, J = 8.4, 28.4 Hz), 7.20 – 7.33 (A + B, 10H, m), 8.27 (B, 1H, dd, J = 8.0, 32.0 Hz).

**Synthesis of (S)-2-(4-methoxybenzylamino)-3-phenylpropan-1-ol (231)**

(S)-Phenylalinol (0.30 g, 2.0 mmol) was dissolved in ethanol (20 mL). p-Anisaldehyde (0.24 mL, 2.0 mmol) was then added and allowed to stir at room temperature until the solution became yellow. MgSO₄ was added to the solution and allowed to stir for a further 30 minutes. The mixture was filtered and sodium borohydride (0.15 g, 4.0 mmol) was added in small portions. The reaction mixture was stirred for another 2 hours and quenched with 2M aqueous HCl. The organics were extracted using ethyl acetate (3 x 50 mL) and subsequently washed with brine (50 mL). The solvent was removed from the combined organics under reduced pressure to afford an oil which was used in the next step without further purification. (0.44 g, 1.6 mmol, 82%)

**Synthesis of (S)-4-benzyl-3-(4-methoxybenzyl)-1,2,3-oxathiazolidine 2-oxide (232)**

(S)-2-(4-Methoxybenzylamino)-3-phenylpropan-1-ol (0.30 g, 1.1 mmol) was dissolved in dichloromethane (30 mL) at 0°C followed by addition of triethylamine (0.33 mL, 2.4 mmol). Thionyl chloride (0.90 mL, 1.3 mmol) was then slowly added. After addition of the thionyl chloride the resulting mixture was brought back to room temperature and allowed to stir for 18 hours. The solution was then washed with water (3 x 50 mL), dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford the product as a white solid. 2:1 mixture of diastereomers A and B (0.23 g, 0.75 mmol, 68%); νmax (film) /cm⁻¹ 2972, 1611, 1513, 1250, 1153, 1109, 1032, 955, 746, 702, 505; ¹H-NMR (400 MHz, CDCl₃) 2.61 (A, 1H, dd, J = 9.2, 13.6 Hz), 2.88 (B, 1H, dd, J = 9.4, 13.4 Hz), 2.97 (A, 1H, dd, J = 5.0, 13.4 Hz), 3.18 (B, 1H, dd, J = 5.0, 13.4 Hz), 3.53 – 3.62 (B, 1H, m), 3.81 (A, 3H, s), 3.82 (B, 3H, s),
3.82 – 3.88 (A, 1H, m), 4.29 (B, 1H, dd, J = 7.6, 15.2 Hz), 4.61 – 4.66 (A + B, 4H, m), 6.87 – 6.91 (A + B, 4H, m), 7.07 (B, 2H, d, J = 6.8 Hz) 7.13 (A, 2H, d, J = 6.8 Hz), 7.19 – 7.36 (A + B, 10H, m); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 38.8 (A, CH\(_2\)), 38.9 (B, CH\(_2\)), 48.4 (A, CH\(_2\)), 48.7 (B, CH\(_2\)), 55.2 (A, OCH\(_3\)), 55.3 (B, OCH\(_3\)), 59.9 (A, CH), 62.2 (B, CH), 74.6 (A, CH\(_2\)), 75.4 (B, CH\(_2\)), 114.0 (A, 2 x Ar.), 114.1 (B, 2 x Ar.), 126.8 (B, Ar.), 127.0 (A, Ar.), 128.7 (B, 2 x Ar.), 128.8 (A, 2 x Ar.), 128.9 (B, 2 x Ar.), 129.0 (A, 2 x Ar.), 129.8 (B, 2 x Ar.), 130.5 (A, 2 x Ar.), 136.9 (A + B, quat.), 137.7 (A + B, quat.), 159.4 (A + B, quat.).

**Synthesis of (R,R)-1,2-Diaminocyclohexane (233)**

\[
\begin{align*}
&\text{NH}_2 &\text{NH}_2 \\
&\text{L-(-)-Tartarate} &\text{AcOH, H}_2\text{O} &1\text{ h, } \Delta \\
&\text{NH}_2 &\text{NH}_2 &\text{5M NaOH} \rightarrow \\
&\text{trans-1,2-diaminocyclohexane} &\text{NH}_2 &\text{NH}_2
\end{align*}
\]

Trans-1,2-diaminocyclohexane (12.0 mL, 100.0 mmol) was dissolved in water (20 mL) with stirring. L-(-)-tartaric acid (7.50 g, 50.0 mmol) was added in portions and the reaction mixture was heated to 90 °C. After dissolution, glacial acetic acid (10 mL) was added dropwise and was allowed to stir under reflux for 1 hour. On cooling, the precipitate was filtered over vacuum and washed with cold methanol. The white solid was then allowed to dry over vacuum to afford a white solid (11.40 g, 43.2 mmol, 86%); \([\alpha]_D = +8.93\) (H\(_2\)O, c 1.0). The salt was then dissolved in 5M aqueous NaOH and stirred at room temperature for 1 hour. The organic material was extracted with dichloromethane (3 x 100 mL), dried over MgSO\(_4\), filtered and the solvent was removed under reduced pressure to afford the free diamine as a pale oil. The crude oil was used without further purification.

**Synthesis of (R,R)-N,N'-bis(2-isopropylphenyl)-1,2-diaminocyclohexane (234)**

\[
\begin{align*}
&\text{NH}_2 &\text{NH}_2 \\
&1\text{-Bromo-2-isopropylbenzene} &\text{Pd}_2(\text{dba})_3, (\pm)-\text{BINAP}, \text{NaOIBu,} &\text{toluene, 18 h, } \Delta \\
&\text{NH}_2 &\text{NH}_2 &\text{HN} &\text{HN} \\
&\text{iPr} &\text{iPr} &\text{iPr} &\text{iPr}
\end{align*}
\]

Into a three-neck round bottomed flask fitted with a reflux condenser and nitrogen bubbler, were dissolved Pd\(_2(\text{dba})_3\) (0.12 g, 0.13 mmol) and (±)-BINAP (0.16 g, 0.26 mmol) in dry toluene (10 mL). The dark red solution was degassed with nitrogen for 10 minutes followed by heating under reflux for 15 minutes in order to activate the
catalyst. On cooling, sodium tert-butoxide (0.59 g, 6.2 mmol), (R,R)-1,2-diaminocyclohexane (0.50 g, 4.4 mmol) and 1-bromo-2-isopropylbenzene (2.18 g, 10.9 mmol) were added to the reaction vessel which was then heated under reflux for another 18 hours. The solution was allowed to cool, filtered through a pad of celite and washed with ethyl acetate. The filtrate was washed with brine (3 x 40 mL) and the organic phase was dried over MgSO₄. Solvent was removed under reduced pressure. The crude oil was purified by column chromatography (20:1 Petrol:EtOAc, Rf = 0.62) to afford a yellow oil (1.16 g, 3.3 mmol, 75%); νmax(film) /cm⁻¹ 3421, 2958, 2860, 1602, 1582, 1505, 1451, 1302, 1254, 1159, 1104, 1039, 744; ¹H-NMR (400 MHz, CDCl₃) 1.09 (6H, d, J = 6.8 Hz), 1.16 (6H, d, J = 6.8 Hz), 1.21-1.35 (2H, m), 1.42-1.49 (2H, m), 1.76-1.83 (2H, m), 2.40 (2H, d, J = 14.0 Hz), 2.70 (2H, sep., J = 6.8 Hz) 3.31-3.36 (2H, m), 3.88 (2H, bs), 6.71-6.77 (4H, m), 7.09-7.15 (4H, m); ¹³C-NMR (100 MHz, CDCl₃) 22.2 (2 x CH₃), 22.4 (2 x CH₃), 24.8 (2 x CH₂), 26.9 (2 x CH), 32.6 (2 x CH₂), 57.6 (2 x CH), 111.1 (2 x Ar.), 117.4 (2 x Ar.), 125.2 (2 x Ar.), 126.6 (2 x Ar.), 133.1 (2 x quat.), 144.3 (2 x quat.) [α]D = -118.2 (CHCl₃, c 1.2).

**Synthesis of Cyclohexene-1-carboxylic acid (236)**

Cyclohexane carboxylic acid (14.10 g, 110 mmol) and bromine (5.64 mL, 110 mmol) were placed in a flask fitted with a double condenser with stirring. PCl₃ was then added via the condenser. The reaction mixture was heated to 150 ºC until for 18 hours at which stage more bromine was added (0.5 mL). Heating was continued until no bromine colour was evident. The crude materiel was dissolved in methanol (70 mL) and KOH (14.4 g, 254.0 mmol) was added with stirring. The reaction mixture was then heated under reflux for 6 hours. It was then diluted with water (100 mL) and acidified to pH4 using conc. HCl. and the organics were extracted with ether (3 x 60 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a light brown oil which was used in the next step directly without further purification (20.3 g, est. 50% purity).
Synthesis of N-(2-iodophenyl)cyclohex-1-enecarboxamide (237)

Cyclohexene-1-carboxylic acid (1.65 g, 13.1 mmol) was dissolved in neat thionyl chloride (8 mL, 111 mmol) and heated to 50 °C for 4 hours. Excess thionyl chloride was then removed under reduced pressure. The crude material was dissolved in dichloromethane followed by the careful addition of 2-iodoaniline (2.87 g, 13.1 mmol) and triethylamine (2.0 mL, 14.4 mmol). The reaction mixture was stirred for 18 hours. The mixture was filtered and the solvent was removed from the filtrate to afford the product as a brown oil. (3.48 g, 10.6 mmol, 81%); ν_max (film) /cm⁻¹ 2930, 2856, 1681, 1581, 1518, 1428, 1292, 1221, 1010, 926, 752; ¹H-NMR (400 MHz, CDCl₃) 1.63-1.69 (2H, m), 1.73-1.79 (2H, m), 2.22-2.27 (2H, m), 2.39-2.44 (2H, m), 6.82 (1H, td, J = 1.6, 8.0 Hz), 6.89-6.93 (1H, m), 7.34 (1H, dt, J = 1.2, 8.0 Hz), 7.76 (1H, dd, J = 1.2, 8.0 Hz), 7.85 (1H, bs), 8.35 (1H, dd, J = 1.2, 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) 21.4 (CH₂), 22.1 (CH₂), 24.4 (CH₂), 25.7 (CH₂), 90.0 (quat.), 121.7 (Ar.), 125.6 (Ar.), 129.3 (Ar.), 133.4 (quat.), 135.7 (CH), 138.4 (quat.), 138.7 (Ar.), 166.3 (quat.).

Synthesis of N-(2-bromophenyl)cyclohex-1-enecarboxamide (238)

Cyclohexene-1-carboxylic acid (1.65 g, 13.1 mmol) was dissolved in neat thionyl chloride (8 mL, 111 mmol) and heated to 50 °C for 4 hours. Excess thionyl chloride was then removed under reduced pressure. The crude material was dissolved in dichloromethane followed by the careful addition of 2-bromoaniline (1.48 mL, 13.1 mmol) and triethylamine (2.0 mL, 14.4 mmol). The reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and the solvent was removed from the filtrate to afford a 1:1 inseparable mixture of starting material and product as a yellow oil which was used directly in the next step. (3.6 g); ¹H-NMR (400 MHz, CDCl₃) 1.61-1.69 (2H, m), 1.73-1.79 (2H, m), 2.22-2.28 (2H, m), 2.37-2.43 (2H, m),
6.84-6.89 (1H, m), 6.95 (1H, td, J = 1.6, 8.0 Hz), 7.29 (1H, td, J = 1.2, 8.0 Hz), 7.53 (1H, dd, J = 1.2, 8.0 Hz), 8.04 (1H, bs), 8.46 (1H, dd, J = 1.2, 8.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 21.4 (CH$_2$), 22.1 (CH$_2$), 24.3 (CH$_2$), 25.7 (CH$_2$), 115.8 (quat.), 121.6 (Ar.), 124.8 (Ar.), 128.4 (Ar.), 132.1 (Ar.), 133.6 (quat.), 135.6 (CH), 135.9 (quat.), 166.2 (quat).

**Synthesis of N-(2-iodophenyl)-N-methylcyclohex-1-enecarboxamide (239)**

![Synthesis reaction](image)

To a suspension of sodium hydride (0.47 g, 11.7 mmol, 60% in mineral oil) in dry tetrahydrofuran (60 mL) under a nitrogen atmosphere was added $N$-(2-iodophenyl)cyclohex-1-enecarboxamide (3.48 g, 10.6 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (0.66 mL, 10.6 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO$_4$ and solvent removed under reduced pressure to afford a crude brown oil which was purified by column chromatography to afford a tan coloured solid (2.07 g, 6.1 mmol, 57%); $\nu_{\text{max}}$(film) /cm$^{-1}$ 2927, 1630, 1576, 1471, 1373, 1300, 1017, 765, 722; $^1$H-NMR (400 MHz, CDCl$_3$) 1.33-1.55 (4H, m), 1.75-1.94 (2H, m), 1.96-2.15 (2H, m), 3.22 (3H, s), 5.89 (1H, s), 6.99 (1H, td, J = 1.6, 8.0 Hz), 7.16 (1H, d, J = 7.2 Hz), 7.35 (1H, t, J = 7.2 Hz), 7.87 (1H, dd, J = 1.6, 8.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 21.4 (CH$_2$), 22.1 (CH$_2$), 24.9 (CH$_2$), 25.9 (CH$_2$), 36.9 (CH$_3$), 99.1 (quat.), 128.9 (Ar.), 129.2 (Ar.), 129.3 (Ar.), 132.4 (≡CH), 134.1 (quat.), 140.0 (Ar.), 172.4 (quat.), 207.0 (quat.).
Synthesis of \( N-(2\text{-bromophenyl})-N\text{-methylcyclohex-1-enecarboxamide} \) (240)

To a suspension of sodium hydride (0.6 g, 15.0 mmol, 60% in mineral oil) in dry tetrahydrofuran (60 mL) was added \( N-(2\text{-iodophenyl})\text{-cyclohex-1-enecarboxamide} \) (3.6 g, 12.9 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (0.81 mL, 13.0 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO\(_4\) and solvent removed under reduced pressure to afford a pale yellow solid; (1.69 g, 5.7 mmol, 44% over two steps) 

\[
\text{\( } \nu_{\text{max}}\text{(film) /cm}^{-1} \text{\( } 2927.9, 1633, 1476, 1372; \text{\( } ^1\text{H-NMR (400 MHz, CDCl}_3\text{) 1.35-1.55 (4H, m), 1.75-1.94 (2H, m), 1.95-2.15 (2H, m), 3.24 (3H, s), 5.85 (1H, s), 7.13-7.21 (2H, m), 7.31 (1H, t, } J = 7.6 \text{ Hz), 7.61 (1H, d, } J = 8.4 \text{ Hz); } ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{) 21.4 (CH}_2\text{), 22.0 (CH}_2\text{), 24.9 (CH}_2\text{), 25.7 (CH}_2\text{), 36.5 (CH}_3\text{), 122.8 (quat.), 128.3 (Ar.), 128.8 (Ar.), 129.9 (Ar.), 132.0 (=CH), 133.6 (Ar.), 134.1 (quat.), 172.6 (quat.), 207.0 (quat.)}}
\]

Synthesis of \( (Z)-N-(2\text{-iodophenyl})-2\text{-methylbut-2-enamide} \) (241)

Tiglic acid (5.0 g, 50.0 mmol) was heated to 50 °C in neat thionyl chloride for 2 hours. Excess thionyl chloride was removed under reduced pressure. The acid chloride was then diluted with dichloromethane (50 mL) and cooled on an ice bath. A solution of pre-stirred 2-iodoaniline (10.95 g, 50.0 mmol) and triethylamine (10.40 mL, 75.0 mmol) in dichloromethane (50.0 mL) was then carefully added to the acid chloride solution with constant stirring. The solution was then allowed to attain ambient temperature and then heated under reflux for 18 hours. The reaction mixture was then washed with water (3 x 50 mL). The organic phase was then dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The brown residue was then taken
up in ethyl acetate and unreacted 2-idoaniline was precipitated by the addition of HCl in methanol. The salted material was filtered off over vacuum. Solvent was removed from the filtrate under reduced pressure to afford a brown oil (11.86 g, 39.4 mmol, 79%); \( \nu_{\text{max}} \text{(film) /cm}^{-1} \) 3390, 1679, 1578, 1515, 1429, 1294, 1012, 751; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.86 (3H, d, \( J = 6.8 \) Hz), 2.02 (3H, s), 6.71 (1H, q, \( J = 6.8 \) Hz), 6.83 (1H, t, \( J = 7.6 \) Hz), 7.35 (1H, t, \( J = 7.6 \) Hz), 7.78 (1H, d, \( J = 8.0 \) Hz), 7.87 (1H, bs), 8.35 (1H, d, \( J = 8.4 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 12.6 (CH\(_3\)), 14.3 (CH\(_3\)), 90.0 (quat.), 121.7 (Ar.), 125.7 (Ar.), 129.3 (Ar.), 132.3 (quat.), 132.7 (CH), 138.5 (quat.), 138.7 (Ar.), 167.1 (quat.).

**Synthesis of (Z)-N-(2-iodophenyl)-N,2-dimethylbut-2-enamide (242)**

\[ \text{TO} \]

To a suspension of sodium hydride (1.60 g, 40.0 mmol, 60% in mineral oil) in dry tetrahydrofuran (100 mL) under a nitrogen atmosphere was added (Z)-N-(2-iodophenyl)-2-methylbut-2-enamide (10.0 g, 33.2 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (2.20 mL, 35.0 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO\(_4\) and solvent removed under reduced pressure to afford a crude brown solid which was recrystallised in dichloromethane/diethyl ether to afford the product as a white solid (5.95 g, 18.9 mmol, 57%); \( \nu_{\text{max}} \text{(film) /cm}^{-1} \) 2922, 1636, 1470, 1356, 1018, 766, 726; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.45 (3H, s), 1.63 (3H, s), 3.23 (3H, s), 5.79 (1H, s), 6.99 (1H, t, \( J = 7.6 \) Hz), 7.14 (1H, d, \( J = 6.4 \) Hz), 7.34 (1H, t, \( J = 7.6 \) Hz), 7.87 (1H, dd, \( J = 1.2, 8.0 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 13.3 (CH\(_3\)), 14.1 (CH\(_3\)), 37.1 (CH\(_3\)), 98.9 (quat.), 128.8 (Ar.), 129.3 (Ar.), 129.4 (Ar.), 132.1 (quat.), 140.1 (Ar.), 173.2 (quat.), 207.1 (quat.).
Synthesis of cyclohexanone cyanohydrin (243)\(^{189}\)

\[
\begin{align*}
\text{O} & \xrightarrow{TMSCN} \text{TMSCN} \\
\text{NMO, CH}_2\text{Cl}_2, \quad 18 \text{ h, r.t.} & \xrightarrow{} \text{TMSO} \xrightarrow{\text{HCl}} \text{HO-CN}
\end{align*}
\]

N-Methylmorpholine oxide (0.41 g, 3.0 mmol) was placed under nitrogen atmosphere and dissolved in anhydrous dichloromethane (30 mL). Cyclohexanone (1.03 mL, 10.0 mmol) was then added to the mixture followed by the careful addition of trimethylsilyl cyanide (2.0 mL, 15 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was then carefully diluted with water (20 mL) and conc. HCl (10 mL) was slowly added. The mixture was allowed to stir at room temperature for a further 2 hours. The mixture was then extracted with dichloromethane (3 x 40 mL), the combined organics were washed with brine (2 x 40 mL) and dried over MgSO\(_4\). Solvent was removed under reduced pressure to afford the product as a colourless solid (0.89 g, 0.7 mmol, 72%); \(\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}\) 3425, 2941, 2862, 2239, 1451, 1346, 1261, 1159, 1095, 974, 931, 904, 850; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.20-1.34 (1H, m), 1.49-1.70 (5H, m), 1.74-1.85 (2H, m), 2.04-2.14 (2H, m), 3.81 (1H, bs).

Heck reaction of N-(2-iodophenyl)-N-methylcyclohex-1-enecarboxamide\(^{190}\)

\[
\begin{align*}
\text{O} & \xrightarrow{220 \text{ (2 mol%)}} \text{Pd(dba)}_3 \text{ (0.5 mol%),} \\
\text{NMP, NaOAc, mw, 20 min, 150 °C} & \xrightarrow{} \text{N} \xrightarrow{\text{245}} \\
\text{I} & \xrightarrow{} \text{246}
\end{align*}
\]

Pd(dba)_2 (2.0 mg, 0.0035 mmol) and 220 (4.8 mg, 0.014 mmol) were stirred in NMP (1 mL) for 3 h at r.t. N-(2-Iodophenyl)-N-methylcyclohex-1-enecarboxamide (0.24 g, 0.7 mmol, substrate/catalyst ratio = 200:1), and sodium acetate (0.1 g, 1.2 mmol) were then added. The flask was crimped and heated at 200 °C under microwave irradiation for 20 minutes. The solution was diluted with toluene (20 mL) and washed with water and brine. Solvent was removed under reduced pressure. The products were separated as a mixture by flash chromatography; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \text{partial data, 245:} 5.29 (1H, d, \(J = 9.2\) Hz), 6.13 (1H, dt, \(J = 3.7, 9.9\) Hz); 246: 5.84 – 5.90 (1H, m), 5.91 – 5.97 (1H, m); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \text{245:} 18.2 (CH\(_2\)), 24.4 (CH\(_2\)), 26.4
(CH₃), 32.1 (CH₂), 49.5 (quat.), 107.9 (Ar.), 122.5 (Ar.), 123.8 (Ar.), 124.8 (CH),
128.3 (Ar.), 131.6 (CH), 134.9 (quat.), 142.9 (quat.), 179.9 (quat.); 246: 21.9 (CH₂),
26.3 (CH₃), 28.2 (CH₂), 31.7 (CH₂), 45.9 (quat.), 107.9 (Ar.), 122.3 (Ar.), 123.9 (Ar.),
124.8 (CH), 126.9 (CH), 127.7 (Ar.), 134.6 (quat.), 142.8 (quat.), 180.8 (quat.);
HPLC conditions: Chiralcel OD column, Hexane:isopropanol (90:10), flow 1.0 mL/min,
compound 246: 5.74 min, compound 245: enantiomer A 6.54 min, enantiomer B 7.26
min.

**Synthesis of 1,3-dimethyl-3-vinylindoline-2-one (247)**

![Chemical Structure](image)

Pd(dba)₂ (2.0 mg, 0.0035 mmol) and 220 (4.81 mg, 0.014 mmol) were stirred in NMP
(1 mL) for 3 h at rt. (Z)-N-(2-iodophenyl)-N,2-dimethylbut-2-enamide (0.22 g, 0.7
mmol, substrate/catalyst ratio = 200:1), and sodium acetate (86.1 mg, 1.1 mmol) were
then added. The flask was crimped and heated at 150°C under microwave irradiation
for 20 minutes. The solution was diluted with toluene (20 mL) and washed with water
and brine. Solvent was removed under reduced pressure. The product was isolated by
flash chromatography; νₓ max (film) /cm⁻¹ 2971, 2929, 1724, 1610, 1490, 1471, 1372,
1346, 1106, 923, 751, 695; ¹H-NMR (400 MHz, CDCl₃) 1.49 (3H, s), 3.21 (3H, s),
5.14 (1H, d, J = 17.2 Hz), 5.16 (1H, d, J = 10.4 Hz), 5.95 (1H, dd, J = 10.4, 17.2 Hz),
6.87 (1H, d, J = 7.6 Hz), 7.09 (1H, t, J = 7.4 Hz), 7.19 (1H, dd, J = 0.4, 7.2 Hz), 7.29
(1H, td, J = 1.2, 7.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) 22.4 (CH₃), 26.3 (CH₃), 51.2
(quart.), 108.2 (Ar.), 115.2 (=CH₂), 122.5 (Ar.), 123.8 (Ar.), 128.1 (Ar.), 132.7 (quat.),
138.1 (Ar.), 143.0 (quat.), 178.6 (quat.); HPLC conditions: Chiralcel OD column,
Hexane:isopropanol (90:10), flow 1.0 mL/min, enantiomer A 14.06 min, enantiomer
B 15.94 min.
Representative Synthesis of N-(2-halophenyl)acetamides (249)\textsuperscript{192}

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{Ac}_2\text{O}, \text{Perchloric Acid}} \quad 4 \text{ h, r.t.} \\
\text{I} & \quad \text{N} \\
\end{align*}
\]

2-Iodoaniline (5.0 g, 22.83 mmol) was dissolved in acetic anhydride (100 mL), perchloric acid (1 mL) was then added to the solution which was allowed to stir at room temperature for 4 hours. The reaction mixture was then poured into water (100 mL) and left aside until the product had precipitated. The mixture was filtered over vacuum to afford the product as a brown solid (5.56 g, 21.3 mmol, 93\%); \(\nu_{\text{max}}\) (nujol) /cm\textsuperscript{-1} 3268, 1659, 1529, 1433, 1293, 1091, 1015, 750; \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}) 2.09 (3H, s), 6.84 (1H, t, \(J = 7.2\) Hz), 7.33 (1H, t, \(J = 7.2\) Hz), 7.77 (1H, d, \(J = 8.0\) Hz), 8.14 (1H, d, \(J = 8.0\) Hz), 7.45-7.56 (1H, bs); \(^{13}\)C-NMR (100 MHz, CDCl\textsubscript{3}) 24.7, (CH\textsubscript{3}), 90.3 (quat.), 122.4 (Ar.), 126.2 (Ar.), 129.2 (Ar.), 138.1 (quat.), 138.8 (Ar.), 168.7 (quat.).

Representative Synthesis of N-(2-halophenyl)-N-methylacetamides (250)\textsuperscript{192}

\[
\begin{align*}
\text{NH} & \quad \xrightarrow{\text{NaH, dimethylsulfate}} \quad \text{THF, 18 h, r.t.} \\
\text{I} & \quad \text{N} \\
\end{align*}
\]

To a suspension of sodium hydride (0.94 g, 23.4 mmol, 60\% in mineral oil) in dry tetrahydrofuran was added N-(2-iodophenyl)acetamide (5.56 g, 21.3 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Dimethylsulfate (2.02 mL, 21.3 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO\textsubscript{4} and solvent removed under reduced pressure to afford a light brown solid (5.05 g, 18.4 mmol, 86\%); \(\nu_{\text{max}}\) (film) /cm\textsuperscript{-1} 3053, 2925, 1659, 1576, 1470, 1419, 1381, 1301, 1198, 1143, 1017, 828, 768, 729; \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}) 1.80 (3H, s), 3.18 (3H, s), 7.09 (1H, td, \(J = 1.6, 7.6\) Hz), 7.29 (1H, dd, \(J = 1.6, 7.6\) Hz), 7.44 (1H, td, \(J = 1.2, 7.6\) Hz), 7.93 (1H, dd, \(J = 1.6, 7.6\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\textsubscript{3}) 22.5 (CH\textsubscript{3}), 35.8 (CH\textsubscript{3}), 99.3 (quat.), 128.8 (Ar.), 129.8 (Ar.), 130.0 (Ar.), 140.1 (Ar.), 146.5 (quat.), 170.2 (quat.).
Synthesis of N-(2-bromophenyl)-N-methylacetamide (251)

\[
\begin{array}{c}
\text{Br} \quad \text{NH}_2 \\
\text{Ac}_2\text{O} \quad \text{Perchloric Acid,} \\
\text{4 h, r.t.} \\
\end{array}
\]

Prepared according to representative procedure from compounds 249 and 250 (3.34 g, 21.5 mmol, 67% over two steps); \( \nu_{\text{max}} \text{(film) /cm}^{-1} \) 3056, 3020, 2927, 1668, 1584, 1476, 1432, 1378, 1302, 1144, 1040, 973, 766, 732, 655, 623; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.81 (3H, s), 3.19 (3H, s), 7.27 (1H, td, \( J = 1.6, 7.6 \) Hz), 7.31 (1H, dd, \( J = 1.6, 8.0 \) Hz), 7.41 (1H, td, \( J = 1.6, 7.6 \) Hz), 7.69 (1H, dd, \( J = 1.2, 8.0 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 22.1 (CH\(_3\)), 35.6 (CH\(_3\)), 123.3 (quat.), 129.0 (Ar.), 129.6 (Ar.), 129.8 (Ar.), 133.8 (Ar.), 143.1 (quat.), 170.4 (quat.).

Synthesis of N-(3,4-dichlorophenyl)acetamide (252)

3,4-Dichloroaniline (10.2 g, 63.3 mmol) was dissolved in acetic anhydride (100 mL). Perchloric acid (1 mL) was then added to the solution which was allowed to stir at room temperature for 4 hours. The reaction mixture was then poured into water (100 mL) and left aside until the product had precipitated. The mixture was filtered over vacuum to afford the product as a light grey solid (10.5 g, 51.7 mmol, 82%); \( \nu_{\text{max}} \text{(film) /cm}^{-1} \) 3295, 3180, 3105, 1667, 1587, 1528, 1474, 1387, 1305, 1255, 1128, 1017, 873, 812; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 2.20 (3H, s) 7.31 - 7.38 (2H, m) 7.76 (1H, d, \( J = 2.0 \) Hz) 7.86-7.94 (1H, br.); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 24.5 (CH\(_3\)), 119.1 (Ar.), 121.6 (Ar.), 127.5 (quat.), 130.4 (Ar.), 132.7 (quat.), 137.3 (quat.), 168.8 (quat.).

Synthesis of N-(3,4-dichlorophenyl)-N-methylacetamide (253)

To a suspension of sodium hydride (1.08 g, 27.0 mmol, 60% in mineral oil) in dry tetrahydrofuran (60 mL) was added N-(3,4-dichlorophenyl)acetamide (5.0 g, 24.6 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl
iodide (1.56 mL, 24.6 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO$_4$ and solvent removed under reduced pressure to afford a brown solid (4.77 g, 22.0 mmol, 89%); $^1$H-NMR (400 MHz, CDCl$_3$) 1.89 (3H, s), 3.22 (3H, s), 7.06 (1H, dd, $J$ = 1.6, 8.4 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 22.4 (CH$_3$), 37.1 (CH$_3$), 126.6 (Ar.), 129.1 (Ar.), 131.3 (Ar.), 132.0 (quat.), 133.5 (quat.), 143.9 (quat.), 170.1 (quat.).

**Synthesis of N-(3,4-dichlorophenyl)isobutyramide (255)**

![Synthesis of N-(3,4-dichlorophenyl)isobutyramide](image)

3,4-dichloroaniline (10.0 g, 62.1 mmol) was dissolved in dichloromethane (100 mL). Triethylamine (9.5 mL, 68.31 mmol) was added and allowed to stir at room temperature for 10 minutes. The reaction mixture was then cooled on an ice bath and isobutyryl chloride (6.5 mL, 62.1 mmol) was added dropwise. The solution was then allowed to stir at room temperature for 3 days. Solvent was removed under reduced pressure and the residue was taken up in EtOAc (60 mL). The mixture was filtered over vacuum to remove any triethylamine salt. The solvent was then removed from the filtrate under reduced pressure to afford the product as a grey solid (13.18 g, 57.1 mmol, 92%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3264, 2970, 1665, 1585, 1518, 1474, 1391, 1293, 1232, 1206, 1093, 1027, 874, 856, 816; $^1$H-NMR (400 MHz, CDCl$_3$) 1.21 (3H, s), 1.23 (3H, s), 2.56 (1H, sep, $J$ = 6.8 Hz), 7.33 (1H, s), 7.40 (1H, d, $J$ = 2.4 Hz), 7.83 (1H, d, $J$ = 2.4 Hz), 7.85 (1H, bs); $^{13}$C-NMR (100 MHz, CDCl$_3$) 19.5 (2 x CH$_3$), 36.6 (CH), 118.9 (Ar.), 121.4 (Ar.), 130.4 (Ar.), 132.7 (quat.), 137.5 (quat.), 175.4 (quat.), 207.1 (quat.).

**Synthesis of N-(3,4-dichlorophenyl)-N-methylisobutyramide (256)**

![Synthesis of N-(3,4-dichlorophenyl)-N-methylisobutyramide](image)

To a suspension of sodium hydride (0.42 g, 10.6 mmol, 60% in mineral oil) in dry tetrahydrofuran (40 mL) was added N-(3,4-dichlorophenyl)isobutyramide (2.23 g, 9.7
mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (0.27 mL, 9.7 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO$_4$ and solvent removed under reduced pressure to afford a crude brown solid. This was purified by column chromatography (9:1 Petrol:EtOAc, R$_f$ = 0.24) to afford a colourless solid (1.89 g, 7.7 mmol, 80%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3264, 2970, 1665, 1585, 1518, 1474, 1391, 1293, 1027, 874, 856, 816; $^1$H-NMR (400 MHz, CDCl$_3$) 1.05 (6H, d, $J$ = 6.8 Hz), 2.43-2.59 (1H, br.), 3.23 (3H, s), 7.07 (1H, dd, $J$ = 2.4, 8.4 Hz), 7.33 (1H, d, $J$ = 2.4 Hz), 7.50 (1H, d, $J$ = 8.4 Hz) $^{13}$C-NMR (100 MHz, CDCl$_3$) 19.6 (2 x CH$_3$), 31.1 (CH), 37.5 (CH$_3$), 126.8 (Ar.), 129.4 (Ar.), 131.4 (Ar.), 131.9 (quat.), 133.5 (quat.), 143.6 (quat.), 177.1 (quat.).

Synthesis of $N,N'$-(4,8-dichlorobiphenylene-1,5-diyl)bis($N,2$-dimethylpropanamide) (258) and 3,4-dichloro-$N$-methylaniline (259)

Diisopropylamine (2.38 mL, 17 mmol) was dissolved in dry tetrahydrofuran (80 mL) under a nitrogen atmosphere in a three necked round bottomed flask fitted with a low temperature thermometer. The solution was then cooled to -78°C on a dry ice/acetone bath. n-BuLi (6.8 mL, 17 mmol, 2.5M in hexanes) was then carefully added. The solution was then allowed to stir at around -20°C for 45 minutes. N-(3,4-dichlorophenyl)-N-methylisobutyramide (0.84 g, 3.4 mmol) and furan (0.25 mL, 3.4 mmol) were dissolved separately in dry tetrahydrofuran (25 mL) and slowly added via syringe to the basic solution. Stirring was continued for 2 hours allowing the mixture to gradually attain room temperature. The reaction was then quenched with aqueous ammonium chloride and the organics were extracted with ethyl acetate (3 x 60 mL). The combined organics were dried over MgSO$_4$ and the solvent was removed under reduced pressure to afford a crude yellow oil. The two products were separated by
column chromatography (9:1 Petrol:EtOAc); 258 Yellow crystalline solid (0.26 g, 0.58 mmol, 17%, R<sub>f</sub> = 0.91); v<sub>max</sub>(film) /cm<sup>-1</sup> 3414, 2974, 2931, 1685, 1590, 1503, 1448, 1387, 1205, 1167, 1121, 1075, 986, 793, 661; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.15 (12H, d, J = 6.8 Hz), 2.75 (3H, s), 2.76 (3H, s), 3.38 (2H, sep, J = 6.8 Hz), 4.71 (2H, bs), 6.51 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 18.1 (4 x CH<sub>3</sub>), 30.3 (2 x CH<sub>3</sub>), 41.6 (2 x CH), 110.3 (Ar.), 120.1 (quat.), 125.9 (quat.), 129.1 (quat.), 131.7 (Ar.), 146.5 (quat.), 210.4 (quat.). 259 Yellow oil (0.43 g, 2.2 mmol, 65%, R<sub>f</sub> = 0.62); v<sub>max</sub>(film) /cm<sup>-1</sup> 3431, 2970, 2931, 2880, 2820, 1685, 1602, 1500, 1318, 1130, 1017, 834, 803; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 2.78 (3H, s), 3.80 (1H, bs), 6.41 (1H, dd, J = 2.8, 8.8 Hz), 6.63 (1H, d, J = 2.8 Hz), 7.17 (1H, d, J = 8.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 30.6 (CH<sub>3</sub>), 112.2 (Ar.), 113.2 (Ar.), 119.4 (quat.), 130.4 (Ar.), 132.7 (quat.), 148.7 (quat.).

**Synthesis of Methyl 2-hydroxy-2-phenylacetate (260)<sup>194</sup>**

\[
\begin{align*}
\text{HO} & \quad \xrightarrow{\text{AcCl, MeOH}} \quad \text{OH} \\
\text{\text{AcO}} & \quad \xrightarrow{2\text{h, }\Delta} \quad \text{\text{O}Me}
\end{align*}
\]

Methanol (150 mL) was cooled on an ice bath followed by the careful addition of acetyl chloride (30 mL). The solution was allowed to warm to room temperature and stirred for 10 minutes. Mandelic acid (10.1 g, 61.2 mmol) was then added and the reaction mixture was heated under reflux for 2 hours. The solution was allowed to cool and most of the solvent was removed under reduced pressure. Dichloromethane (50 mL) was added and the organic phase was washed with brine (3 x 50 mL). Drying of the organic phase with MgSO<sub>4</sub> and removal of solvent under reduced pressure afforded a red oil. (8.52 g, 51.3 mmol, 76%); v<sub>max</sub>(film) /cm<sup>-1</sup> 3421, 1734, 979, 892, 782, 730; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 3.64 (3H, s), 4.04 (1H, s), 5.15 (1H, s), 7.26-7.33 (3H, m), 7.36-7.41 (2H, m); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 52.8 (OCH<sub>3</sub>), 73.0 (CH), 126.3 (Ar.), 128.3 (Ar.), 128.4 (Ar.), 138.4 (quat.), 174.0 (quat.).
Synthesis of methyl 2-methoxy-2-phenylacetate (261)^195

Methyl 2-hydroxy-2-phenylacetate (8.0 g, 48.19 mmol) was dissolved in dry THF (100 mL). Sodium hydride (1.27 g, 53 mmol, 60% in mineral oil) was then added to the solution and allowed to stir for 20 minutes. Methyl iodide (3.01 mL, 48.19 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with 2M HCl followed by extraction with EtOAc (3 x 60 mL). The combined organic phases were dried over MgSO₄ and solvent was removed under reduced pressure to afford a yellow oil (7.18 g, 39.91 mmol, 83 %); v_max(film)/cm⁻¹ 2950, 2827, 1751, 1492, 1436, 1260, 1197, 1105, 1011, 731, 698; ^1H-NMR (400 MHz, CDCl₃) 3.39 (3H, s), 3.70 (3H, s), 4.78 (1H, s), 7.30 - 7.40 (3H, m), 7.41 - 7.47 (2H, s); ^13C-NMR (100 MHz, CDCl₃) 52.3 (OCH₃), 57.3 (OCH₃), 82.5 (CH), 126.6 (Ar.), 128.6 (Ar.), 128.8 (Ar.), 136.1 (quat.), 171.1 (quat.).

Synthesis of 2-methoxy-2-phenylacetic acid^196 (262)

Methyl 2-methoxy-2-phenylacetate (5.12 g, 28.4 mmol) was added to a round bottomed flask containing 1M NaOH (90 mL). The mixture was heated under reflux for one hour and once cooled was carefully acidified to pH 3 using conc. HCl. The organics were extracted with EtOAc (3 x 50 mL), dried over MgSO₄ and solvent removed under reduced pressure to afford a brown oil (3.27 g, 19.7 mmol, 69%); v_max(nujol)/cm⁻¹ 1725, 1196, 1104, 988, 721, 697; ^1H-NMR (400 MHz, CDCl₃) 3.39 (3H, s), 4.77 (1H, s), 7.26 - 7.33 (3H, m), 7.38 - 7.43 (2H, m) 11.2-11.9 (1H, br); ^13C-NMR (100 MHz, CDCl₃) 57.3 (OMe), 82.0 (CH), 127.3 (Ar.), 128.7 (Ar.), 129.0 (Ar.), 135.4 (quat.), 175.9 (quat.).
Synthesis of N-(2-chlorophenyl)-2-methoxy-2-phenylacetamide (263)

2-Methoxy-2-phenylacetic acid (3.27 g, 19.66 mmol) was heated to 50 °C in neat thionyl chloride for 2 hours. Excess thionyl chloride was removed under reduced pressure. A solution of pre-stirred 2-chloroaniline (2.07 mL, 19.66 mmol) and triethylamine (3.01 mL, 21.63 mmol) in dichloromethane (50 mL) was added to the crude acid chloride and allowed to stir at room temperature for 3 days. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (60 ml). Triethylamine hydrochloride was filtered off over vacuum and the filtrate solvent was evaporated under reduced pressure to afford a brown oil. The crude material was used in the next step without purification.

Synthesis of N-(2-chlorophenyl)-2-methoxy-N-methyl-2-phenylacetamide (264)

N-(2-Chlorophenyl)-2-methoxy-2-phenylacetamide (3.37 g, 12.2 mmol) was dissolved in dry THF (100 mL). Sodium hydride (0.54 g, 13.5 mmol, 60% in mineral oil) was then added to the solution and allowed to stir for 20 minutes. Methyl iodide (0.76 mL, 12.2 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (50 mL) followed by extraction with EtOAc (3 x 60 mL). The combined organic phases were dried over MgSO₄ and solvent was removed under reduced pressure to afford a dark brown oil which was purified by column chromatography (2:1 petrol:EtOAc, Rf = 0.44) to afford a light brown oil (2.27 g, 7.8 mmol, 64%); v_max(nujol) /cm⁻¹: 2930, 2821, 1672, 1481, 1379, 1289, 1194, 1104, 975, 757, 732, 698; ¹H-NMR (400 MHz, CDCl₃) 3.21 (3H, s), 3.37 (3H, s), 4.36 (1H, s), 6.59 (1H, dd, J = 1.6, 8.0 Hz), 7.01-7.05 (2H, m) 7.10 (1H, td, J = 1.6, 8.0 Hz), 7.22-7.27 (3H, m), 7.31 (1H, td, J = 1.6, 8.0 Hz), 7.55 (1H, dd, J = 1.2, 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) 36.4 (CH₃), 57.6 (OCH₃), 81.6 (CH), 127.8 (Ar.), 128.1 (Ar.), 128.2 (Ar.), 128.3 (Ar.), 128.4 (Ar.),
128.6 (Ar.), 128.7 (Ar.), 129.9 (Ar.), 130.5 (Ar.), 131.3 (Ar.), 132.8 (quat.), 136.3 (quat.), 139.5 (quat.), 169.9 (quat.).

**Synthesis of 1,3-dimethyl-3-(1-(triisopropylsilyloxy)vinyl)indolin-2-one**

\[ \begin{align*}
\text{Ar} & \quad \text{TIPS} \\
\text{N} & \quad \text{=CH}_2 \\
\end{align*} \]

Diisopropylamine (0.28 mL, 2 mmol) was dissolved in dry tetrahydrofuran (40 mL) under a nitrogen atmosphere in a three necked round bottomed flask fitted with a low temperature thermometer. The solution was then cooled to -78°C on a dry ice/acetone bath. n-BuLi (0.8 mL, 2 mmol, 2.5M in hexanes) was then carefully added. The solution was then allowed to stir at around -20°C for 45 minutes. N-(3,4-Dichlorophenyl)-N-methylisobutyramide (0.16 g, 0.4 mmol) was dissolved separately in dry tetrahydrofuran (25 mL) and slowly added via syringe to the basic solution. Stirring was continued for 2 hours allowing the mixture to gradually attain room temperature. The reaction was then quenched with aqueous ammonium chloride and the organics were extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over MgSO\(_4\) and the solvent was removed under reduced pressure to afford a yellow oil. (66.4 mg, 0.2 mmol, 49%); \(\nu_{\text{max}}\) (film) /cm\(^{-1}\) 3028, 2933, 1714, 1610, 1512, 1304, 1250, 1148, 1031, 910, 832, 749, 701; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 0.86 and 0.90 (18H, d, \(J = 7.2\) Hz) 0.98-1.09 (3H, m), 1.48 (3H, s), 3.20 (3H, s), 4.24 (1H, d, \(J = 2.4\) Hz), 4.43 (1H, d, \(J = 2.4\) Hz), 6.80 (1H, d, \(J = 7.6\) Hz), 7.02 (1H, td, \(J = 0.8, 7.6\) Hz), 7.18 (1H, dd, \(J = 0.8, 7.2\) Hz), 7.24 (1H, td, \(J = 1.2, 7.6\) Hz); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) 17.7 (3 x CH), 17.8 (6 x CH\(_3\)), 20.4 (CH\(_3\)), 26.3 (CH\(_3\)), 54.2 (quat.) 88.7 (=CH\(_2\)), 107.7 (Ar.), 122.2 (Ar.), 122.8 (Ar.), 127.9 (Ar.), 133.7 (quat.), 143.9 (quat.), 157.9 (quat.), 178.1 (quat.).

**Synthesis of ethyl 2-methyl-3-oxobutanoate (267)**

\[ \begin{align*}
\text{EtO} & \quad \text{CH}_2 \text{CO} \quad \text{CH}_2 \text{CO} \\
\text{NaH, MeI} & \quad \text{THF, 18 h, r.t.} \\
\text{EtO} & \quad \text{CH}_2 \text{CO} \quad \text{CH}_2 \text{CO} \\
\end{align*} \]

To a suspension of sodium hydride (5.2 g, 130 mmol, 60% in mineral oil) in dry tetrahydrofuran (100 mL) was added ethyl acetoacetate (15 mL, 118.1 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Dimethylsulphate
(11.17 mL, 118.1 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 60 mL). The combined organic phases were dried over MgSO\(_4\) and solvent removed under reduced pressure to afford an orange oil which was used directly for the next step (17.66 g, 122.7 mmol, 94%); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\) 2984, 2940, 1715, 1454, 1359, 1244, 1203, 1154, 1098, 1019, 858; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.28 (3H, t, \(J = 7.2 \text{ Hz}\)), 1.34 (3H, d, \(J = 7.2 \text{ Hz}\)), 2.26 (3H, s), 3.52 (1H, q, \(J = 7.2 \text{ Hz}\)), 4.20 (2H, q, \(J = 7.2 \text{ Hz}\)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 15.4 (CH\(_3\)), 29.1 (CH\(_3\)), 55.4 (CH), 121.8 (Ar.), 123.4 (quat.), 125.0 (Ar.), 127.6 (Ar.), 129.6 (Ar.), 134.4 (quat.), 167.6 (quat.), 207.7 (quat.).

**Synthesis of N-(2-chlorophenyl)-2-methyl-3-oxobutanamide (268)**

![Chemical structure](image)

Ethyl 2-methyl-3-oxobutanoate (11.0 g, 76.3 mmol) was added to an ice-cooled solution of 1M NaOH (100 mL) and was allowed to stir for 2 hours. The solution was then left to stand overnight in the fridge. The flask was once again placed on ice again with stirring and the solution carefully acidified to pH 3 making sure the temperature did not rise above 5 °C. The organics were then extracted with EtOAc (3 x 60 mL) and dried over MgSO\(_4\). Solvent was removed under reduced pressure making sure that the bath temperature did not exceed 30°C. This afforded a clear oil (2.63 g, 22.6 mmol) which was dissolved in dichloromethane (100 mL). \(N\)-Methyl morpholine (5.17 mL, 24.9 mmol) and 2-chloroaniline (2.38 mL, 22.6 mmol) were then added to the solution and allowed to stir for 10 minutes at room temperature. EDCI (2.52 g, 24.9 mmol) was added slowly and allowed to stir for a further 18 hours. The reaction was then washed with brine (40 mL) and saturated NaHCO\(_3\) solution (40 mL). The organic phase was then dried over MgSO\(_4\) and the solvent was removed under reduced pressure to afford a crude orange oil. Diethyl ether (20 mL) was added and the resulting precipitate was filtered over vacuum to afford the product as a colourless solid (4.0 g, 17.8 mmol, 23%); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\) 3243, 2934, 1720, 1650, 1589, 1442, 1360, 1158, 1056, 755; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.55 (3H,d, \(J = 7.2 \text{ Hz}\)), 2.34 (3H, s), 3.62 (1H, q, \(J = 7.2 \text{ Hz}\)), 7.05 (1H, td, \(J = 1.6, 8.0 \text{ Hz}\)), 7.21-7.25 (1H, m), 3.98 (2H, s), 7.45 (1H, d, \(J = 8.0 \text{ Hz}\)), 7.58 (1H, td, \(J = 1.6, 7.2 \text{ Hz}\)), 7.61 (1H, d, \(J = 8.0 \text{ Hz}\)), 7.94 (1H, td, \(J = 1.6, 7.2 \text{ Hz}\)), 8.06 (1H, d, \(J = 8.0 \text{ Hz}\)), 8.20-8.27 (1H, m), 8.31 (1H, d, \(J = 8.0 \text{ Hz}\)).
7.38 (1H, dd, J = 1.6, 8.0 Hz), 8.31 (1H, dd, J = 1.6, 8.0 Hz), 8.79 (1H, s); $^{13}$C-NMR (100 MHz, CDCl$_3$) 15.4 (CH$_3$), 29.1 (CH$_3$), 55.4 (CH), 121.8 (Ar.), 123.4 (quat.), 125.0 (Ar.), 127.6 (Ar.), 129.6 (Ar.), 134.4 (quat.), 167.6 (quat.), 207.7 (quat.).

**Synthesis of N-(2-chlorophenyl)-2-methyl-3-(triisopropylsiloxy)butanamide (269)**

N-(2-Chlorophenyl)-2-methyl-3-oxobutanamide (1.6 g, 7.1 mmol) was dissolved in dichloromethane (40 mL). Triethylamine (1.5 mL, 10.6 mmol) was added and allowed to stir at room temperature for 10 minutes. Triisopropylsilyl trifluoromethanesulfonate (2.15 mL, 8 mmol) was then added. The solution was then allowed to stir at room temperature for 5 hours. The organics were washed with brine (3 x 40 mL), dried over MgSO$_4$ and the solvent was removed under reduced pressure to afford a crude colourless oil which was used directly in the next step without purification (2.99 g).

**Synthesis of N-(2-chlorophenyl)-N,2-dimethyl-3-(triisopropylsilyl)butanamide (265)**

To a suspension of sodium hydride (0.35 g, 8.6 mmol, 60% in mineral oil) in dry tetrahydrofuran (50 mL) was added crude N-(2-chlorophenyl)-2-methyl-3-(triisopropylsiloxy)butanamide (2.99 g). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (0.5 mL, 8.0 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 60 mL). The combined organic phases were dried over MgSO$_4$ and solvent removed under reduced pressure to afford a crude which was purified by bulb to bulb distillation to afford a colourless oil (0.98 g, 2.5 mmol, 35% over two steps); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2941, 2864, 1639, 1481, 1462, 1386, 1365, 1263, 1247, 1188, 1010, 882, 850, 745, 678; $^1$H-NMR (400 MHz, CDCl$_3$) 1.12-1.40 (18H, m), 1.17-1.29 (3H, m), 1.41 (3H, s), 1.56 (3H, s), 3.18 (3H, s), 7.17 (1H, td, J = 1.6, 7.6 Hz), 7.24 (1H, td, J = 1.6, 7.6 Hz), 7.40 (1H, dd, J = 1.6, 8.0 Hz), 7.55 (1H, dd, J = 1.6, 8.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$)
13.0 (3 x CH), 13.9 (CH₃), 17.9 (CH₃), 18.1 (6 x CH₃), 35.1 (CH₃), 110.9 (quat.), 126.9 (Ar.), 128.9 (Ar.), 129.7 (Ar.), 129.8 (Ar.), 132.1 (quat.), 141.3 (quat.), 144.3 (quat.), 171.5 (quat.).

**p-Methoxybenzylalcohol (270)**

![Chemical Structure](image)

νₑₓ(max) /cm⁻¹ 3347, 1610, 1512, 1246, 1173, 1032.1, 816; ¹H-NMR (400 MHz, CDCl₃) 3.81 (3H, s), 4.62 (2H, s), 6.89 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) 55.3 (OCH₃), 65.1 (CH₂), 113.9 (2 x Ar.), 128.7 (2 x Ar.), 113.1 (quat.), 159.2 (quat.).

**Synthesis of 4-allyl-2-(4-methoxyphenyl)-4-methyloxazol-5(4H)-one (275)**

![Chemical Reaction](image)

Pd(dba)₂ (1 mg, 0.017 mmol) and triphenylphosphine (9 mg, 0.036 mmol) were dissolved in dry THF (10 mL) under nitrogen atmosphere and allowed to stir at room temperature until the solution became bright yellow. Allyl 2-(4-methoxyphenyl)-4-methyl-4,5-dihydrooxazol-5-yl carbonate (0.17 g, 0.58 mmol) was then added and allowed to stir for a further 10 minutes. The solution was filtered through a pad of celite and silica which were washed with ethyl acetate. Solvent was removed under reduced pressure to afford a yellow oil (0.14 g, 0.6 mmol, 97%); νₑₓ(max) /cm⁻¹ 3079, 2979, 2934, 1816, 1653, 1609, 1512, 1322, 1305, 1258, 1172, 1017, 1000, 889, 841, 693; ¹H-NMR (400 MHz, CDCl₃) 1.52 (3H, s), 2.57 (1H, dd, J = 9.6, 14.8 Hz), 2.62 (1H, dd, J = 8.4, 14.0 Hz) 3.87 (3H, s), 5.09 (1H, dd, J = 0.8, 10.4 Hz), 5.17 (1H, dd, J = 1.6, 17.2 Hz), 5.67 (1H, ddt, J = 9.2, 9.6, 17.6 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.93 (2H, d, J = 8.8 Hz); ¹³C-NMR (100 MHz, CDCl₃) 23.4 (CH₃), 42.4 (CH₂), 55.5 (OCH₃), 69.6 (quat.), 114.2 (2 x Ar.), 118.2 (quat.), 120.3 (CH₂), 129.8 (2 x Ar.), 131.0 (CH), 159.5 (quat.), 163.2 (quat.), 180.7 (quat.); HPLC conditions: Chiralcel
OD column, Hexane:isopropanol (99.5:0.5), flow 0.5 mL/min, enantiomer A 7.54 min, enantiomer B 9.40 min.

**Synthesis of N-(tert-butoxycarbonyl)-3-methyl-2-oxindole (277)**

![Chemical structure](image)

3-Methyl-2-oxindole (1.0 g, 6.8 mmol) was dissolved in tetrahydrofuran (150 mL). Di-tert-butyldicarbonate (3.71 g, 17 mmol) and sodium carbonate (7.5 g, 70.8 mmol) were added to the solution and the resulting mixture was stirred at room temperature overnight. The mixture was then filtered and the filtrand washed with tetrahydrofuran. The resulting filtrate was concentrated under reduced pressure. The crude yellow oil was purified by bulb to bulb distillation to afford a tan coloured solid at room temperature (0.44 g, 1.8 mmol, 26%); ν_max(film) / cm⁻¹ 2981, 1796, 1767, 1729, 1481, 1297, 1151, 844, 753; ¹H-NMR (400 MHz, CDCl₃) 1.52 (3H, d, J = 7.6 Hz), 1.65 (9H, s), 3.56 (1H, q, J = 7.6 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.81 (1H, d, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) 15.9 (CH₃), 28.1 (3 x CH₃), 41.0 (CH), 84.3 (quat.), 114.9 (Ar.), 123.4 (Ar.), 124.3 (Ar.), 128.1 (Ar.), 129.4 (quat.), 139.7 (quat.), 146.7 (quat.), 149.3 (quat.), 176.9 (quat.).

**Synthesis of 3-allyl-1-tert-butyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (278)**

![Chemical structure](image)

N-(tert-butoxycarbonyl)-3-methyl-2-oxindole (0.33 g, 1.3 mmol) and triethylamine (0.2 mL, 1.4 mmol) were dissolved in tetrahydrofuran under nitrogen atmosphere. The solution was cooled on an ice bath and allowed to stir for 5 minutes. Allyl chloroformate (0.15 mL, 1.4 mmol) was carefully added to the flask and allowed to stir overnight while attaining ambient temperature. Solvent was then removed under reduced pressure. The remaining material was dissolved in diethyl ether (50 mL) and subsequently washed with 1M HCl (2 x 40 mL). The organic phase was then dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford an oily white solid (0.39 g, 1.2 mmol, 91%); ν_max(film) / cm⁻¹ 2981, 2931, 1777, 1736, 1647,
1457, 1354, 1330, 1235, 1144, 947, 841, 753; $^1$H-NMR (400 MHz, CDCl$_3$) 1.62 (9H, s), 2.14 (3H, s), 4.76 (2H, dt, $J = 1.3, 5.7$ Hz), 5.32 (1H, dd, $J = 1.2, 10.4$ Hz), 5.43 (1H, dd, $J = 1.2, 10.4$ Hz), 5.43 (1H, dd, $J = 1.2$ Hz, 17.2 Hz), 5.85 (1H, ddt, $J = 5.8, 10.4, 17.2$ Hz), 7.23 (1H, td, $J = 1.2, 7.6$ Hz), 7.29 (1H, td, $J = 1.4, 8.0$ Hz), 7.43 (1H, dd, $J = 0.8, 7.6$ Hz), 8.06 (1H, $J = 8.0$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 6.84 (CH$_3$), 28.1 (3 x CH$_3$), 69.8 (CH$_2$), 84.1 (quat.), 104.3 (quat.), 115.3 (Ar.), 118.6 (Ar.), 119.6 (dCH$_2$), 122.8 (Ar.), 124.3 (Ar.), 127.7 (quat.), 130.7 (dCH), 132.2 (quat.), 148.8 (quat.), 152.3 (quat.); m/z 354.1303; C$_{18}$H$_{21}$O$_5$N (M+Na) requires 354.1312.

**Synthesis of tert-butyl 3-allyl-3-methyl-2-oxoindoline-1-carboxylate (279)**

$$
\begin{align*}
\text{N} & \quad \text{O} \\
& \quad \text{Boc}
\end{align*}
$$

Pd(dba)$_2$ (0.6 mg, 0.001 mmol) and triphenylphosphine (0.5 mg, 0.002 mmol) were dissolved in dry THF (10 mL) under nitrogen atmosphere and allowed to stir at room temperature until the solution became bright yellow. 3-allyl-1-tert-butyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (30 mg, 0.1 mmol) was then added and allowed to stir for a further 5 minutes. The solution was filtered through a pad of celite. Solvent was removed under reduced pressure to afford a pale oil (28 mg, 0.098 mmol, 98%); $\nu_{\text{max}}$(film) $\text{cm}^{-1}$ 2979, 2929, 1792, 1765, 1730, 1350, 1292, 1150, 775, 753; $^1$H-NMR (400 MHz, CDCl$_3$) 1.42 (3H, s), 1.64 (9H, s), 2.50 (1H, dd, $J = 7.0, 13.4$ Hz), 2.58 (1H, dd, $J = 7.8, 13.4$ Hz) 4.97 (1H, d, $J = 10.4$ Hz), 5.00 (1H, d, $J = 18.4$ Hz), 5.48 (1H, ddt, $J = 7.4, 9.6, 17.2$ Hz), 7.13-7.22 (2H, m), 7.29 (1H, dd, $J = 2.0, 7.2$ Hz), 7.82 (1H, d, $J = 8.0$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 23.6 (CH$_3$), 28.1 (3 x CH$_3$), 43.3 (CH$_2$), 48.6 (quat.), 84.2 (quat.), 114.9 (Ar.), 119.3 (dCH$_2$), 122.8 (Ar.), 124.3 (Ar.), 127.9 (Ar.), 131.9 (dCH), 132.4 (quat.), 138.8 (quat.), 149.3 (quat.), 178.8 (quat.).

**Synthesis of 3-allyl-3-methylindolin-2-one (280)**

$$
\begin{align*}
\text{N} & \quad \text{O} \\
& \quad \text{Boc}
\end{align*}
$$

3-allyl-3-methylindolin-2-one (28 mg, 0.097 mmol) was dissolved in dichloromethane (10 mL). Trifluoroacetic acid (4 equiv.) was then added and allowed to stir at room
temperature for 30 minutes. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (10 mL). The organic phase was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a pale oil (17 mg, 0.091 mmol, 94%); υ_max(film) /cm⁻¹ 2924, 1708, 1620, 1471, 753; ¹H-NMR (400 MHz, CDCl₃) 1.40 (3H, s), 2.51 (1H, dd, J = 7.0, 13.4 Hz), 2.56 (1H, dd, J = 7.6, 13.6 Hz), 4.95 (1H, d, J = 10.0 Hz), 5.02 (1H, dd, J = 1.8, 17.0 Hz), 5.50 (1H, ddt, J = 7.2, 9.6, 17.2 Hz), 6.87 (1H, d, J = 7.6 Hz), 7.04 (1H, td, J = 0.9, 7.5 Hz), 7.16-7.23 (2H, m), 7.73 (1H, bs); ¹³C-NMR (100 MHz, CDCl₃) 22.8 (CH₃), 42.4 (CH₂), 48.6 (quat.), 109.5 (Ar.), 118.8 (=-CH₂), 122.4 (Ar.), 123.3 (Ar.), 127.7 (Ar.), 132.4 (=CH), 134.0 (quat.), 144.0 (quat.), 181.9 (quat.); HPLC conditions: Chiralpack IB-3 column, Hexane:isopropanol (95:5), flow 0.5 mL/min, enantiomer A 16.84 min, enantiomer B 18.35 min.

**Synthesis of N-Methylistain (281)**

To a suspension of sodium hydride (2.10 g, 52.3 mmol, 60% in mineral oil) in dry tetrahydrofuran (60 mL) was added isatin (7.0 g, 47.5 mmol). The mixture was allowed to stir at room temperature for 20 minutes. Methyl iodide (3.27 mL, 52.3 mmol) was then added and the reaction mixture was allowed to stir for a further 18 hours. The reaction was quenched with aqueous ammonium chloride and the organics extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over MgSO₄ and solvent removed under reduced pressure to afford an orange solid. The product was taken up in chloroform and excess isatin was filtered. The product was then recrystallised in ether to afford the product as an orange solid (6.46 g, 40.1 mmol, 84%); υ_max(film) /cm⁻¹ 1725, 1606, 1467, 1367, 1326, 1090, 756; ¹H-NMR (400 MHz, CDCl₃) 3.26 (3H, s), 6.90 (1H, d, J = 8.0 Hz), 7.14 (1H, t, J = 7.6 Hz), 7.59-7.64 (2H, m); ¹³C-NMR (100 MHz, CDCl₃) 26.2 (CH₃), 109.9 (Ar.), 117.5 (quat.), 123.9 (Ar.), 125.3 (Ar.), 138.4 (Ar.), 151.5 (quat.), 158.3 (quat.), 183.4 (quat.).
Synthesis of 3-hydroxy-1,3-dimethylindolin-2-one (282)\textsuperscript{101}

\[
\text{MeMgBr} \rightarrow \text{MeMgBr}
\]

Methylisatin (1.69 g, 10.5 mmol) was dissolved in dry tetrahydrofuran (30 mL) under a nitrogen atmosphere and cooled to -78°C. A solution of MeMgBr (3.0M in Et\textsubscript{2}O, 3.85 mL, 11.54 mmol,) was added via syringe and stirred at low temperature for an hour. The solution was allowed to stir at room temperature for a further 24 hours before quenching with saturated aqueous ammonium chloride. The organics were extracted with diethyl ether (3 x 50 mL) and washed with brine (50 mL). The organics were dried with MgSO\textsubscript{4}, filtered and solvent was removed under reduced pressure to afford a yellow solid (1.45 g, 8.19 mmol, 78%); \(\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}\) 3339, 2924, 1709, 1472, 1124, 752; \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}) 1.59 (3H, s), 3.18 (3H, s), 3.62-3.89 (1H, bs), 6.83 (1H, d, \(J = 7.6\) Hz), 7.10 (1H, t, \(J = 7.6\) Hz), 7.31 (1H, td, \(J = 1.2, 7.6\) Hz), 7.41 (1H, d, \(J = 0.8, 7.2\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\textsubscript{3}) 24.8 (CH\textsubscript{3}), 26.2 (CH\textsubscript{3}), 73.7 (quat.), 108.5 (Ar.), 123.3 (Ar.), 123.4 (Ar.), 129.5 (Ar.), 131.6 (quat.), 142.7 (quat.), 178.9 (quat.).

Synthesis of 1,3-dimethylindolin-2-one (283)\textsuperscript{101}

3-hydroxy-1,3-dimethylindolin-2-one (1.45 g, 8.26 mmol) was dissolved in a 15:1 mixture of AcOH:HCl (50mL). SnCl\textsubscript{2}.H\textsubscript{2}O (3.71 g, 16.5 mmol) was then added and then heated under reflux for 2 hours. After cooling to room temperature the solution was diluted with water and the product was extracted with diethyl ether. The organic layer was washed with 1M aqueous NaOH. It was then dried with MgSO\textsubscript{4}, filtered and the solvent was removed under reduced pressure to afford (0.60 g, 3.72 mmol, 45%); \(\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}\) 3055,2972, 2933, 1711, 1614, 1493, 1471, 1376, 1348, 1129, 1092, 751; \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}) 1.74 (3H, d, \(J = 8.0\) Hz), 3.21 (3H, s), 3.45 (1H, q, \(J = 8.0\) Hz), 6.83 (1H, d, \(J = 7.6\) Hz), 7.06 (1H, td, \(J = 0.9, 7.5\) Hz), 7.24 (1H, dd, \(J = 0.6, 7.4\) Hz), 7.28 (1H, t, \(J = 7.6\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\textsubscript{3}) 15.3 (CH\textsubscript{3}), 26.2
(CH₃), 40.6 (CH), 108.6 (Ar.), 122.5 (Ar.), 123.5 (Ar.), 127.9 (Ar.), 130.7 (quat.), 143.9 (quat.), 176.7 (quat.).

**Synthesis of ethyl 4-methoxyphenylcarbamate (285)**

\[
\text{MeO} \quad \begin{array}{c}
\text{NH}_2 \\
\vline \\
\text{CH} \quad \text{ClCO}_2 \text{Et} \\
\end{array}
\quad \begin{array}{c}
\text{MeO} \\
\vline \\
\text{NH} \quad \text{OEt} \\
\end{array}
\]

\(-\text{EtCl, (i-Pr)}_2\text{NEt, DMAP, THF, 30 min, } 0 \degree \text{C}\)  

\(-\text{Anisidine (10.0 g, 81.2 mmol), dimethylaminopyridine (1 g, 8.1 mmol) and diisopropylethylamine (15.5 mL, 89.3 mmol) were dissolved in tetrahydrofuran (60 mL) under nitrogen atmosphere. The resulting solution was cooled on an ice bath with stirring. Ethyl chloroformate (7.76 mL, 81.2 mmol) was then carefully added by syringe and allowed to stir for a further 30 minutes. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with brine (2 x 50 mL). The organic phase was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a brown solid (14.2 g, 72.8 mmol, 90%); } \nu_{\text{max}}^{\text{film}} / \text{cm}^{-1} 3317, 2983, 2838, 1711, 1619, 1540, 1249, 1236, 1079, 827, 776, 633; ^1\text{H-NMR (400 MHz, CDCl}_3) 1.28 (3H, t, J = 7.2 Hz), 3.77 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 6.83 (2H, d, J = 8.8 Hz), 6.94 (1H, bs) 7.30 (2H, bd, J = 7.2 Hz); ^13\text{C-NMR (100 MHz, CDCl}_3) 14.4 (CH₃), 55.5 (OCH₃), 67.9 (CH₂), 114.2 (2 x Ar.), 120.7 (2 x Ar.), 131.2 (quat.), 154.2 (quat.), 155.8 (quat.).

**Synthesis of 4-methoxy-N-methylaniline (286)**

\[
\text{MeO} \quad \begin{array}{c}
\text{NH} \\
\vline \\
\text{OEt} \\
\end{array} 
\quad \begin{array}{c}
\text{MeO} \\
\vline \\
\text{NH} \\
\end{array}
\]

\(-\text{LiAlH}_4, \text{THF, 18 h, } \Delta\)  

Ethyl 4-methoxyphenylcarbamate (10.0 g, 51.2 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL) and carefully added to an ice cooled suspension of lithium aluminium hydride (4.28 g, 112.8 mmol) in tetrahydrofuran (100 mL) with stirring under nitrogen atmosphere. The resulting mixture was heated under reflux for 18 hours. The reaction mixture was allowed to cool to room temperature before quenching with saturated aqueous potassium sodium tartrate. The mixture was filtered over vacuum. Tetrahydrofuran was evaporated under reduced pressure and the organics were extracted with ethyl acetate (3 x 60 mL) and washed with brine (60 mL). The combined organic phases were dried over MgSO₄, filtered and solvent was
removed under reduced pressure to afford a crude brown oil which was purified by bulb to bulb distillation to afford a tan coloured solid at room temperature (1.6 g, 11.6 mmol, 23%); \( \nu_{\text{max}} \) (film) /cm\(^{-1}\) 3402, 2935, 2899, 1515, 1465, 1237, 1033, 820; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 2.79 (3H, s), 3.74 (3H, s), 6.58 (2H, d, \( J = 8.8 \) Hz), 6.80 (2H, d, \( J = 9.2 \) Hz); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) 31.6 (CH\(_3\)), 55.9 (OCH\(_3\)), 113.6 (2 x Ar.), 114.9 (2 x Ar.), 143.7 (quat.), 152.1 (quat.).

**Synthesis of monoallyl malonate (288)**

![Diagram](attachment:diagram.png)

Meldrum’s acid (8.0 g, 55.5 mmol) in allyl alcohol (16 mL) was heated under reflux for 18 h. Excess allyl alcohol was then evaporated under reduced pressure. The residue was dissolved in methanol (30 mL) and aqueous ammonia (35% v/v; 7 mL) was added and stirred for 15 minutes. Solvent was then removed under reduced pressure and the residue was washed with a 1:1 mixture of hexanes and diethyl ether (30 mL) to remove traces of allyl alcohol. The residue was then dissolved in water (50 mL) and acidified to pH 4 using aqueous hydrochloric acid (2M). The organics were extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over MgSO\(_4\), filtered and solvent was removed under reduced pressure to afford a pale yellow oil (3.54 g, 24.5 mmol, 44%); \( \nu_{\text{max}} \) (film) /cm\(^{-1}\) 3231, 2951, 1737, 1414, 1370, 1323, 1155, 992, 935; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 3.47 (3H, s), 4.67 (2H, d, \( J = 6.0 \) Hz), 5.28 (1H, d, \( J = 10.4 \) Hz), 5.36 (1H, d, \( J = 1.2, 17.2 \) Hz), 5.92 (1H, ddt, \( J = 6.4, 10.4, 17.2 \) Hz), 9.65 (1H, bs); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) 40.9 (CH\(_2\)), 66.4 (CH\(_2\)), 119.1 (=CH\(_2\)), 131.2 (=CH), 166.3 (quat.), 171.6 (quat.).

**Synthesis of allyl 3-((4-methoxyphenyl)(methyl)amino)-3-oxopropanoate (290)**

![Diagram](attachment:diagram.png)

Monoallyl malonate (1.68 g, 11.7 mmol) and 4-methoxy-N-methylaniline (1.60 g, 11.7 mmol) were dissolved in dichloromethane (60 mL) with stirring at 0\(^\circ\)C. Triethylamine (1.8 mL, 12.9 mmol) and 2-chloro-1-methylpyridinium iodide (3.30 g, 12.9 mmol) were then added in succession to the solution. After 1 hour, the reaction
mixture was washed with water (40 mL) and saturated aqueous sodium hydrogen carbonate solution (40 mL). The organic phase was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a brown oil which was used without further purification. (2.03 g, 7.71 mmol, 66%); \( \text{\textit{v}}_{\text{max}} \text{(film) /cm}^{-1} \text{ 2940, 2839, 1739, 1659, 1512, 1249, 1028, 841;} \); \(^1\text{H-NMR (400 MHz, CDCl}_3\text{)} 3.24 \text{ (2H, s, 3.27 (3H, s, 3.83 (3H, s, 4.68 (2H, d, } J = 6.0 \text{ Hz), 5.22 (1H, dd, } J = 1.2, 10.8 \text{ Hz), 5.29 (1H, dd, } J = 1.4, 17.0 \text{ Hz), 5.88 (1H, ddt, } J = 5.6, 10.4, 17.2 \text{ Hz) 6.92 (2H, d, } J = 9.2 \text{ Hz), 7.15 (2H, d, } J = 8.8 \text{ Hz);} \); \(^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)} 37.6 \text{ (CH}_3\text{), 41.4 \text{ (CH}_2\text{), 55.7 \text{ (OCH}_3\text{), 65.7 \text{ (CH}_2\text{), 114.9 (2 x Ar.), 118.5 (=CH}_2\text{), 128.4 (2 x Ar.), 131.7 (=CH), 136.2 (quat.), 159.2 (quat.), 166.2 (quat.), 167.4 (quat.); } m/z \text{ 262.1088; } \text{C}_{14}\text{H}_{16}\text{NO}_4 \text{ (M-H) requires 262.1079.} \)

**Synthesis of allyl 3-((4-methoxyphenyl)(methyl)amino)-2-methyl-3-oxopropanoate (291)**

![Chemical Reaction](image)

Allyl 3-((4-methoxyphenyl)(methyl)amino)-3-oxopropanoate (1.72 g, 6.53 mmol) and potassium tert-butoxide (0.80 g, 7.18 mmol) were dissolved in anhydrous tetrahydrofuran (30 mL) under nitrogen atmosphere and allowed to stir for 20 minutes at room temperature. Iodomethane (0.426 mL, 6.85 mmol) was then added and allowed to stir for a further hour. The reaction was quenched with saturated aqueous ammonium chloride, diluted with ethyl acetate (50 mL) and washed with brine (2 x 30 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a brown oil which was used without further purification (1.21 g, 4.4 mmol, 67%); \( \text{\textit{v}}_{\text{max}} \text{(film) /cm}^{-1} \text{ 2939, 1742, 1659, 1512, 1248, 1182, 1031, 840;} \); \(^1\text{H-NMR (400 MHz, CDCl}_3\text{)} 3.13 \text{ (3H, d, } J = 7.2 \text{ Hz), 3.27 (3H, s, 3.45 (1H, q, } J = 7.2 \text{ Hz), 3.83 (3H, s, 4.53 (1H, dd, } J = 5.8, 12.0 \text{ Hz), 4.58 (1H, dd, } J = 6.2 \text{ Hz, 10.8 Hz), 5.22 (1H, dd, } J = 1.2, 10.4 \text{ Hz), 5.30 (1H, dd, } J = 1.6, 17.2 \text{ Hz), 5.87 (1H, ddt, } J = 6.0, 10.4, 17.2 \text{ Hz), 6.92 (2H, d, } J = 8.8 \text{ Hz), 7.16 (2H, d, } J = 9.2 \text{ Hz);} \); \(^{13}\text{C-NMR (100 MHz, CDCl}_3\text{)} 14.1 \text{ (CH}_3\text{), 37.8 \text{ (CH}_3\text{), 43.4 \text{ (CH), 55.5 \text{ (CH}_3\text{), 65.6 \text{ (CH}_2\text{), 114.9 (2 x Ar.), 118.2 (=CH}_2\text{), 128.5 (2 x Ar.), 131.9 (=CH), 136.3 (quat.), 159.2 (quat.), 170.3 (quat.), 170.5 (quat.).} \)
Synthesis of allyl 5-methoxy-1,3-dimethyl-2-oxindoline-3-carboxylate (292)

 Allyl 3-((4-methoxyphenyl)(methyl)amino)-2-methyl-3-oxopropanoate was dissolved in dimethylformamide, this was followed by addition of potassium tert-butoxide which was allowed to stir for 10 minutes. Copper (II) acetate monohydrate was then added and the reaction mixture was heated to 120°C for 18 hours. After cooling to room temperature the reaction was quenched with saturated aqueous ammonium chloride (10 mL), diluted with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford a mixture of two products which were separated by column chromatography (Petrol:EtOAc 1:1 293 Rₜ = 0.72 292 Rₜ = 0.19); 292 (0.45 g, 1.6 mmol, 39%); νₘₐₓ(film) /cm⁻¹ 2937, 1744, 1713, 1601, 1499, 1229, 1112, 1038, 812; ¹H-NMR (400 MHz, CDCl₃) 1.66 (3H, s), 3.23 (3H, s), 3.79 (3H, s), 4.55 (1H, ddt, J = 1.6, 5.2, 13.6 Hz), 4.60 (1H, ddt, J = 1.6, 5.2, 13.6 Hz), 5.12 – 5.14 (1H, m), 5.17 (1H, dd, J = 1.4, 8.2 Hz), 5.78 (1H, ddt, J = 5.2, 10.8, 16.8 Hz), 6.77 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.88 (1H, s); ¹³C-NMR (100 MHz, CDCl₃) 20.2 (CH₃), 26.6 (CH₃), 55.4 (quat.), 55.9 (OCH₃), 66.0 (CH₂), 108.8 (Ar.), 110.4 (Ar.), 113.4 (Ar.), 117.9 (=CH₂), 131.2 (quat.), 131.4 (quat.), 137.1 (=CH), 156.2 (quat.), 169.4 (quat.), 174.7 (quat.); m/z 298.1043; C₁₅H₁₇NO₄Na (M+Na) requires 298.1055.

293²⁰⁵ (0.14 g, 0.7 mmol, 16%); νₘₐₓ(film) /cm⁻¹ 3281, 2926, 1698, 1604, 1495, 1476, 1287, 1237, 1121, 1038; ¹H-NMR (400 MHz, CDCl₃) 1.59 (3H, s), 3.18 (3H, s), 3.81 (3H, s), 6.75 (1H, d, J = 8.8 Hz), 6.85 (1H, dd, J = 2.4, 8.4 Hz), 7.04 (1H, d, J = 2.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) 23.9 (CH₃), 25.3 (CH₃), 54.8 (OCH₃), 73.0 (quat.), 107.9 (Ar.), 109.5 (Ar.), 113.1 (Ar.), 131.7 (quat.), 135.1 (quat.), 155.5 (quat.), 177.4 (quat.); m/z 230.0788; C₁₁H₁₇NO₄Na (M+Na) requires 230.0793.
Synthesis of 3-allyl-5-methoxy-1,3-dimethylindolin-2-one (294) \(^{92}\)

\[
\begin{array}{c}
\text{MeO} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{THF,} \\
5 \text{ min, r.t.}
\end{array}
\begin{array}{c}
\text{MeO} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\end{array}
\]

Pd(dba)\(_2\) (3.1 mg, 0.0055 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in dry THF (10 mL) under nitrogen atmosphere and allowed to stir at room temperature until the solution became bright yellow. Allyl 5-methoxy-1,3-dimethyl-2-oxindoline-3-carboxylate (30.0 mg, 0.109 mmol) was then added and allowed to stir for a further 5 minutes. The solution was filtered through a pad of celite. Solvent was removed under reduced pressure to afford a yellow oil (24.8 mg, 0.107 mmol, 98%); \(\nu_{\text{max}}\) (film) /\(\text{cm}^{-1}\) 2928, 1709, 1499, 1292, 1039; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.36 (3H, s), 2.47 (1H, dd, \(J = 7.2, 13.6\)), 2.58 (1H, dd, \(J = 8.0, 13.6\) Hz), 3.17 (3H, s), 3.80 (3H, s), 4.93 (1H, d, \(J = 10.0\) Hz), 5.00 (1H, dd, \(J = 1.8, 17.0\) Hz), 5.46 (1H, ddt, \(J = 7.6, 10.0, 17.2\) Hz), 6.71-6.83 (3H, m); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 22.7 (CH\(_3\)), 26.1 (CH\(_3\)), 42.4 (CH\(_2\)), 48.7 (quat.), 55.8 (OCH\(_3\)). 108.1 (Ar.), 110.7 (Ar.), 111.6 (Ar.), 118.7 (=CH\(_2\)), 132.5 (=CH), 135.1 (quat.), 136.7 (quat.), 155.9 (quat.); \(m/z\) 254.1150; \(C_{14}H_{17}NO_2\) (M+Na) requires 254.1157; HPLC conditions: chiralcel OJ column, Hexane:isopropanol (93:7), flow 0.8 mL/min, enantiomer A 12.32 min, enantiomer B 13.35 min.

Synthesis of tert-butyl 4-methoxyphenylcarbamate (295) \(^{206}\)

\[
\begin{array}{c}
\text{MeO} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{di-tert-butyl dicarbonate, sulfamic acid, MeOH,} \\
5 \text{ min, r.t.}
\end{array}
\begin{array}{c}
\text{MeO} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\end{array}
\]

\(p\)-Anisidine (2.0 g, 16.23 mmol), di-tert-butyl dicarbonate (3.90 g, 17.8 mmol), and sulfamic acid (0.09 g, 0.92 mmol) were combined in a flask and dissolved in methanol (15 mL). The resulting mixture was stirred at room temperature for 5 minutes. The mixture was then filtered over vacuum to afford a purple solid (3.90g, 17.48 mmol, 98%); \(\nu_{\text{max}}\) (film) /\(\text{cm}^{-1}\) 3365, 1694, 1521, 1235, 1160, 1023, 823; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.51 (9H, s), 3.77 (3H, s), 6.83 (2H, d, \(J = 9.2\) Hz), 7.26 (2H, bd, \(J = 8.4\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 28.4 (3 x CH\(_3\)), 31.2 (quat.), 55.5 (CH\(_3\)), 85.2 (quat.), 114.2 (2 x Ar.), 120.5 (2 x Ar.), 131.5 (quat.), 155.7 (quat.).
Synthesis of 4-methoxy-N-(4-methoxybenzylidene)aniline (297)

\[
\text{Anisaldehyde} \xrightarrow{\text{EtOH, 15 min, r.t.}} \text{4-methoxy-N-(4-methoxybenzylidene)aniline (297)}
\]

\[
\text{MeO} \quad \text{OMe} \quad \text{MeO}
\]

\[
\begin{align*}
p-\text{Anisidine (10.0 g, 81.3 mmol) was dissolved in ethanol (100 mL). This was} \\
\text{followed by the addition of 4-methoxybenzaldehyde (9.89 mL, 81.8 mmol) and a} \\
\text{spatula tip of } p-\text{toluenesulfonic acid. The solution was allowed to stir at room} \\
temperature for 10 minutes. The precipitated imine was then filtered and dried over} \\
vacuum (19.21 g, 79.7 mmol, 98\%); \quad ^1\text{H-NMR (400 MHz, CDCl}_3\text{) 3.77 (3H, s), 3.83} \\
(3H, s), 6.97 (2H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.25 (2H, d, J = 8.8 Hz), \\
7.86 (2H, d, J = 8.8 Hz), 8.54 (1H, s); \quad ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{) 55.2 (OCH}_3\text{),} \\
55.3 (OCH}_3\text{), 56.0 (CH}_2\text{), 114.2 (2 x Ar.), 114.3 (2 x Ar.), 122.2 (2 x Ar.), 129.2} \\
(\text{quat.}), 130.1 (2 x Ar.), 144.4 (\text{quat.}), 157.6 (\text{quat.}), 157.7 (\text{quat.}), 161.6 (\text{quat.}).
\end{align*}
\]

Synthesis of 4-methoxy-N-(4-methoxybenzyl)aniline (298)

\[
\text{MeO} \quad \text{OMe} \quad \text{MeO} \quad \text{MeO}
\]

\[
\begin{align*}
4-\text{methoxy-N-(4-methoxybenzylidene)aniline (10.0 g, 41.5 mmol) was dissolved in} \\
dichloromethane (80 mL), this solution was diluted with ethanol (80 mL). Sodium \\
borohydride (3.15 g, 83.3 mmol) was added carefully in small portions and allowed to \\
stir at room temperature for 18 hours. The reaction was quenched with saturated \\
aqueous ammonium chloride (30 mL) followed by dilution with water (60 mL). \\
Ethanol was removed under reduced pressure and the aqueous solution was extracted \\
with ethyl acetate (3 x 50 mL). The combined organics were dried with MgSO}_4\text{,} \\
filtered and solvent was removed under reduced pressure to afford a brown solid \\
which was used without further purification. (6.49 g, 26.7 mmol, 64\%); \quad ^1\text{H-NMR (400} \\
\text{MHz, CDCl}_3\text{) 3.74 (3H, s), 3.79 (3H, s), 4.20 (2H, s), 6.60 (2H, d, J = 8.8 Hz), 6.77} \\
(2H, d, J = 8.8 Hz), 6.87 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 8.8 Hz); \quad ^{13}\text{C-NMR (100} \\
\text{MHz, CDCl}_3\text{) 48.8 (CH}_2\text{), 55.3 (OCH}_3\text{), 55.8 (OCH}_3\text{), 114.0 (2 x Ar.), 114.2 (2 x Ar.),} \\
114.9 (2 x Ar.), 128.8 (2 x Ar.), 131.7 (\text{quat.}), 142.5 (\text{quat.}), 152.2 (\text{quat.}), 158.8} \\
(\text{quat.}).
\end{align*}
\]
Synthesis of allyl 3-((4-methoxybenzyl)(4-methoxyphenyl)amino)-3-oxopropanoate (299)

Monoallyl malonate (1.0 g, 6.95 mmol) was dissolved in dichloromethane (50 mL) followed by the addition of triethylamine (1.05 mL, 7.63 mmol). The solution was allowed to stir for 5 minutes before the addition of 2-chloro-1-methylpyridinium iodide (1.95 g, 7.63 mmol) and 4-methoxy-N-(4-methoxybenzyl)aniline (1.78 g, 6.95 mmol). The mixture was stirred at room temperature overnight and washed with water (2 x 50 mL). The crude mixture was purified by column chromatography (2:1 Petrol:EtOAc, $R_f = 0.37$) to afford a brown oil (0.40 g, 1.09 mmol, 16%); $\nu_{\text{max}}$(film) /cm$^{-1}$ 2937, 2837, 1740, 1512, 1248, 1032, 840; $^1$H-NMR (400 MHz, CDCl$_3$) 3.22 (2H, s), 3.76 (3H, s), 3.77 (3H, s), 4.56 (2H, d, $J = 5.6$ Hz), 4.80 (2H, s), 5.22 (1H, dd, $J = 1.2, 10.4$ Hz), 5.29 (1H, dd, $J = 1.6, 17.2$ Hz), 5.87 (1H, ddt, $J = 5.6, 10.4, 16.0$ Hz) 6.78 (2H, d, $J = 8.4$ Hz), 6.80 (2H, d, $J = 8.8$ Hz), 6.89 (2H, d, $J = 9.2$ Hz), 7.12 (2H, d, $J = 8.8$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) 41.7 (CH$_2$), 52.5 (CH$_2$), 55.2 (OCH$_3$), 55.4 (OCH$_3$), 65.8 (CH$_2$), 113.7 (2 x Ar.), 114.7 (2 x Ar.), 118.6 ($=\text{CH}_2$), 129.2 (quat.), 129.5 (2 x Ar.), 130.3 (2 x Ar.), 131.7 ($=\text{CH}$), 134.3 (quat.), 158.9 (quat.), 159.3 (quat.), 166.1 (quat.), 167.5 (quat.); $m/z$ (368.1508); C$_{21}$H$_{22}$NO$_5$ (M-1) requires 368.4051.

Synthesis of allyl 3-((4-methoxybenzyl)(4-methoxyphenyl)amino)-2-methyl-3-oxopropanoate (300)

Allyl 3-((4-methoxybenzyl)(4-methoxyphenyl)amino)-3-oxopropanoate (0.40 g, 1.1 mmol) was dissolved in tetrahydrofuran (20 mL) followed by the addition of potassium tert-butoxide (0.14 g, 1.2 mmol), the solution was allowed to stir for 10 minutes before the addition of iodomethane (0.08 mL, 1.2 mmol). The reaction mixture was allowed to stir for a further hour before quenching with saturated aqueous ammonium chloride. (20 mL). Ethyl acetate (60 mL) was added and the mixture was
washed with brine (2 x 40 mL). The organics were dried with MgSO₄, filtered and solvent was removed under reduced pressure to afford a yellow oil which was used without further purification (0.24 g, 0.62 mmol, 56%); ¹H-NMR (400 MHz, CDCl₃) 1.33 (3H, d, J = 6.8), 3.39 (1H, q., J = 7.2 Hz), 3.78 (6H, s), 4.55 (2H, dd, J = 1.2, 5.6 Hz), 4.64 (1H, d, J = 14.0 Hz), 4.95 (1H, d, J = 14.0 Hz), 5.22 (1H, dd, J = 1.2, 10.4 Hz), 5.28 (1H, dd, J = 1.6, 17.2 Hz) 5.86 (1H, ddt, J = 5.6, 10.4, 17.2 Hz), 6.76-6.84 (4H, m), 6.88 (2H, d, J = 9.2 Hz), 7.12 (2H, d, J = 8.8 Hz); ¹³C-NMR (100 MHz, CDCl₃) 14.1 (CH₃), 43.7 (CH), 52.6 (CH₂), 55.2 (OCH₃), 55.4 (OCH₃), 65.6 (CH₂), 113.7 (2 x Ar.), 114.7 (2 x Ar.), 118.3 (=CH₂), 129.7 (2 x Ar.), 130.2 (2 x Ar.), 131.8 (=CH), 134.3 (quat.), 158.9 (quat.), 159.2 (quat.), 170.2 (quat.), 170.5 (quat.).
Appendix A: X-Ray Crystallography

Table 1: Crystal data and structure refinement for 2,5-Dimesityl-1,2,5-thiadiazolidine-1-oxide

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<th>Value</th>
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</tr>
<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
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<td>Unit cell parameters</td>
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<td>α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 11.0658(4) Å</td>
</tr>
<tr>
<td></td>
<td>β = 100.6007(5)°</td>
</tr>
<tr>
<td></td>
<td>c = 21.4780(8) Å</td>
</tr>
<tr>
<td></td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Cell volume</td>
<td>1880.60(12) Å</td>
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<tr>
<td>Z</td>
<td>4</td>
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<tr>
<td>Calculated density</td>
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<tr>
<td>Absorption coefficient μ</td>
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<tr>
<td>F(000)</td>
<td>736</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>colourless, 0.89 × 0.77 × 0.69 mm³</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>10335 (θ range 2.58 to 30.56°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker APEX 2 CCD diffractometer</td>
</tr>
<tr>
<td>α rotation with narrow frames</td>
<td></td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>1.93 to 30.59°</td>
</tr>
<tr>
<td>Index ranges</td>
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<td>Intensity decay</td>
<td>0%</td>
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<td>Description</td>
<td>Details</td>
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<td>-----------------------------------</td>
<td>----------------------------------------------</td>
</tr>
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<td>Independent reflections</td>
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<td>Reflections with $F^2 &gt; 2\sigma$</td>
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</tr>
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<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
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<td>Min. and max. transmission</td>
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<td>direct methods</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
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<td>Weighting parameters a, b</td>
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<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Final R indices [F^2&gt;2σ]</td>
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<tr>
<td>R indices (all data)</td>
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</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.056</td>
</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.001 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.444 and $-0.242$ e Å$^{-3}$</td>
</tr>
</tbody>
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Table 2: Atomic coordinates and equivalent isotropic displacement parameters (Å$^2$). $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

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<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
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<td>0.15163(4)</td>
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<td>S(1)</td>
<td>0.72993(3)</td>
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<td>0.179151(12)</td>
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<td>C(1)</td>
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### Table 3: Bond lengths [Å] and angles [°].

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Table 4: Hydrogen coordinates and isotropic displacement parameters (Å$^2$).

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**Table 5:** Torsion angles [°].

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Table 1: Crystal data and structure refinement for 1-((R)-1-phenylethyl)-3-((S)-1-phenylethyl)-1,3-dihydrobenzo[c][1,2,5]thiadiazolidine-1-oxide.

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<td>(\beta = 90^\circ)</td>
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<td>Min. and max. transmission</td>
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<tr>
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Table 2: Atomic coordinates and equivalent isotropic displacement parameters (Å$^2$). $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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

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Table 4: Hydrogen coordinates and isotropic displacement parameters (Å$^2$).

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Table 5: Torsion angles [°].

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<td>0.5(3)</td>
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Table 1: Crystal data and structure refinement for (2R)-4-Diphenyl-2,4,5,7-tetrahydro-6-oxa-3-thia-1,2,3a-triaza-indene (3S)-oxide.

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<th>Property</th>
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<tr>
<td>Radiation, wavelength</td>
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<tr>
<td>Crystal system, space group</td>
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<tr>
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<tr>
<td></td>
<td>b = 8.8835(5) Å</td>
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<tr>
<td></td>
<td>c = 12.0593(7) Å</td>
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<tr>
<td></td>
<td>α = 90°</td>
</tr>
<tr>
<td></td>
<td>β = 105.7428(8)°</td>
</tr>
<tr>
<td></td>
<td>γ = 90°</td>
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<tr>
<td>Cell volume</td>
<td>760.38(7) Å³</td>
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<tr>
<td>Z</td>
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<tr>
<td>Calculated density</td>
<td>1.369 g/cm³</td>
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<tr>
<td>Absorption coefficient μ</td>
<td>0.223 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>328</td>
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<tr>
<td>Crystal colour and size</td>
<td>colourless, 1.05 × 0.61 × 0.06 mm³</td>
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<tr>
<td>Reflections for cell refinement</td>
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<td>Data collection method</td>
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<td></td>
<td>ω rotation with narrow frames</td>
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<td>θ range for data collection</td>
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<td>Completeness to θ = 30.55°</td>
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<td>Intensity decay</td>
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<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
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<td>Absorption correction</td>
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<tr>
<td>Min. and max. transmission</td>
<td>0.800 and 0.987</td>
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<td>Structure solution</td>
<td>direct methods</td>
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<td>Refinement method</td>
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<td>Weighting parameters a, b</td>
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<tr>
<td>Data / restraints / parameters</td>
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<td>Final R indices [F^2 &gt; 2\sigma]</td>
<td>R1 = 0.0323, wR2 = 0.0806</td>
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<td>R indices (all data)</td>
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<td>Absolute structure parameter</td>
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</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.000 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.299 and -0.199 e Å^{-3}</td>
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Table 2: Atomic coordinates and equivalent isotropic displacement parameters (Å²). 

$U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

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Table 4: Hydrogen coordinates and isotropic displacement parameters (Å$^2$).

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Table 5: Torsion angles [°].

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<th>Torsion Angle [°]</th>
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<td>1.0(3)</td>
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N(1)–S(1)–N(1)–C(5) 164.84(10)
N(3)–S(1)–N(1)–C(5)  23.04(13)
N(1)–N(2)–C(1)–C(4)  −173.68(14)
N(2)–C(1)–N(3)–C(2)  −24.85(19)
N(2)–C(1)–N(3)–S(1)  −164.67(11)
N(1)–S(1)–N(3)–C(1)  −25.53(10)
N(1)–S(1)–N(3)–C(2)  −167.25(10)
S(1)–C(1)–N(3)–C(11) −62.00(13)
S(1)–N(3)–C(2)–C(3)  174.08(9)
C(11)–C(2)–C(3)–O(2) −178.86(12)
C(3)–O(2)–C(4)–C(1)  −53.96(16)
N(3)–C(1)–C(4)–O(2)  31.35(19)
S(1)–N(1)–C(5)–C(6)  −118.04(14)
S(1)–N(1)–C(5)–C(10) 58.88(15)
N(1)–C(5)–C(6)–C(7)  177.43(16)
N(1)–C(5)–C(6)–C(7)  177.43(16)
C(6)–C(5)–C(10)–C(9) −176.75(13)
N(1)–C(5)–C(10)–C(9) −176.75(13)
C(3)–C(2)–C(11)–C(16) −113.58(14)
C(3)–C(2)–C(11)–C(12) −67.37(17)
C(2)–C(11)–C(12)–C(13) 178.65(13)
C(12)–C(13)–C(14)–C(15) 0.3(3)
C(12)–C(11)–C(16)–C(15) −0.3(2)
C(12)–C(11)–C(16)–C(15) −0.3(2)
C(14)–C(15)–C(16)–C(11) 1.0(3)
Table 1: Crystal data and structure refinement for 2,5-di(2,6-diisopropylphenyl)-

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<th>Description</th>
<th>Value</th>
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<tr>
<td>Temperature</td>
<td>150(2) K</td>
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<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2_1/n</td>
</tr>
<tr>
<td>Unit cell parameters</td>
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</tr>
<tr>
<td>Cell volume</td>
<td>2442.2(4) Å³</td>
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<tr>
<td>Z</td>
<td>4</td>
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<tr>
<td>Calculated density</td>
<td>1.160 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient µ</td>
<td>0.152 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>928</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>colourless, 0.57 × 0.21 × 0.10 mm³</td>
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<td>Reflections for cell refinement</td>
<td>6250 (θ range 2.55 to 28.32°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker APEX 2 CCD diffractometer</td>
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<tr>
<td>θ range for data collection</td>
<td>1.71 to 28.35°</td>
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<tr>
<td>Index ranges</td>
<td>h –25 to 25, k –8 to 8, l –27 to 27</td>
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<td>Reflections with $F^2 &gt; 2\sigma$</td>
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<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
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<td>Min. and max. transmission</td>
<td>0.919 and 0.985</td>
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<td>Structure solution</td>
<td>direct methods</td>
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<td>Final R indices $[F^2 &gt; 2\sigma]$</td>
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<td>R indices (all data)</td>
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<td>0.000 and 0.000</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.439 and $-0.338$ e Å$^{-3}$</td>
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Table 2: Atomic coordinates and equivalent isotropic displacement parameters (Å$^2$). $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

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<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
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<td>0.6198(2)</td>
<td>0.44024(6)</td>
<td>0.0279(3)</td>
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<tr>
<td>S(1)</td>
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<td>0.53526(6)</td>
<td>0.468779(19)</td>
<td>0.01812(10)</td>
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<td>0.0186(3)</td>
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<td>0.0221(3)</td>
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Table 3: Bond lengths [Å] and angles [°].

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<th>Bond</th>
<th>Length [Å]</th>
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O(1)–S(1)–N(2) 108.20(7) O(1)–S(1)–N(1) 111.83(7)
N(2)–S(1)–N(1) 89.42(7) C(3)–N(1)–C(1) 122.10(12)
C(3)–N(1)–S(1) 118.53(11) C(1)–N(1)–S(1) 112.63(10)
N(1)–C(1)–C(2) 102.94(13) N(2)–C(2)–C(1) 104.25(13)
C(15)–N(2)–C(2) 119.08(13) C(15)–N(2)–S(1) 118.81(11)
C(2)–N(2)–S(1) 116.51(10) C(8)–C(3)–C(4) 121.21(15)
C(8)–C(3)–N(1) 121.62(14) C(4)–C(3)–N(1) 117.16(14)
C(5)–C(4)–C(3) 118.36(15) C(5)–C(4)–C(9) 121.14(15)
C(3)–C(4)–C(9) 120.47(14) C(4)–C(5)–C(6) 121.11(16)
C(7)–C(6)–C(5) 119.75(16) C(6)–C(7)–C(8) 121.63(16)
C(7)–C(8)–C(3) 117.82(15) C(7)–C(8)–C(12) 118.79(15)
C(3)–C(8)–C(12) 123.39(15) C(4)–C(9)–C(10) 110.64(15)
C(4)–C(9)–C(11) 113.42(15) C(10)–C(9)–C(11) 110.00(15)
C(8)–C(12)–C(14) 111.00(15) C(8)–C(12)–C(13) 110.95(15)
C(14)–C(12)–C(13) 111.39(16) C(20)–C(15)–C(16) 121.16(15)
C(20)–C(15)–N(2) 118.16(15) C(16)–C(15)–N(2) 120.64(14)
C(17)–C(16)–C(15) 118.20(16) C(17)–C(16)–C(21) 119.47(15)
C(15)–C(16)–C(21) 122.29(15) C(18)–C(17)–C(16) 120.95(17)
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<th>Angle (°) (°)</th>
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Table 4: Hydrogen coordinates and isotropic displacement parameters (Å\(^2\)).

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<td>0.6962</td>
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Table 5: Torsion angles [°].

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References


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