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Development of Enantioselective and Catalytic Cyclisation Reactions Using Hypervalent Iodine Compounds

University of HUDDERSFIELD

Department of Chemical Sciences

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March 2017

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Abbreviations

Ac: Acetyl.

OAc: Acetate.

Ar: Aryl.

Bz: Benzoyl.

Cbz: benzyloxycarbonyl.

CSA: Camphorsulfonic acid.

CTAB: Cetyltrimethylammonium bromide.

d.r.: Diastereomeric ratio.

DIAD: diisopropyl azodicarboxylate.

DIC: Diisopropylcarbodiimide.

DIPEA: Diisopropylethylamine.

DMAP: 4-Dimethylaminopyridine.

DMF: N,N-dimethylformamide.

DMP: Dess–Martin periodinane.

DMSO: dimethylsulfoxide.

DMEDA: N,N′-dimethylethylenediamine.

ee: Enantiomeric excess.

h: hour.

HFIP: 1,1,1,3,3,3-hexafluoroisopropanol.

HPLC: High pressure liquid chromatography.

HRMS: High resolution mass spectrometry.

LDA: Lithium diisopropylamide.

M: Molarity (mol/l).

m-CPBA: 3-Chloroperoxybenzoic acid.

Min: Minute.
m.p.: Melting point.

MS: mass spectrometry.

NMR: nuclear magnetic resonance.

IR: Infrared.

PIDA: phenyliodine(III) diacetate.

PIFA: [Bis(trifluoroacetoxy)iodo]benzene.

$P$-TsOH: $p$-toluenesulfonic acid monohydrate.

rt: room temperature.

TFA: trifluoroacetic anhydride.

TFE: 2,2,2-Trifluoroethanol.

TfOH: Triflic acid.

THF: tetrahydrofuran.

TMSOTf: Trimethylsilyl triflate.

$T_3$P: 1-Propanephosphonic anhydride.

Ts: Tosyl (4-toluenesulfonyl).
Abstract

In this thesis, iodoarene and chiral iodoarene reagents have been developed and used catalytically in the enantioselective cyclisation reaction of unsaturated esters, amides and β-amidoketones. The results in this thesis are divided into three parts.

In the first part, the development of the catalytic enantioselective cyclisation of 4-methoxybut-3-enyl benzoate to the 3-hydroxytetrahydrofuran ester using enantiomerically pure chiral hypervalent iodine reagents generated in situ is described. A good enantioselectivity of 77% ee was obtained with moderate yield.

In the second part, the development of catalytic conditions for the cyclisation of N-alkenylarylamides induced by iodoarenes leading to the formation of different ring sizes is demonstrated. In addition, the catalytic enantioselective cyclisation of N-alkenylarylamides employing chiral iodoarenes giving dihydrooxazines in good yields and moderate enantioselectivities of up to 64% is achieved.

In the third part, the catalytic cyclisation of both propargyl amides and β-amidoketones using 2-iodoanisole to afford 2-oxazolines in good yields is described.
Moreover, the catalytic enantioselective cyclisation of β-amidoketones using several chiral iodoarenes is detailed but, unfortunately almost no enantioselectivities was observed.
1. Introduction to Hypervalent Iodine

1.1. Iodine

Iodine is the chemical element with the symbol I and atomic number 53. Iodine, I₂, is a bluish-black, lustrous solid that is classified as a nonmetal. It has the highest atomic number and atomic weight of the stable Group 17 elements (halogens) where it is the least electronegative and the greatest polarisable element.¹ It forms compounds with most elements, but is less reactive than the other halogens. Iodine is essential in many biological organisms including in the human body, where it is present as a hormone in the thyroid gland Thyroxine 1. This is important in metabolism regulation.¹

```
O
O
O

H₂N

CH

Thyroxine 1
```

1.2. Hypervalent iodine compounds

In 1969 J. I. Musher defined the term hypervalent as molecules of the elements of group 15–18 having more than eight electrons in a valence shell.² The first hypervalent iodine compound iodobenzene dichloride (PhICl₂) was prepared by German chemist C. Willgerodt in 1886.³,⁴

When iodine is complexed with monovalent ligands, usually electronegative atoms or electron withdrawing groups such as chlorine or acetate, stable polycoordinate, multivalent compounds called hypervalent iodine compounds are formed.⁵
Iodine compounds exist in the +3 oxidation state as iodine(III) or $\lambda^3$-iodanes or in the +5 oxidation state as iodine(V) or $\lambda^5$-iodanes. These compounds contain a central iodine atom with an unusual bond called an iodine hypervalent bond (Figure 1) that contains a linear three-center, four-electron (3c–4e) bond (L–I–L) formed by the overlap of the 5p orbital on iodine with the orbitals on the two ligands L. This 3c-4e bond is commonly named as a “hypervalent bond”. This bond is highly polarised and is weaker and longer than a normal covalent bond. The existence of this bond in hypervalent iodine compounds is responsible for their strongly electrophilic reactivity. As two electrons are in a nonbonding orbital, there are not greater than eight electrons on the iodine atom. Therefore, the original definition of hypervalent is not valid. In addition, the bond order of the I-L bonds is formally 0.5 this explains their long length and relative weakness.$^5$-$^7$

![Figure 1](image1.png)

The most common hypervalent iodine compounds are ArIL₂ and their geometry are pseudotrigonal bipyramidal. The reason for that is the 3c-4e bond dictates the structure.$^5$,$^6$

The following common classes of iodine(III) compounds have found extensive applications in organic synthesis (Figure 2).$^7$
1.3. Reactivity of Trivalent Iodine compounds

Trivalent iodine compounds are widely used as reagents in organic synthesis. Their reactivity is based on the number of carbon and heteroatom ligands on the iodine atom. The most common type consist of one carbon ligand and two heteroatom ligands i.e RIL$_2$. The two heteroatom ligands occupy the apical positions of the pseudotrigonal bipyramid and these iodanes are typically oxidants. Iodine(III) centres are highly electrophilic, making them liable to nucleophilic attack, and the two L ligands act as good leaving groups. The leaving process is termed reductive elimination, in which the $\lambda^3$-iodanyl group eliminates with energetically favourable reduction of the hypervalent iodide I(III) to normal valence I(I).
In recent years, the organic chemistry of hypervalent iodine compounds has received considerable attention, due to their oxidising properties and the fact that they are mild and highly selective, possess low toxicity and high stability, and are easy to handle and relatively environmentally friendly. Similar reactivity can be observed with highly toxic heavy-metal oxidisers, such as lead(IV), mercury(II) and thallium(III) reagents as well as expensive and rare transition metals. In addition, metal contamination in drug molecules is an important issue and minimising the use of metals in syntheses is one way to resolve this problem. Moreover, the possibility of forming a covalent chiral backbone on the iodine raises the possibility of enantioselective synthesis.\textsuperscript{6-8}

1.4. Chiral Hypervalent Iodine(III) Reagents

The first chiral hypervalent iodine compound, diphenyliodonium tartrate was prepared in 1907 by Pribram.\textsuperscript{9} However, the utility of chiral I(III) reagents in oxidative reactions, has only been realised in the past few decades.\textsuperscript{6-8} The investigation of chiral hypervalent iodine reagents in asymmetric transformations is an increasingly noteworthy area of research.\textsuperscript{10}

1.5. General Reactivities of Chiral Hypervalent Iodine Reagents

In recent years, great effort has been dedicated to the employment of enantiomerically pure hypervalent iodine reagents in asymmetric synthesis. Examples include the oxidation of sulfids to sulfoxides, $\alpha$-functionalisation of carbonyl compounds, the dearomatisation of phenols, the functionalisation of alkenes, rearrangement reactions, and heterocyclisations.\textsuperscript{5-8}
In addition, enantioselective oxidation reactions have been accomplished under catalytic conditions with chiral hypervalent iodine reagents, in which a catalytic amount of chiral iodoarene is oxidised to the hypervalent iodine species \textit{in situ} using a stoichiometric co-oxidant. In the catalytic variant of the reaction, it is not necessary to prepare the hypervalent iodine compounds, and only a catalytic amount of chiral iodoarene is used as a precursor.\textsuperscript{11,12}

1.5.1. Oxidation of Sulfids to Sulfoxides

The first synthetically useful application of a chiral iodine(III) was illustrated by Imamoto\textsuperscript{13} with 10a-c and later by Koser\textsuperscript{14} with 11 who performed the oxidation of sulfides 8 to sulfoxides 9 in moderate to good yield with selectivities of up to 53\% ee with 10 (Scheme 1).

\[ R^1 \cdot S \cdot R^2 + 10 \text{ or } 11 \xrightarrow{\text{acetone, rt, 2.5-3 h}} R^1 \cdot S \cdot R^2 + O \]

\( R^1 = \text{Aryl, alkyl} \)
\( R^2 = \text{Me, t-Bu} \)

With 10: 71-95\% yield, 5-53\% ee
With 11: \( R^1 = \text{Ph} \), \( R^2 = \text{Me} \)
81\% yield, 30\% ee

Scheme 1

Kita reported that 10 mol\% of a chiral tartaric acid derivative and 20 mol\% of cetyltrimethylammonium bromide (CTAB) used with iodoxybenzene (PhIO\textsubscript{2}) in a cationic reversed micellar system led to the oxidation of sulfides 8 to sulfoxides 9 in high yields and
moderate enantioselectivities of up to 72% ee (Scheme 2). This is the first example of the asymmetric oxidation of sulfides to sulfoxides by using hypervalent iodine(V) reagents.\textsuperscript{15}

![Scheme 2]

The same research group in 2000, reported that this oxidation was successful with excellent yields and moderate enantioselectivities using only water as a solvent in the presence of magnesium bromide to increase the enantioselectivity.\textsuperscript{16}

In 1990, another type of chiral iodane (+)-12 was prepared by Koser and Ray. These were employed in the oxidation of sulfides and afforded mixtures of salts (+)-13 with high yields and moderate diastereomeric excesses. These salts were separated by recrystallisation and hydrolysed to obtain chiral sulfoxides 9 in excellent enantiopurities (Scheme 3).\textsuperscript{17}

![Scheme 3]

Other research groups such as those of Chen and Xia,\textsuperscript{18} Zhdankin et al.\textsuperscript{19,20} and Wirth et al.\textsuperscript{21} have prepared new chiral hypervalent iodine reagents and tested them in the oxidation of
sulfides to sulfoxides. Unfortunately, relatively poor enantioselectivities were observed in all cases.

1.5.2. Dearomatisation reaction

In recent years, there have been several interesting studies in the literature relating to the chiral hypervalent iodine-mediated oxidative-dearomatisation of phenols (Scheme 4). In these reactions either dimerisation or the formation of *ortho*-quinone monoketals or quinol intermediates can result.\(^{22}\)

\[
\text{PhI} \rightleftharpoons \text{PhI}^* \rightleftharpoons \text{PhI} - \text{X}
\]

Scheme 4

In 2008 Kita *et al.*\(^{23}\) reported the first enantioselective dearomatisation reaction using a chiral hypervalent iodine(III) reagent (*R*)-16. Iodane (*R*)-16 has a rigid spirobiindane and it converted 4-substituted \(\alpha\)-naphthols 14 into *ortho*-spirolactones 15 with moderate to good enantioselectivities and good yields (Scheme 5).
The same group observed that the reaction could be made catalytic by employing 0.15 equiv of the corresponding iodoarene 17 and using \( m \text{CBPA} \) as a co-oxidant which generates chiral hypervalent iodine \textit{in situ} (Scheme 6).\textsuperscript{24} This catalytic reaction has to be performed at a higher temperature to enable oxidation of I(I) to I(III) and the enantioselectivities are diminished as a consequence.
In 2013, Kita et al.\textsuperscript{25} reported higher enantioselectivities for this spirolactonisation using a new pre-catalyst (\(R\))-20. This spirobiindane derivative has an ethyl group in the \(o\)-position to the iodine and when applied to the spirolactonisation of different naphthol derivatives 18. The 19 were afforded in excellent yields and enantioselectivities of up to 92% ee (Scheme 7).

[\textbf{Scheme 7}]

In 2010 Ishihara \textit{et al.}\textsuperscript{26} designed and prepared several \(C_2\)-symmetric chiral iodoarenes 21 and examined them in catalytic oxidative spirolactonisation reactions. Similar to Kita’s catalyst ((\(R\))-20) higher enantioselectivities of up to 92% ee were observed by using 10 mol% of (\(R,R\))-21 and 1.5 equiv of \(m\)CPBA as co-oxidant which generated the chiral iodane(III) catalyst \textit{in situ} (Scheme 8). The same authors showed that the selective oxidation of the double bond into an epoxide occurred when using an excess of \(m\)CPBA in this reaction with good yields and diastereoselectivity.\textsuperscript{27}
In 2013, Ishihara et al.\textsuperscript{28} employed their $C_2$-symmetric chiral iodoarene 25 in the tandem enantioselective catalytic oxidative dearomatisation of phenols 22 and the Diels–Alder reaction. The active hypervalent iodine(III) species 26 was generated \textit{in situ} from the $C_2$-symmetric chiral iodoarene 25 and \textit{m}CPBA. As a result high to excellent enantioselectivities were observed for the desired cyclohexadienone spirolactones 23 and the subsequent Diels–Alder adducts 24 (Scheme 9).
In 2013, Harned et al.\textsuperscript{29} prepared the new chiral aryl iodide pre-catalyst 29 derived from 8-iodotetralone and tartaric acid and used it with 2.2 equivalents of mCPBA as co-oxidant in the asymmetric oxidation of phenols 27 to provide the \textit{para}-quinols 28 with moderate to good yields and enantioselectivities (Scheme 10).
1.5.3. Functionalisation of Carbonyl Compounds

Another important application of chiral hypervalent iodine reagents is the α-functionalisation of carbonyl compounds.

In 1997 Wirth and co-workers reported the first enantioselective α-oxytosylation of propiophenone utilizing chiral hypervalent iodine(III) compounds as stoichiometric reagents. They obtained the expected product with 15% ee demonstrating that this was a viable strategy for the preparation of non-racemic chiral compounds (Scheme 11).
In 1998, the same groups reported derivatives of chiral hypervalent iodine reagent 32 in which they installed an extra ortho substituent on the benzene ring and examined these catalysts in the enantioselective α-oxytosylation of propiophenone, which afforded tosylates in up to 28% ee.\(^\text{31}\) and with slightly improved enantioselectivities of up to 40% ee in 2001.\(^\text{32}\)

In 2007, Wirth et al.\(^\text{33}\) investigated the first enantioselective catalytic reactions of α-oxytosylation of ketones by chiral hypervalent iodine catalyst. One year later, they synthesised several chiral iodoarenes reagents and used them in the α-oxytosylation of propiophenone derivatives 30 using 10 mol% of 33 and mCPBA as a stoichiometric oxidant and para-toluenesulfonic acid (TsOH) afforded the product 35 in up to 39% ee (Scheme 12).\(^\text{34}\)

![Scheme 12](image)

In 2010, Wirth et al.\(^\text{35}\) prepared more chiral iodoarene catalysts 37 and employed them in the enantioselective α-oxytosylation of propiophenone but only 26% ee was obtained with 70% yield. Furthermore, they investigated this catalyst in the lactonisation reaction of 5-oxo-5-phenylpentanoic acid 35, however poor or no enantioselectivity was obtained for the desired product 36 (Scheme 13).
One year later, in 2011, Zhang et al. prepared new chiral iodoarene ($S$)-40 and derivatives containing a spirobiindane scaffold and tested their chiral inducing ability as a catalyst in the asymmetric α-tosyloxylation of ketones 38 using $m$CPBA as a stoichiometric oxidant. An enantioselectivity of up to 58% ee was achieved for the α-tosyloxylated ketones 39 (Scheme 14).
In 2012, Moran and Rodríguez\textsuperscript{37} prepared chiral iodoarenes 41a and 41b and they tested 41a as a pre-catalyst with \textit{m}CPBA as the co-oxidant in the \(\alpha\)-oxytosylation of propiophenone 30 observing a good yield (67\%) and 18\% ee. Also, an improved enantioselectivity of up to 51\% ee was obtained for the lactonisation of 5-oxo-5-phenylpentanoic acid 38 by employing pre-catalyst 41b and \textit{m}CPBA to obtain the corresponding lactone 36 in 47\% yield (Scheme 15).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_15.png}
\end{center}

\textbf{Scheme 15}

In 2012, Legault \textit{et al.}\textsuperscript{38} published the activity of new chiral iodoarenes 42a-d as catalysts in the \(\alpha\)-oxytosylation of propiophenone 30. They found that the enantioselectivity slightly improved to up to 54\% ee by employing this new family of iodooxazoline-based catalysts in the enantioselective \(\alpha\)-oxytosylation of propiophenone 30 with moderate yields (Scheme 16).

23
Berthiol and co-workers designed a new family of hypervalent iodoarene organocatalysts based on 3,3′-diiodo-BINOL-fused maleimides 43. By applying these new catalysts in the propiophenone oxidation reaction, the enantioselectivity for the expected product was similar to that previously reported using structurally different organocatalysts (Scheme 17).39
In 2015, Legault and Basdevant proposed a new strategy for this reaction in which the possibility of higher enantioselectivity could be achieved by using enol derivatives instead of ketone substrates. This would force the reaction to proceed through a C-bonded intermediate pathway instead of through an O-bonded iodane intermediate (Scheme 18).

**Scheme 17**

**Scheme 18**
Using this approach, Legault and Basdevant achieved enantioselectivities of up to 90% ee using chiral iodoarene reagents 45 with enol esters 44 as substrates. Enol 44 can be synthesised readily from the corresponding ketones or alkynes (Scheme 19). Both stoichiometric and catalytic conditions successfully worked in this reaction. The excellent enantioselectivity was obtained when the reaction was carried out in a catalytic system, using 20 mol% of the catalyst 45 with slow addition of a 1:1 mixture of \textit{m}CPBA/TsOH.

![Scheme 19](image)

Wirth and Mizar showed that the lactate-based hypervalent iodine reagent 21 can be successfully employed in stereoselective reactions of cyclic enol ethers 46 by nucleophilic attack on the silyl enol ether. This process provided access to several nitrogen and oxygen substituted cyclic ketones 47 with moderate to high enantioselectivities and yields (Scheme 20).
In 2014, Kita et al. developed an asymmetric fluorination reaction of β-dicarbonyl compounds catalysed by chiral iodoarene. This was the first example of the enantioselective fluorination reaction of β-ketoesters employing a catalytic system consisting of a chiral iodoarene catalyst, HF/pyridine as the fluorine source and mCPBA as the co-oxidant which afforded the α-fluorinated β-ketoesters with moderate yields and enantioselectivities (Scheme 21).
1.5.4. Functionalisation of alkenes

One of the most important reactions in organic synthesis is the asymmetric oxidation of alkenes which allows the fast preparation of polyfunctional chiral compounds. In particular, investigations using chiral hypervalent iodine reagents for this purpose have been reported by numerous research groups.

In 1997 Wirth and Hirt prepared three different chiral hypervalent iodine(III) compounds and tested them in the asymmetric oxidation of styrene under the same conditions that they previously utilised in the α-oxytosylation of ketones (Scheme 11 and 12). Either the dioxytosylated products or the mono(tosyloxy) mono(hydroxy) products were obtained in up to 21% ee. Shortly after, Wirth and Hirt functionalised these reagents further by introducing a methoxy group in the ortho-position to the iodine atom and the enantioselectivity was slightly increased up to 53% ee with for dioxytosylated products. Three years later, the same research group achieved up to 65% ee for dioxytosylated product using chiral iodine(III) (Scheme 22).
Scheme 22

In 2004, Zhdankin et al. prepared new chiral amino acid-derived iodobenzene dicarboxylate (S,S)-56. They employed this reagent with iodide anion in the β-iodocarboxylation reaction of cyclohexene 54 and dihydropyran 55 which afforded a 1:1 mixture of both diastereomers of 57 and 58 in high yield (Scheme 23).
In 2007, Fujita et al.\textsuperscript{47} prepared two optically active chiral hypervalent iodine(III) reagents (R)-62 in which chiral ester derivatives were used instead of chiral amides. They employed these reagents in the development of a tetrahydrofuranylation process of acyloxybutenes (Z/E)-59. The tetrahydrofuran products 60 were obtained in up to 64\% ee with a small amount of oxo-butyl benzoate 61 being formed (Scheme 24). They also showed that the enantioselectivity was dependent on the electrophilic addition of iodine(III) toward the double bond, the substituents on the acyloxybutene substrates and the nucleophilic addition of the acyloxy group toward the double bond.
Three years later, Fujita et al. synthesized a new family of lactate-derived optically active hypervalent iodine(III) reagents \((R)-64c-e\) and \((R,R)-68\). They utilized these reagents in the enantioselective oxidative lactonization of ortho-alkenylbenzoate \(67\) using stoichiometric amounts of these iodanes in the presence of para-toluenesulfonic acid or acetic acid. The corresponding δ-lactones \(69\) were formed with high regioselectivity and up to 97% ee (Scheme 25).
The same research group prepared several oxyisochromanone natural products following their process using chiral hypervalent iodine reagent generated \textit{in situ} by applying a catalytic amount of chiral lactate-based iodoarene with a stoichiometric amount of \textit{m}CPBA in the enantioselective oxylactonisation of an \textit{ortho}-alkenylbenzoate derivatives \textit{66}. 4-Hydroxyisochroman-1-one derivatives \textit{67} were obtained in excellent enantioslectivities with moderate yields which resulted from the realisation of racemic anti-products by a direct oxidation of \textit{66} by \textit{m}CPBA. They indicated that the lactate moiety on the chiral iodoarene precatalyst could be responsible for the high enantioselectivity of oxylactonisation (Scheme 26).^{49}
In 2017, Masson et al.\textsuperscript{50} reported the first enantioselective sulfonyl- and phosphoryl-
oxylactonisation of 4-pentenoic acids derivatives 69 mediated by a chiral aryl-\(\lambda^3\)-iodane. They used a stoichiometric or catalytic amount of chiral iodoarene 21 and achieved moderate to excellent enantioselectivities for sulfonyloxy- and phosphoryloxy-\(\gamma\)-butyrolactones 70 and 71 with acceptable yields (Scheme 27). Notably, high enantioselectivities with lower yields were obtained when a stoichiometric amount of chiral iodoarene was employed. However, using a catalytic amount of chiral iodoarene provided the desired product with lower enantioselectivities and higher yields.
In 2011 Fujita et al.\textsuperscript{51} developed the enantioselective Prévost and Woodward reactions by employing hypervalent iodine(III) reagents (\(R\))-62a and (\(R\))-62c in the oxylactonisation of alkenes 72. They selectively observed two products depending on the nature of the nucleophile. When the water was added at the 2-position of 1,3-dioxolan-2-yl cation intermediate 74 the \textit{syn} products (\textit{syn}-73) were obtained in moderate yields with up to 96% ee. However, when the acetic acid was added at the 4-position of the cation intermediate 74 the \textit{anti} products (\textit{anti}-73) were isolated in good yield and up to 96% ee (Scheme 28).
Muñiz et al.\textsuperscript{52} successfully achieved the first example of an enantioselective diamination of an alkene using Fujita’s iodane (\textit{R,R})-\textsuperscript{65}. They employed this chiral hypervalent iodine(III) reagent in the enantioselective diamination of styrene derivatives \textbf{75} which generated enantiopure diamines \textbf{76} in moderate to good yields with excellent enantioselectivities of up to 95\% (Scheme 29). In 2013, the same research group investigated new dinuclear binaphthyl iodine(III) reagents in the same reaction and obtained the product \textbf{76} with up to 32\% ee.\textsuperscript{53}
In 2016, Ishihara et al.\textsuperscript{54} illustrated that the important structural force in chiral hypervalent iodine reagents is a selective hydrogen bonding arrangement (Figure 4).

They described the first enantioselective catalytic diacetoxylation of styrenes by employing chiral hypervalent iodine \textit{78b} as a catalyst under mild conditions and the corresponding dioxygenation products \textit{77} were afforded in good to high yields with up to 94\% ee (Scheme 30).
In 2007, Wirth et al.\textsuperscript{55} reported the first efforts towards the enantioselective aziridination of alkenes employing two methods. First, employing chiral iodoarene \textsuperscript{50} under Che’s conditions,\textsuperscript{56} and second using stoichiometric Imamoto’s reagent\textsuperscript{10} \textsuperscript{10}. Both reagents provided the expected aziridine \textsuperscript{81} in low enantioselectivity (Scheme 31).
In 2012, Wirth et al.\textsuperscript{57} investigated the first stereoselective oxyaminations of alkene-urea derivatives \textbf{82} promoted by Ishihara's reagent\textsuperscript{26} \((R,R)-21\), to give bicyclic compounds \textbf{83} in good yields and up to 96% ee. However, derivatives of \textbf{83} were cyclised in only low to moderate enantioselectivities (Scheme 32).

\begin{center}
\textbf{Scheme 32}
\end{center}

In 2014, Wirth et al.\textsuperscript{58} synthesised a new chiral hypervalent iodine(III) reagent \textbf{90} and used it as an efficient reagent for the enantioselective intramolecular diamination of alkenes. A stoichiometric amount of \textbf{90} afforded the desired bicyclic products \textbf{88} in good yields with excellent enantioselectivities of up to 94%. They also achieved moderate enantioselectivities using 20 mol\% of precatalyst \textbf{91} with sodium perborate as a co-oxidant. This led to formation
of the bicyclic products in good yields and up to 86% ee. The Cbz and (X) groups were easily removed by reduction using lithium aluminium hydride and resulted in free diamine products 92 (Scheme 33).

Scheme 33

In 2013, Nevado et al.\textsuperscript{59} reported the first regioselective aminofluorination of alkenes by the synthesis of a new chiral arylido difluoride reagent 94. The aminofluorination of alkenes 92
proceeded with high regioselectivity without any additive by employing stoichiometric amounts of 94. The six-endo-cyclised products 93 were isolated in 79% yield with up to 88% ee. The same authors expanded the procedure to give seven-membered β-fluorinated azepanes 96 in good yields and up to 77% ee using 94 although a catalytic amount of a gold complex ([2-PicAuNTf₂]) was required (Scheme 34).

\[
\begin{align*}
\text{R} & = \text{Ts, Cbz} \\
\text{R}^1 & = \text{aryl} \\
\text{R}^2 & = \text{alkyl}
\end{align*}
\]

\[
\begin{align*}
\text{RHN} & \rightarrow \text{NHR} \\
\text{CH}_2\text{Cl}_2 & \rightarrow \text{N}_\text{R}\text{R}_1\text{R}_1 \\
\text{63-90% yield} & \text{ 61-88% ee}
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{Ts, Cbz} \\
\text{R}^1 & = \text{aryl} \\
\text{R}^2 & = \text{alkyl}
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{Ts, Cbz} \\
\text{R}^1 & = \text{aryl} \\
\text{R}^2 & = \text{alkyl}
\end{align*}
\]

\[
\begin{align*}
\text{63-90% yield} & \text{ 61-88% ee}
\end{align*}
\]

\[
\begin{align*}
\text{tBuO} & \rightarrow \text{O} \\
\text{O} & \rightarrow \text{O} \\
\text{Bu} & \rightarrow \text{Bu}
\end{align*}
\]

\[
\begin{align*}
\text{RHN} & \rightarrow \text{NHR} \\
\text{CH}_2\text{Cl}_2 & \rightarrow \text{N}_\text{R}\text{R}_1\text{R}_1 \\
\text{46-64% yield} & \text{ 61-77% ee}
\end{align*}
\]

Scheme 34

One year later, Kita at el.\textsuperscript{42} developed a catalytic system for the enantioselective intramolecular aminofluorination of alkenes. They used a catalytic amount of chiral iodoarene 50 in the presence of \textit{m}CBPA as the co-oxidant and the less costly fluorine source
HF. The expected fluorinated products 97 were obtained in good yields and up to 70% ee (Scheme 35).

Very recently, Jacobsen *et al.* described the enantioselective catalytic difluorination of alkenes by a chiral iodoarene with a nucleophilic fluoride source and mCPBA as a stoichiometric oxidant. They prepared chiral aryl iodide 100 and utilised it in the enantioselective 1,2-difluorination of cinnamide 98. The expected product 99 was obtained in moderate yield and excellent enantioselectivity of 93% ee (Scheme 36).
In the same year, the same authors reported the development of an enantioselective catalytic fluorolactonisation reaction for the synthesis of 4-fluoroisochromanones 101 induced by chiral iodoarene reagents 102 using HF-pyridine as a nucleophilic fluoride source and mCPBA as co-oxidant. The expected products containing fluorine-bearing stereogenic centres were formed with excellent enantioselectivity (Scheme 37).61 They also found that the regioselectivity of the lactonisation reactions obtained using this nucleophilic fluorination systems was the same as when using asymmetric electrophilic fluorination systems previously established.60
In 2016, Fujita et al.\textsuperscript{62} achieved enantioselective oxidative C-C bond formation with chiral hypervalent iodine reagents under metal-free conditions. They applied their lactate-based chiral hypervalent iodine reagents 62 and 65 in the enantioselective intramolecular oxyarylation of alkene substrates 103. This afforded the carbocyclisation products 104 with high enantioselectivities of up to 95\% ee. The presence of a silyl protecting group on the alcohol led to higher selectivities (Scheme 38).
In 2013, Wirth et al.\textsuperscript{63} achieved the first stereoselective rearrangement reactions of aryl substituted alkenes \textsuperscript{105} mediated by chiral hypervalent iodine(III) reagents \textsuperscript{21}. The rearranged product \textsuperscript{106} was obtained in high yield with enantioselectivities up to 99\% ee (Scheme 39). They proposed a reaction mechanism in which the double bond of the alkene is activated by the hypervalent iodine reagent to generate intermediate A which is stabilised by the formation of a phenonium ion B followed by a second nucleophile attack to generate the 1,2-migration products \textsuperscript{106} (Scheme 40).

Scheme 39
Very recently, Wirth et al.\textsuperscript{64} developed the stereoselective rearrangement of different disubstituted alkenes \textbf{107} under base-free conditions using chiral hypervalent iodine(III) derivatives. They observed α-arylated ketones \textbf{108} in moderate to good yields with high enantioselectivities of up to 92\% (Scheme 41).

Scheme 41
In 2016, Silva Jr et al.\textsuperscript{65} investigated the asymmetric oxidative rearrangement of non-functionalised olefins mediated by chiral hypervalent iodine(III) species generated \textit{in situ} form chiral iodoarene 111. They utilised various 1,2-dihydronaphthalenes derivatives 109 in the asymmetric ring contraction reaction using their metal free conditions and obtained optically active 1-substituted indanes 110. These were isolated as either an acetal or an alcohol in high enantioselectivities of up to 78\% ee with very short reaction times (Scheme 42).

![Scheme 42](image)

In 2014, Muñiz \textit{et al.}\textsuperscript{66} studied the oxidative amination of allenes mediated by a chiral hypervalent iodine reagent 68. They subjected 1-phenyl allenes 112 to their conditions without any additive and the corresponding internal propargylic amines 113 were obtained with low enatioselectivity and moderate diastereoselectivity. After the combination of the hypervalent iodine reagent with triphenylphosphine oxide the internal regioisomer was observed with a slight improvement in diastereoselectivity and an increase of the enantiomeric excess up to 22\% ee (Scheme 43).
(R'R)\textsuperscript{68} (1.1 equiv) HNTs\textsubscript{2} (2.2 equiv)
CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 18 h

112

\begin{align*}
\text{Ph} & \text{CH} & \text{CH} \\
\text{NTs} & \text{2} & + \\
\text{Ph} & \text{NTs} & \text{2}
\end{align*}

\begin{align*}
\text{113} & \text{114} \\
\text{NTs} & \text{2} & \text{NTs} & \text{2} \\
\text{Ph} & \text{Ph} & \\
\text{113}/\text{114} & = 3:5:1 \text{ dr, 11% ee (113)}
\end{align*}

\begin{align*}
\text{112} & \text{Ph} & \text{Ph} & \text{NTs} & \text{2} \\
\text{113} & \text{114} & \text{NTs} & \text{2} & \text{NTs} & \text{2} \\
\text{113}/\text{114} & = 4:9:1 \text{ dr, 11% ee (113)}
\end{align*}

Scheme 43
2. Aims and objectives

Tetrahydrofuranylation of but-3-enyl benzoate 115 was carried out by Fujita et al.\textsuperscript{47} using the optically active hypervalent iodine(III) reagents 62b in the presence of BF$_3$.OEt$_2$ in dichloromethane at -78 °C. This process gave exclusively 3-benzoyloxytetrahydrofuran 116 in 48% yield and up to 58% ee.

\begin{equation}
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{Ph} \quad \text{O} \quad \text{O} \quad \text{I(OAc)$_2$} \quad \text{BF$_3$.OEt$_2$ (1.3 equiv)} \quad \text{CH$_2$Cl$_2$, -78 °C} \quad \text{yield} = 48\% \quad \text{ee} = 58\%
\end{equation}

\textbf{Scheme 44}

1. The objective of this work was to develop a \textbf{catalytic} enantioselective cyclisation reaction of substituted but-3-enyl benzoates mediated by \textit{in–situ} generated chiral hypervalent iodine species at \textbf{room temperature}.

2. The second objective of this work was to develop a catalytic enantioselective cyclisation of amide analogues using chiral aryl iodides at room temperature.
3. The third objective of this work was to develop catalytic conditions for the cyclisation of propargyl amides and the enantioselective cyclisation of β-amidoketones.

\[
\begin{align*}
\text{Ar} & \text{N} \equiv \text{R} \\
\text{OR} & \\
\text{Ar} & \text{N} \equiv \text{Ar} & \text{N} \equiv \text{R}
\end{align*}
\]

\[\text{in-situ} \text{ generation of iodine(III)}\]

\[\text{Oxidant} \rightarrow \text{Solvent} \]

\[\begin{array}{c}
\text{Ar} \\
\text{N} \equiv \text{O} \\
\text{R}
\end{array}\]
3. Results and Discussions

3.1. Cyclisation reactions of esters containing a pendent alkene.

Previously in the Moran group (D.Hammett and E.Bennett unpublished results) optically active iodoarenes were prepared and employed as catalysts in the oxidative cyclisation of substituted but-3-enyl benzoates 115 to form the 3-hydroxytetrahydrofuran esters 116 (Scheme 45).

![Scheme 45](image)

It was found that separation conditions for the phenyl cyclisation product 116a (R = H) could not be obtained on our chiral HPLC columns therefore enantioselectivity could not be ascertained. For this reason simple derivatives 115b-h were prepared and studied. All of the products 116b-h could be separated by chiral HPLC.

The cyclisation reactions were performed, first with iodobenzene to generate racemic samples of products 115 in yields ranging from 10-68%. Then the reactions were repeated using catalytic amounts of the chiral aryl iodide 120a and 123a to generate the chiral iodine(III) species *in situ* in the presence of Selectfluor as oxidant (Scheme 46).
The analogues 116b-h were synthesised to see how the various arene substituents affected the yield and enantioselectivity and the results of these cyclisations are summarised in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Yield a,b %</th>
<th>ee c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115b</td>
<td>120a</td>
<td>71</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>115c</td>
<td>120a</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>115d</td>
<td>120a</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>115e</td>
<td>120a</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>115f</td>
<td>120a</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>
The reaction was typically carried out in acetonitrile (1mL), \( p\text{-TsOH}, \text{rt}, 18\text{-}36\text{ h.} \)
[b] Yield calculated after column chromatography.
[c] Determined by chiral HPLC analysis.

<table>
<thead>
<tr>
<th>6</th>
<th>115g</th>
<th>120a</th>
<th>18</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>115h</td>
<td>120a</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>115b</td>
<td>123a</td>
<td>20</td>
<td>87</td>
</tr>
</tbody>
</table>

[a] The reaction was typically carried out in acetonitrile (1mL), \( p\text{-TsOH}, \text{rt}, 18\text{-}36\text{ h.} \)
[b] Yield calculated after column chromatography.
[c] Determined by chiral HPLC analysis.

Table 1

Generally, the highest yields were observed when \( R \) was an electron donating group such as \( p\text{-methoxy} \ 116b \) and \( p\text{-}t\text{-butyl} \ 116e \) as these groups rendered the ester more reactive. Other analogues were prepared, but these cyclised in very low yields. The highest enantioselectivity obtained was 87% ee for the \( p\text{-MeO} \) substrate 115b using 2:1 MeOH:MeCN as solvent, dimethylamine derived amide catalyst 123a, and TFA as acid.

Importantly, the catalytic reaction was only found to occur using Selectfluor as the oxidant: \( m\text{CBPA}, \text{Oxone, H}_2\text{O}_2 \) and sodium perborate were all found to be ineffective and starting material was recovered.

With these results in hand, the intention to reproduce and improve the previous results of our group was attempted again. First, starting material 115b used for the cyclisation reaction was prepared in 93% yield in one step from treatment of readily available \( p\text{-methoxybenzoyl chloride with 3-butenol in CH}_2\text{Cl}_2 \) in the presence of base (Et3N) and DMAP at 0 °C.\textsuperscript{57} Combound 115c was also prepared by our group in 74% yield (Scheme 47).
Next, the synthesis of several chiral iodoarenes using a Mitsunobu reaction was attempted. Following the literature procedure reported by Tsujiyama and coauthors, 2-iodoresorcinol \( \text{118} \) was prepared from resorcinol \( \text{117} \) with iodine using NaHCO\(_3\). Then a double Mitsunobu reaction of \( \text{118} \) with optically active ethyl lactate \( \text{119a} \) was effected with diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine (PPh\(_3\)) to give the ethyl lactate derived aryl iodide (\( \text{120a} \)) in 73% yield. Diester \( \text{120a} \) was hydrolysed with NaOH to give the chiral \( C_2 \)-symmetric acid \( \text{121} \) in quantitative yield. The chiral acid \( \text{121} \) was converted into the acid chloride \( \text{122} \) using oxalyl chloride and treated with dimethyl amine to generate amide \( \text{123a} \) in 60% yield. We also synthesised the novel \( C_2 \)-symmetric chiral iodoarene \( \text{120b} \) and \( \text{123b} \) via esterification to give \( \text{120b} \) in 50% yield and amidation to give \( \text{123b} \) in 54% yield (Scheme 48).
The utility of using catalytic amounts of these chiral iodoarenes for the enantioselective cyclisation of 115b to tetrahydrofuran 116b in the presence of Selectfluor as oxidant using different acids and solvents was examined (Table 2). Firstly, the reaction with 120a using the conditions shown in scheme 49 was repeated. Unfortunately the yield was very low and as a result, the enantioselectivity was not obtained (entry 1). The use of diester 120b gave 116b with 41% ee (entry 2). In contrast, the use of bis(N-dialkylamides) 123a and 123b further increased the enantioselectivity (entries 3 and 4). Bis(N-dimethyl amide) 123a was the best precatalyst for enantioselectivity giving 116b with 77% ee but with low yield 20% (entry 3).
and the use of bis(N-diisopropyl amide) slightly dropped the enantioselectivity to 65% ee but with better yield 34% (entry 4).

The cyclisation reaction of 115b was carried out previously in our group with chiral catalyst 123a and the enantioselectivity for tetrahydrofuran 116b reported was 87% ee. However, separation of the peaks via chiral HPLC was not complete when using 3% isopropanol and 97% hexane. This analysis was repeated to improve the separation by washing the chiral HPLC column with ethanol (HPLC grade) and changing the HPLC conditions to 3% ethanol and 97% hexane. This resulted in complete separation of the peaks and the highest enantioselectivity observed was 77% ee.

![Scheme 49](image_url)

**Scheme 49**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>Solvent</th>
<th>Acid</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120a</td>
<td>MeOH:MeCN (2:1)</td>
<td>TFA</td>
<td>&gt;10</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>120b</td>
<td>MeOH:MeCN (2:1), 10 equiv H2O</td>
<td>Triflic acid</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>123a</td>
<td>MeOH:MeCN (2:1)</td>
<td>TFA</td>
<td>20</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>123b</td>
<td>MeOH:MeCN (2:1), 5 equiv H2O</td>
<td>Bis(trifluoromethane)sulfonimide</td>
<td>35</td>
<td>65</td>
</tr>
</tbody>
</table>

N.D. = Not Determined

**Table 2**
The use of $t$-butyl ester catalyst 120b was investigated next (Scheme 50) and the results are showed in Table 3. Previous investigations within our group and others,\textsuperscript{57,66} have shown that the solvent composition is important in enantioselective reactions with iodine(III) reagents. First MeCN in the presence of TFA for the cyclisation reaction with 10 mol % of 120b was screened, which afforded the product in low ee and 22% yield (entry 1). However, it was decided to use the same optimised conditions (2:1 MeOH:MeCN, acid and Selectfluor at rt) that were used by our group for this reaction with 120a. The use of a 2:1 mixture of methanol and acetonitrile with either TFA or triflic acid did not improve the yield of 116b (entry 2, 3). However, when 10 equivalents of H$_2$O and triflic acid were used, the enantioselectivity of 116b increased to 41% ee and the yield increased to 33% (entry 5). In contrast using the stronger acid bis(trifluoromethane)sulfonamide afforded 116b in low yield (entry 6). Unfortunately other solvent ratios of methanol and acetonitrile gave the product in very low conversion therefore the enantioselectivity was not obtained.

Scheme 50
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>TFA</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>MeOH:MeCN (2:1)</td>
<td>TFA</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>MeOH:MeCN (2:1)</td>
<td>Triflic acid</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>MeOH:MeCN (2:1), 5 equiv H2O</td>
<td>Triflic acid</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>5</td>
<td>MeOH:MeCN (2:1), 10 equiv H2O</td>
<td>Triflic acid</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>MeOH:MeCN (2:1), 10 equiv H2O</td>
<td>Bis(trifluoromethane)</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

N.D. = Not Determined

**Table 3**

Next, the reaction conditions were optimised with catalyst **123a** in the presence of Selectfluor at room temperature (Scheme 51). As shown in Table 4, the highest enantioselectivity of **116b** was up to 77% ee, which was obtained with low yield when a 2:1 mixture of methanol and acetonitrile with trifluoroacetic acid (TFA) were used together (entry 3). Otherwise, the use of a 2:1 mixture of trifluoroethanol and acetonitrile increased the yield up to 83% but the enantioselectivity unfortunately dropped off to 35% ee (entry 6).

As mentioned above the enantiomeric excess was not determined when the product **116b** was obtained with very low conversion using other solvent ratios of methanol and acetonitrile (entries 2 and 4). Notably, solvents such as dichloromethane (CH2Cl2), tetrahydrofuran (THF), and toluene were also screened but no cyclisation product was formed.
Scheme 51

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>TFA</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>MeOH:MeCN (1:1)</td>
<td>TFA</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>MeOH:MeCN (2:1)</td>
<td>TFA</td>
<td>20</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>MeOH:MeCN (5:1)</td>
<td>TFA</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>5</td>
<td>MeOH:MeCN (1:5)</td>
<td>TFA</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>TFE:MeCN (2:1)</td>
<td>TFA</td>
<td>83</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>MeOH:MeCN (2:1), Bis(trifluoromethane)</td>
<td>TFA</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>5 equiv H$_2$O sulfonimide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.D. = Not Determined

Table 4
Next, these investigations we carried out using a catalytic amount of chiral aryl iodide \(123b\) in the enantioselective cyclisation reaction of \(115b\) in the presence of both different acids and solvents (Table 5). When the reaction was performed with bis(trifluoromethane)sulfonimide using a 2:1 mixture of methanol and acetonitrile as solvent with the addition of water (5 equiv), a slightly higher enantioselectivity up to 65 % ee and 35 % yield of the desired product \(116b\) was obtained (entry 4) compared to performing the reaction without water (entry 3). In contrast, low conversion to \(116b\) was observed by employing 10 equivalents of water with bis(trifluoromethane)sulfonimide. Lower yields of the product \(116b\) were observed when trifluoroacetic acid (TFA) and triflic acid were used in a 2:1 mixture of methanol and acetonitrile. Therefore, an ee was not obtained in these cases (entry 1, 2 and 5). The product \(116b\) was not produced by using bis(trifluoromethane)sulfonimide as acid and a mixture of 2,2,2-trifluoroethanol (TFE) and acetonitrile as solvent.

![Diagram of the reaction](image)

**Scheme 52**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH:MeCN (2:1)</td>
<td>TFA</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

59
Table 5

<table>
<thead>
<tr>
<th></th>
<th>MeOH:MeCN (2:1)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Enantiomeric Excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Triflic acid</td>
<td></td>
<td>13</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>MeOH:MeCN (2:1)</td>
<td>Bis(trifluoromethane) sulfonamide</td>
<td>32</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>MeOH:MeCN (2:1), 5 equiv H₂O</td>
<td>Bis(trifluoromethane) sulfonimide</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>MeOH:MeCN (2:1), 10 equiv H₂O</td>
<td>Bis(trifluoromethane) sulfonimide</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>6</td>
<td>TFE:MeCN (2:1)</td>
<td>Bis(trifluoromethane) sulfonimide</td>
<td>N.R.</td>
<td>-</td>
</tr>
</tbody>
</table>

N.R. = No Reaction, N.D. = Not Determined

finally tried another substrate 115f was examined with both chiral catalysts 123a and 123b with the best conditions for formation of the product 116b but unfortunately the reaction with these conditions gave the product 116f in very low yield so the enantioselectivity was not obtained.

A plausible mechanism for the cyclisation reaction is shown in Scheme 53. Utilising Selectfluor in the oxidation of chiral iodoarenes will produce the active hypervalent iodine(III) species, which then coordinates to the alkene substrate and the lone pair on the carbonyl oxygen attacks the activated alkene, resulting in six-membered ring formation 124. Methanol acts as nucleophile and attacks the ring 124 to give the carbocation 125 which then hydrolysed then followed by proton transfer and ring opening to form alcohol 126 which can re-cyclise to give the tetrahydrofuran product 116 with elimination of the iodoarene.
3.1.1. Conclusion and future work

In conclusion, three different chiral aryl iodides were synthesised and screened as catalysts (120b and 123a, b). In general the cyclisation reaction of substituted but-3-enyl benzoate 115 proceeded with low to moderate enantioselectivity by using dimethylamine derived aryl iodide (123a) but with low yield. Our future work is to find better conditions and catalysts to obtain higher selectivities and yields and apply these conditions with different substrates.
3.2. Cyclisation Reactions of Amides Containing a Pendent Alkene

Based on the cyclisation reactions of the ester mentioned in the previous chapter, it was wished to extend this concept towards the cyclisation of amides. The work was started using catalytic amounts of PhI applying similar conditions to those used for the ester to cyclise the amide analogues 128 (Scheme 54). Although, it seemed likely that an activating group would be required on the nitrogen atom to permit formation of pyrrolidine 129.

\[
\begin{align*}
\text{Ar} & \text{N} \quad \text{O} \\
R & \quad \text{Ar} \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhI}^+ \quad \text{Oxidant}^- \quad \text{Acid} \\
\text{MeCN} \quad \text{rt}^{-} \\
\end{align*}
\]

Scheme 54

Analogous to the ester mechanism, the active hypervalent iodine(III) species would be produced through the oxidation of the chiral aryl iodide using Selectfluor. This could coordinate to the alkene substrate 128 and the lone pair on the nitrogen atom could attack the activated alkene resulting in six-membered ring formation i.e. 130. Methanol could be act as nucleophile and attack the ring 130 to give the carbocation 131 which could be hydrolysed then followed by proton transfer and ring opening to form amine 132 which could re-cyclise to give the pyrrolidine product 129 with elimination of the iodoarene (Scheme 55).
This study commenced with the synthesis of substrate 130a in high yield (86%) using a literature procedure. The reaction of 1-amino-3-butene hydrochloride 132 with benzoyl chloride 133a in dry dichloromethane in the presence of base (Et₃N) formed 130a (Scheme 56).
The next plan was to perform the cyclisation reaction using these conditions: 0.2 equiv. of PhI, 2 equiv of Selectfluor, 2 equiv of TFA in MeCN at room temperature. After the reaction was performed we were surprised to find that the $^1$H spectrum was different to that expected for 129. After further investigations, it was determined that six-membered ring 134a was formed in moderate yield (Scheme 57). Obviously, the initial ring closure was successful but the subsequent ring opening and re-cyclisation did not occur.

Pleased with this result, we decided to investigate to see the effects on the yields of the cyclisation with different amides. These substrates were synthesised applying the same method as for 128a by treating the amines hydrochloride with different acid chlorides 133b-f to give products 128b-f in good yields (Scheme 58).
The addition of a catalytic amount of PhI and Selectfluor to an acetonitrile solution of different alkenyl amides 128b-e led to the direct cyclisation to afford 5,6-dihydro-4-H-1,3-oxazine derivatives (134a-e) in low to moderate yield as shown in Table 6. It is noteworthy that, complete conversion was observed from the NMR but in general the yield was low. The highest yield (40%) was obtained when the Ar was p-nitro substituted phenyl (entry 2). However, the lowest yield (14%) was observed when the aryl group was a furan ring (entry 5). Whereas, when the Ar incorporated electronically donating groups at the p-position of the phenyl ring (p-MeO) the yield was 28% (entry 1). When Ar was a p-chloro substituted phenol the yield obtained for the product 134d was only 23% (entry 4). It is worth mentioning that the acetamide analogue 128f was prepared in excellent yield, but it failed to cyclise (entry 5).


<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Table 6

Concurrent work in the Moran group had shown that 2-iodoanisole can act as a superior catalyst than iodobenzene in similar reactions. Considering our results above, we decided to use 2-iodoanisole instead of iodobenzene with the same conditions and the cyclisation reaction worked well for a variety of arylamides affording the corresponding products in high in good to high yields (Table 7). The highest yield 83% was obtained when the arylamides
bearing phenyl ring. Arylamide derivatives bearing electron-donating substituents such as methoxyl at the \textit{para}-positions of benzene ring provided the desired oxazine in 58\% yield (entry 2). While arylamides derivatives bearing electron-withdrawing substituents such as nitro and chloro group at the \textit{para}-positions of benzene ring afforded the desired oxazine in slightly higher yields, 65\% and 68\% respectively (entry 3 and 4). Additionally, heterocycle substrate, 2-furyl, also successful reacted to provide the desired oxazine in 62\% yield (entry 5).

![Scheme 60](image-url)
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="128a.png" alt="Image" /></td>
<td><img src="134a.png" alt="Image" /></td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="128b.png" alt="Image" /></td>
<td><img src="134b.png" alt="Image" /></td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td><img src="128c.png" alt="Image" /></td>
<td><img src="134c.png" alt="Image" /></td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td><img src="128d.png" alt="Image" /></td>
<td><img src="134d.png" alt="Image" /></td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td><img src="128e.png" alt="Image" /></td>
<td><img src="134e.png" alt="Image" /></td>
<td>62</td>
</tr>
</tbody>
</table>

**Table 7**

Below is the proposed mechanism for the cyclisation reaction. The iodoarene is oxidised to the iodine(III) species by the Selectfluor, which then coordinates to the alkene of the substrate. The lone pair on the carbonyl oxygen attacks the activated alkene, thus forming the six membered rings. Displacement of the iodoarene by TFA generates an unstable species which can be hydrolysed by aqueous sodium hydroxide solution to form the stable alcohols 134 (Scheme 61).
Under similar reaction conditions, the formation of five membered rings has been investigated by another member of the Moran group (Ali Alhalib) in which various N-allylamides 137 were prepared in a similar fashion to the above and these amides cyclised to oxazoline 138 in good yields. Annulations of aromatic substituents bearing electron-withdrawing groups such as o-Me and p-OMe worked well and provided the desired products 138b and 138c in slightly high yields compared to electron-donating groups such as p-NO₂ and p-Cl that afforded the products 138d and 138e in 69% yield in both cases. Similarly, the heteroaromatic 2-furyl substrate was tolerated well under these cyclisation conditions and afforded the interesting biheterocyclic product 138f in 79% yield. The success of the cyclisation reaction of di- and tri-substituted alkenes was found to be dependent on the alkene substituent. When 1,1-disubstituted alkenes were subjected to the cyclisation conditions the cyclisation reaction worked with the methyl derivative and afforded the product 138g in a
superior yield of 81% whereas the cyclisation did not work with the phenyl derivative. One diastereomer 138i was observed in 56% yield when cis-1,2-disubstituted alkene was subjected to the cyclisation conditions. However, the cyclisation reaction of tri-substituted alkene was unsuccessful (Scheme 62).

Scheme 62
With a desire to prepare more substituted products, amides 137j and 137k were prepared by a known literature procedure.\textsuperscript{70,71} \(N\)-Alkenyl phthalimides 140j and 140k were synthesised by the reaction of alkenyl halides 139 with potassium phthalimide using K\(_2\)CO\(_3\) in DMF at 140 °C. Compounds 140j and 140k were treated with ethylenediamine in ethanol at 78 °C to give the free alkenylamines which were directly converted to the amides 137j and 137k by addition of the acid chloride to provide the products in good yield (Scheme 63).

\[
\begin{align*}
\text{139j: } & \text{ } X = \text{Cl, } R_1 = \text{CH}_3 \\
& \text{ } R_2 = R_3 = \text{H} \\
\text{139k: } & \text{ } X = \text{Br, } R_1 = \text{H} \\
& \text{ } R_2 = R_3 = \text{CH}_3 \\
\end{align*}
\]

Scheme 63

Finally, by applying reaction conditions to these two amides the cyclisation worked with 137j giving the corresponding cyclised product 138j as a 1:1 mixture of diastereomers in 74% combined yield (Scheme 64).

\[
\begin{align*}
\text{137j} & \xrightarrow{2^-\text{iodoanisole (20 mol%) Selectfluor (2 equiv)}} \text{138j} \\
& \xrightarrow{TFA (2 equiv) MeCN} \text{74% yield 1:1 d.r.}
\end{align*}
\]

Scheme 64
In contrast, no cyclisation reaction occurred when trisubstituted alkene 137k was used instead fluorine containing bis-amide 141 was obtained in 33% yield. (Scheme 65).

A plausible reaction mechanism for this reaction is proposed in Scheme 66. First, fluorine cation produced from Selectfluor attacks the double bond generating intermediate (I) followed by insertion of the acetonitrile into intermediate (I) (a Ritter reaction) producing nitrilium ion (II) which undergoes hydrolysis to the corresponding amide 141 upon aqueous work-up.
Pleased with the formation of five- and six-membered rings using our catalytic conditions, the scope of the process was wished to expand to include seven- and eight-membered ring formation. Substrates 144 and 145 were prepared according to the literature procedure reported by Michael and Cochran.\textsuperscript{72} \(N\)-Alkylation of phthalimide with the corresponding alcohol under Mitsunobu conditions produced 142 and 143 in good yield. This was cleaved with ethylenediamine in ethanol at 78 °C to give free alkenylamines which were used directly in the second step to prepare 144 and 145 by addition of the benzoyl chloride to provide the products in moderate yield (Scheme 67).
Then, the cyclisation reaction of 144 and 145 was attempted using our standard conditions. The seven-membered ring 146 was successfully formed in 30% yield. However, the eight-membered ring 147 was not formed (Scheme 68).

With an effective cyclisation process in hand, it was turned the attention to the use of chiral iodoarene catalysts in order to see if high levels of enantioselectivity were possible (Scheme 69).
The work on iodoarenes 120a, 120b, 123a, 123b and 123c was focused as these chiral iodoarene afforded the best enantioselectivities in the cyclisation of the ester analogues and have been shown to be effective in several enantioselective oxidation reactions of styrene derivatives.\textsuperscript{13} The results of this study of precatalysts is summarised in Table 8.

The use of dimethylamide catalyst 123a led to formation of 134a in very good yield with moderate enantioselectivity of 64% ee (entry 1). Interestingly, the amount of catalyst could be lowered to 10 mol\% without a drop in yield. Varying the temperature of the cyclisation was also attempted in the hope of improving selectivity. Performing the reaction at 50 °C and at -10 °C afforded the product in low selectivity in the former case and about the same in the latter (entries 2 and 3). In the same way, lower selectivity was obtained when bistrifluoromethanesulfonimide was used instead of TFA (entry 4). Also, when methanol was used as a solvent instead of performing acetonitrile only the formation of methyl ether 148 was observed but in low yield and low selectivity (26%) (entry 5). However, performing the
reaction with 1:1 or 2:1 acetonitrile/methanol mixture as solvent led to separable mixtures of 134a and 148 being formed (entries 6 and 7). In this case, the enantioselectivity of ether 148 was 62% this was the same as the highest enantioselectivity recorded for 134a. After that, a few other related catalysts 120-123 were screened but unfortunately no improvement in selectivity was observed. With diisopropylamide catalyst 123b, complete conversion to ether 148 with enantiomeric excess 50% ee was observed by changing the solvent to a 1:2 mixture of MeCN and MeOH (entry 9) instead of MeCN that afforded the desired product with very low conversion therefor the enantioselectivity was not determined (entry 8). Both pr-catalysts mesityl amide 123c and ethers 120a provided the desired product in moderate yields and enantioselectivites (entries 10-11). With t-butyl ester catalyst 120b and the mixed solvent system lower selectivity was observed for both products 134a and 148 but a swap in the major enantiomer formed was noted (entry 12).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield %a</th>
<th>ee %b</th>
<th>Yield %a</th>
<th>ee %b</th>
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<tr>
<td>1</td>
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<td>MeCN</td>
<td>86</td>
<td>64</td>
<td>0</td>
<td>-</td>
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<tr>
<td>2c</td>
<td>123a</td>
<td>MeCN</td>
<td>75</td>
<td>34</td>
<td>0</td>
<td>-</td>
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<tr>
<td>3d</td>
<td>123a</td>
<td>MeCN</td>
<td>10</td>
<td>58</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4e</td>
<td>123a</td>
<td>MeCN</td>
<td>11</td>
<td>26</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>123a</td>
<td>MeOH</td>
<td>0</td>
<td>-</td>
<td>10</td>
<td>26</td>
</tr>
</tbody>
</table>
Table 8

At this point, thinking about developing some novel catalyst structures but based on the pioneering work of others was decided. Specifically, it were intrigued by the possibility of using chiral vinyl iodides as catalysts instead of aryl iodides following on from the seminal work of Wirth using achiral vinyl iodides (Figure 5).

![Figure 5](image-url)
It was envisaged that a hydrogen-bond between the N-H and the ligand oxygen would enable formation of a macrocyclic ring similar to that reported for the Ishihara-Fujita catalyst (Scheme 9) and Figure 4. The work was initiated with the preparation of chiral amide 152. The first step was the treatment of but-2-ynoic acid 149 with 47% aq. HI solution at 90 °C which resulted in the formation of (Z)-3-iodobut-2-enoic acid 150 in 71% yield. In the next step, amide 152 was prepared accordingly to the procedure reported by Moran. (Z)-3-Iodobut-2-enoic acid 150 was coupled with (S)-methyl 2-amino-3-phenylpropanoate hydrochloride using T3P which provided the corresponding amide 152 in 40% yield (Scheme 70).

In addition, the ester analogue 154 was prepared by a similar pathway in two steps. First, ester 153 was prepared according to a literature procedure via esterification of but-2-ynoic acid 149 with (L)-lactic acid ethyl ester using DMAP and DIC in 29% yield. Then the alkynyl ester 153 was stereo- and regioselectively transformed into β-iodo-alkenyl ester 154 by AcOH in the presence of NaI to provide 154 in moderate yield (58%) (Scheme 71).
Lastly, these new catalysts 152 and 154 were applied in the cyclisation reaction of N-allylbenzamide substrate 137a for the preparation of five-membered rings but, unfortunately there was no product found by $^1$H NMR analysis of the crude mixture in both cases. The starting material was recovered (Scheme 72).
3.2.1. Conclusion and future work

The catalytic oxidative cyclisation reaction of \(N\)-alkenylarylamides using iodoarenes with Selectfluor as oxidant at room temperature to generate I(III) has been demonstrated for several examples in good yields. Five- six- and seven-membered heterocycles were successfully formed however eight-membered rings were not obtained. In addition, chiral aryl iodides have been evaluated in the cyclisation reaction of \(N\)-alkenylarylamides with good yields and moderate enantioselectivities being obtained. This work has been published.\(^77\)

Future work

Pleased with the successes of the cyclisation of \(N\)-alkenylamides using conditions of 2-iodoanisole as the catalyst and Selectfluor as oxidant, the attention was turned to prepare further heterocyclic products. The substrate 155 was prepared following the literature procedure.\(^78\) Specifically, \(N\)-(but-3-en-1-yl)benzamide 128a was coupled with itself using the second generation Grubb’s catalyst providing the desired product in 44% yield. Then, the cyclisation reaction of 155 was attempted using our cyclisation conditions. The reaction worked well and the cyclised product 156 was isolated in 69% yield (Scheme 73).

![Scheme 73](image_url)

Future work will focus on the development of this tandem cyclisation process to generate products with a mixture of ring sizes and substituent.
3.3. Cyclisation Reactions of propargyl amides and β-amidoketones

After the success with alkene substrates, the extension of this methodology to the catalytic cyclisation of related propargyl amides and β-amidoketones was decided to investigate. In these cases in-situ generated iodine(III) species were expected to mediate formation of substituted 2-oxazolines bearing a ketone rather than an alcohol group (Scheme 74).

![Scheme 74](image)

Previously, the Moran group reported a catalytic procedure for the diastereoselective intramolecular cyclisation of δ-alkynyl β-ketoesters using iodobenzene under oxidative conditions (mCPBA as the oxidant in the presence of p-TsOH in MeCN at room temperature) that generated iodine(III) species in situ. These iodine(III) species mediated the cyclisation of δ-alkynyl β-ketoesters 157 to provide cyclopentanes 158 in moderate to high yields with excellent diastereoselectivity (Scheme 75).

![Scheme 75](image)
Initially, alkyne substrate 160 was synthesised in good yield (73%) by a known literature procedure via the amidation of propargyl amine using benzoyl chloride in CH$_2$Cl$_2$ in the presence of triethylamine (Scheme 76).

With N-(3-phenylprop-2-yn-1-yl)benzamide 160 in hand, its cyclisation was investigated using reaction conditions previously reported. Representative results are shown in Table 9. In agreement with our previous results with N-alkenylamides the use of 2-iodoanisole instead of iodobenzene provided the desired oxazine heterocycles 134 in high yield. For that reason we decided to use 2-iodoanisole as precatalyst and mCPBA as stoichiometric oxidant in the presence of p-TsOH in acetonitrile at room temperature, after reaction for 12 h, the cyclised product 161a was formed in 92% yield as determined by $^1$H NMR analysis of the crude reaction mixture (entry 1). Whereas, subjecting iodobenzene as precatalyst the yield for 161a decreased to 60% (entry 2). It was evidenced that, the 2-iodoanisole was the best iodoarenes for this type of the cyclisation. In contrast, the reaction did not proceed in the absence of iodoarene catalysts and the starting material 160a was completely recovered (entry 3). In the same way, a small amount of product (<5%) was detected when the Oxone was used as oxidant (entry 4). Switching the acid to TFA dropped the yield of 161a significantly to 19% (entry 5). In addition, only 37% yield for 161a was obtained by switching the solvent to less polar solvent as CH$_2$Cl$_2$ (entry 6). To study the effect of the number of equivalents of oxidant and/or acid various ratios were investigated 2 equiv mCPBA and 2 equiv TsOH.H$_2$O, 1:1 and
3:1 afforded the desired product with low yields (entries 7-9). Notably, the formation of the six-membered ring was not observed under any conditions studied.

\[ \text{Ph} \quad \text{Ph} \quad \text{N} \quad \text{H} \quad \text{O} \quad 2\text{-iodoanisole (20 mol\%)} \]
\[ m\text{-CPBA (3 equiv)} \]
\[ p\text{-TsOH.H}_2\text{O (3 equiv)} \]
\[ \text{MeCN, rt} \]
\[ "\text{standard conditions}" \]
\[ \text{ON} \quad \text{Ph} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \quad 160^a \quad 161^a \]
\[ \text{N} \quad \text{O} \quad \text{Ph} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \quad 162 \quad \text{not observed} \]

**Scheme 77**

<table>
<thead>
<tr>
<th>Entry</th>
<th>deviations from &quot;standard conditions&quot;</th>
<th>Yield %$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>92 (73)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>iodobenzene instead of 2-iodoanisole</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>no 2-iodoanisole</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Oxone instead of $m$-CPBA</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>TFA instead of TsOH.H$_2$O</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$Cl$_2$ instead of MeCN</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>2 equiv $m$CPBA and 2 equiv TsOH.H$_2$O</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>1 equiv $m$CPBA and 1 equiv TsOH.H$_2$O</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>3 equiv $m$CPBA and 1 equiv TsOH.H$_2$O</td>
<td>41</td>
</tr>
</tbody>
</table>

$a$) Yield determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

$b$) Yield of isolated compound.

**Table 9**
With the suitable reaction conditions established, the scope and generality of the cyclisation process for different propargyl amides 160 was set out to extend. Initially, various propargyl amides substrates 160a-f were synthesised in moderate to good yield following the procedure reported by Frank Rominger,\(^8\) started from the reaction of 3-arylprop-2-yn-1-amine hydrochloride 159a-f with benzoyl chloride in CH\(_2\)Cl\(_2\) in the presence of trimethylamine at room temperature. As illustrated in Scheme 78, all of the desired alkyne amides were obtained in good to excellent yields. The propargyl amide was obtained in good yield (73%) when the aryl group was a phenyl ring. In the case of aryl groups containing electron-donating groups (OMe and Me) the amide products were obtained in good yields. However, electron-withdrawing groups (NO\(_2\) and Cl) at the para position of the phenyl ring afforded the amides with good to excellent yields (84-99%). Additionally, a heterocyclic substrate containing 2-furyl a substituent provided the corresponding amide in excellent yield.

![Scheme 78](image-url)
In addition, alkyl-substituted propargylic amides substrates 160g-o were synthesised by a Sonogoshira reaction from the appropriate aryl iodide and propargylamides with a palladium catalyst PdCl$_2$(PPh$_3$)$_2$ and with CuI as co-catalyst in THF in the presence of Et$_3$N at room temperature (Scheme 79). In general these substrates were isolated in moderate yields with the exception of the 2-thienyl product 160o which was afforded in very low yield. Under these conditions, relatively high Pd loadings were required to achieve moderate conversions of amide.

Scheme 79
Various phenyl amide and alkyne substituents $160\text{a-o}$ were then subjected to the optimised catalytic conditions to test the scope of the cyclisation and the results are summarised in Table 10 and Table 11. In general, the yields were moderate to good with different phenyl amide and alkyne substituents. Substituents on the phenyl amide were examined, and substrates successfully cyclised with para-methoxy and the moderately electron-withdrawing para-chloro group affording the corresponding 2-oxazoline derivatives in 50 and 75% yields respectively (entries 1 and 2). However, the substrates bearing a mesityl or $p$-nitrophenyl group did not work (entry 3 and 4). Presumably, the electron-withdrawing nitro group reduces the nucleophilicity of the amide and prevents the cyclisation from occurring. It is unclear why the mesityl group prevents cyclisation, although its large steric bulk is its most notable feature.

![Scheme 80](image-url)
Table 10

Similarly, substrates with different alkyne substituents were examined and were cyclised giving the corresponding 2-oxazoline products in varying yields depending on the position of the substitution on the alkyne as shown in Table 11. Alkyl substituents on the phenyl ring led to diminished yields (entries 1 and 2). Chlorine and methoxy were well tolerated at the para position and the corresponding 2-oxazoline derivatives were produced in 52 and 68% yield respectively (entries 3 and 4). However, when the functional groups methoxy and nitro were in the meta position, the yields were lower than their para-substituted in case of methoxy group (entries 5) whereas in the case of nitro group, the reaction did not occur (entries 6). This can be explained by the electron-withdrawing nitro group reduces the nucleophilicity of the amide and prevents the cyclisation from occurring.
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[structure of 160g]</td>
<td>[structure of 161g]</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>[structure of 160h]</td>
<td>[structure of 161h]</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>[structure of 160i]</td>
<td>[structure of 161i]</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>[structure of 160j]</td>
<td>[structure of 161j]</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>[structure of 160k]</td>
<td>[structure of 161k]</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>[structure of 160l]</td>
<td>no reaction</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 11**

With a desire to expand the scope of this transformation further, other aromatic rings were installed and they were all tolerated and the results are summarised in Table 12. 2-Furanyl substituted 160f worked well under these conditions and the desired 2-oxazoline products 161f was obtained in good yield (entries 1). When the naphthyl ring substrate 160m was treated with the optimised cyclisation conditions the desired 2-oxazoline products 161m was formed with a high yield of 75% (entries 2). In the same way, the reaction proceeded well
and the cyclised product 160n was obtained in 82% yield, when compound 160n with biphenyl substituent on the alkyne moiety was subjected to reaction conditions (entry 3).

However, the cyclisation failed to produce the 2-oxazoline when a thienyl group was attached to the alkyne (entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160f</td>
<td>161f</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>160m</td>
<td>161m</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>160n</td>
<td>161n</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>160o</td>
<td>No reaction</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 12**

The plausible reaction pathway for the cyclisation of propargyl amides is illustrated in Scheme 81. The initial step is the active hypervalent iodine(III) species is generated *in-situ* from oxidation of the aryl iodide by mCPBA and TsOH. The next step is the electrophilic iodine(III) species activates the triple bond leading to intramolecular attack by the oxygen of the amide moiety resulting in a 5-*exo-dig* cyclisation. Subsequent addition of water lead to
loss of the iodoarene form alkenyl(aryl)iodine intermediate 165 generates enol 166.

Tautomerisation of the resulting enol can provide the oxazoline product 161.

With these results in hand, β-amidoketones 172 were selected to test our iodoarene-catalysed cyclisation strategy as the products would provide an alternative approach to 2-oxazoline formation. These are readily prepared by alkylation of the corresponding β-ketoester followed by decarboxylation (Scheme 82).
Firstly, following a literature procedure reported by Wang,\textsuperscript{82} compounds 169 were prepared in good to high yields by the alkylation of the corresponding β-ketoester using \( N \)-\( (\text{hydroxylmethyl}) \)benzamide in the presence of boron trifluoride etherate (Scheme 83). All the desired products were obtained in moderate to excellent yields. With a phenyl ring in both the amide moiety and in the β-ketoester the respective product 169a was isolated in 96% yield. Similarly, an excellent yield of 94% was obtained when the phenyl ring at the α-position of the amide group was substituted with a \( \text{para} \)-methoxy group whereas a \( \text{para} \)-nitro group led to low yield of product. The corresponding α-benzamido β-keto esters 169i and 169j were obtained in 81 and 92% yield respectively when the β-ketoester phenyl ring was substituted with the moderately electron-withdrawing \( \text{para} \)-chloro and \( \text{para} \)-methoxy groups. 2-Furyl substituted β-keto ester 169p was also prepared in 46% yield. Other α-benzamido aliphatic β-ketoesters 169q-s were also prepared in yields ranging from 48 to 82%.
A plausible mechanism for the reaction is described in Scheme 84. First the Lewis acid BF$_3$ activates the hydroxyl group making it a good leaving group which results in the formation of iminium cation intermediate 170. Nucleophilic attack of enolate 171 results in the formation of $\alpha$-benzamido $\beta$-keto esters 169.
Scheme 84

The next step in the syntheses of β-amidoketones 172 was the decarboxylation of substrates 169 via a known procedure developed by Kaku, by treatment of compounds 169a-s with DMSO, LiCl and water under reflux for 24 h (Scheme 85). Both alkyl- and aryl β-amidoketones were prepared in moderate to good yields. The β-amidoketone 172a was obtained in 50% yield, and 172b was obtained in 41% when the phenyl ring on the amide group was substituted with a para-methoxy group while the presence of a para-nitro group led to a superior 73% yield. Modification of the aryl ring next to the ketone with para-chloro, para-methoxy and 2-furyl groups, led to the corresponding β-amidoketones 172i, 172j and 172p being prepared in 29%, 85% and 54% yields respectively. In addition, switching the aryl rings next to the ketone with alkyl groups afforded the corresponding β-amidoketones 172q-s in yields ranging from 31 to 65%.
A plausible mechanism for the Krapcho decarboxylation reaction is shown in Scheme 86. The reaction follows an S_N2 mechanism. Chloride ion attacks the alkyl carbon resulting in the elimination of an alkyl halide which provides an anionic intermediate which undergoes decarboxylation to provide enolate intermediate which is protonated to the final product.
The cyclisation of β-amidoketones 172 was successful under the same conditions as propargyl amides 160 (Scheme 87). In accordance with the results for the propargyl amides, iodobenzene was an inferior pre-catalyst to 2-idoanisole and subjecting other oxidants, acids and solvents led to lower yields of 161.

The scope of the β-amidoketone substrates and the functional group compatibility was investigated under our optimal cyclisation conditions (Table 13). A variety of β-amidoketones having electron-donating and electron-withdrawing groups on the amide aryl ring were tested. The cyclisation of $N$-(3-oxo-3-phenylpropyl)benzamide 172a afforded 2-oxazoline in good yield (77%) (entry 1). Similarly, substrate 172b having a $p$-methoxy
substituent afforded the product 161b in 77\% yield (entry 2). However, the expected oxazoline was not observed when substrate 172d with a p-nitro group was subjected to the reaction conditions (entry 3). Presumably, the nitro group lowered the nucleophilicity of the amide. Next, substrates with electron-donating and electron-withdrawing substituents in the para-position of the ketone aryl ring were successfully tolerated in this cyclisation. In the case of the p-Cl substituent, the corresponding 2-oxazoline 172i was isolated in high yield (84\%) compared to the p-OMe substituent 172j which gave the corresponding 2-oxazoline 161j in 46\% yield (entries 4 and 5). A 2-furyl group was also tolerated and the desired cyclisation product 161p was isolated in excellent yield (95\%) (entry 6). Alkyl ketone substrates were also successfully converted in to 2-oxazolines with moderate to good yields. For example, the substrates 172q and 172r with methyl and ethyl groups underwent cyclisation to give the 2-oxazolines in 63\% and 56\% yields, respectively (entries 7 and 8). Interestingly, the presence of a methyl group adjacent to the ketone led to the corresponding 2-oxazoline 161s being isolated in 75\% yield (entry 9).
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="172a" /></td>
<td><img src="image" alt="161a" /></td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="172b" /></td>
<td><img src="image" alt="161b" /></td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="172d" /></td>
<td>no desired product</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="172i" /></td>
<td><img src="image" alt="161i" /></td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="172j" /></td>
<td><img src="image" alt="161j" /></td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="172p" /></td>
<td><img src="image" alt="161p" /></td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="172q" /></td>
<td><img src="image" alt="161q" /></td>
<td>63</td>
</tr>
</tbody>
</table>
Table 13

Unexpectedly, \textit{p}-nitrophenylamide, 172d did not yield the cyclised product. Instead, alcohol 175 was isolated in 66\% yield. It is possible that, the product 161d may have formed under the reaction conditions but it was instantly hydrolysed due to the influence of the electron-withdrawing nitro group on the aromatic ring (Scheme 88).

Scheme 88

In addition, the effect of introducing substituents on the tether of the \(\beta\)-amidoketones was investigated to explore how these affected the cyclisation reaction.
Compound 172t was prepared following the procedure reported by Takasu, by conjugate addition reaction of benzamide with 1-phenylbut-2-en-1-one using a catalytic amount of Pd(PhCN)₂Cl₂. Then, the cyclisation reaction was attempted using our conditions. Cyclisation was very efficient although no diastereoselectivity was observed (Scheme 89).

![Scheme 89]

Amides 172u and 172v were prepared in moderate yields via the procedure developed by Khan and coauthors. Accordingly, acetophenone, benzaldehyde, and various nitriles were treated with acetyl chloride and FeCl₃ at room temperature (Scheme 90).

![Scheme 90]
The probable mechanism reported for this reaction is described in Scheme 91. First, aldol condensation occurred via nucleophilic attack by the enolate on the carbonyl carbon of benzaldehyde generating an intermediate 177 followed by acetylation to form an intermediate 178. Subsequent insertion of the alkyl or aryl nitrile into intermediate 178 (a Ritter reaction) would produce nitrilium ion 179 with removal of acetate and by hydrolysis and tautomerisation would provide the desired β-amido ketone 172.

Then both amides 172u and 172v were treated with our standard reaction conditions, but unfortunately with amide 172u there was no product observed, whereas with 172v a moderate yield of the desired cyclised product 161v was observed. Unfortunately, no diastereoselectivity was observed in the formation of 161v but interestingly, switching the acid from trifluoroacetic acid to p-toluenesulfonic acid improved the selectivity for 161v to 5:1, albeit with loss of yield (Scheme 92).
A plausible reaction mechanism for this cyclisation is proposed in Scheme 93. First, 2-iodoanisole is oxidised to generate the active iodine(III) species by utilising \( m \)CPBA and \( p \)-TsOH. Second, the active iodine(III) species activates the carbonyl ketone leading to the formation of iodine(III)-enolate 181. The next step is the oxygen of the amide moiety attacks the enolate intermediate 181 which results in a 5-exo-trig cyclisation providing the oxazoline product 161 with reductive elimination of the iodoarene.

**Scheme 93**

The catalytic cyclisation reaction of both propargyl amides 160 and \( \beta \)-amidoketones 172 using 2-iodoanisole are successfully achieved providing the oxazoline products 161 with
moderate to good yields however the reaction with β-amidoketones shows superior substrate scope. In addition, the cyclisation of propargyl amides 160 cannot be rendered enantioselective by the use of a chiral iodoarene whereas the enantioselective cyclisation of β-amidoketones 170 should be possible using a chiral iodoarene (Scheme 94).

\[
\begin{align*}
\text{Ar} & \quad \text{N} & \quad \text{O} \\
\text{Ar'} & & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{N} & \quad \text{O} \\
\text{Ar'} & & \\
\end{align*}
\]

Scheme 94

With an effective cyclisation reaction in hand, an enantioselective cyclisation of β-amidoketone substrate 172s was investigated as the product 161s contains a stereogenic centre. Several chiral iodoarenes were screened for their ability to mediate the enantioselective cyclisation of 161s and it seemed that the results were in stark contrast to the enantioselective cyclisation of N-alkenylamides 128 (Scheme 95).

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{H} & \quad \\
\text{Ph} & & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{H} & \quad \\
\text{Ph} & & \\
\end{align*}
\]

Scheme 95
As shown in Table 14. The best results were obtained using the esters 120a and 120b which
gave the product in high yields (82-91%) and a slight increase in enantioselectivity (entry 1
and 2). Interestingly, the use of 120b led to the formation of the product with opposite
configuration. Moreover, using 1:1 MeCN/MeOH mixture as solvent led to a decrease in
yield and enantioselectivity (entry 3). Using amide precatalysts 123a and 123b provided the
product 161s in good to high yield 67% and 94% respectively, but with poor
enantioselectivity (entry 4 and 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120a</td>
<td>MeCN</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>120b</td>
<td>MeCN</td>
<td>82</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>120b</td>
<td>MeCN:MeOH (1:1)</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>123a</td>
<td>MeCN</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>123b</td>
<td>MeCN</td>
<td>67</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 14

Considering the mechanistic similarities between the process by Moran and Rodríguez
illustrated earlier (Scheme 15) and the one under investigation, it was decided to test their
catalyst and a new C₂-symmetric chiral iodoarene 188. First, pseudoephedrine derivative 185
was prepared by converting 2-iodo-3-methylbenzoic acid 182 to 2-iodo-3-methylbenzoyl
chloride 183 and then adding a solution of (1S,2S)-pseudoephedrine hydrochloride 184. In
line with the published procedure, 185 were isolated in moderate yield as a mixture of four
rotamers (Scheme 96).37
Second, the new chiral iodoarene 188 was synthesised in a similar manner as pseudoephedrine derivative 185 but from commercially available 2-iodoisophthalic acid 186. This was converted into 2-iodoisophthaloyl dichloride 187 which was then added slowly to a solution of (1S,2S)-pseudoephedrine hydrochloride 184. Gratifyingly, the desired compound 188 was obtained as a white solid in 48% yield (Scheme 97).
Next, the cyclisation reaction of 172t was attempted using pseudoephedrine derivative 185 and new catalyst 188 under our conditions (Table 15). Employing pseudoephedrine derivative 185 provided almost racemic product with low yield when MeCN was used as a solvent (entry 1). The cyclisation of 172s did not occur when the solvent was changed to methanol (entry 2). In contrast, using our new catalyst bispseudoephedrine derivative 188 led to very poor conversion of the starting material 172s into 161s when MeCN was used as a solvent; consequently, the selectivity was not determined (entry 3). However, no cyclised product was observed when utilising other solvents such as MeOH, CH₂Cl₂ and DMSO. It was apparent that 188 exhibited very poor solubility in all of these solvents, which probably explains the lack of conversion to product (entry 4, 5 and 6).

![Chemical structure](image)

**Scheme 98**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>185</td>
<td>MeCN</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>185</td>
<td>MeOH</td>
<td>N.R.</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>188</td>
<td>MeCN</td>
<td>&lt;5</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>188</td>
<td>MeOH</td>
<td>N.R.</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>188</td>
<td>CH₂Cl₂</td>
<td>N.R.</td>
<td>-</td>
</tr>
</tbody>
</table>
Next, we applied the new catalysts 152 and 154 in our cyclisation reaction but, unfortunately the cyclisation of 172s did not occur when employing our new chiral organoiodines 152 and 154 and this was confirmed by $^1$H NMR analysis of the crude mixture in both cases. The starting material was recovered in both cases (Scheme 99).

**Scheme 99**

At this point, other types of chiral iodoarenes were decided to test in the cyclisation reaction and to see whether both the selectivity and yield could be improved.

The efficacy of bis-iodide (R)-190 as a catalyst was decided to investigate in the cyclisation of 172s. It was synthesised according to the to the literature procedure.87 (R)-(+-)-2,2'-Diamino-1,1'-binaphthyl 189 was treated with potassium iodide and sodium nitrite and then added 47% aqueous HBr to provide the catalyst (R)-190 in 47% yield (Scheme 100).
Using 20 mol% of 50 under our conditions led to formation of cyclised product 161s in high yield but with essentially no enantioselectivity (Scheme 101).

Next, the β-amidoketone 172a was decided to convert to the corresponding enol acetates in a bid to improve the enantioselective cyclisation inspired by the work reported by Basdevant and Legault. It was anticipated that treatment of β-amidoketones 172a with LDA followed by acetic anhydride would generate enol acetate 191. Unfortunately, the expected product was not observed and the β-amidoalcohol 192 was obtained in 24% yield (Scheme 102). It seemed that, after the formation of the enolate the acetic anhydride was not reacted as a
nucleophile and the enolate intermediate was reduced to provide β-amidoalcohol 191 instead of the corresponding enol acetates 190. The reductive transformation of 172a into 192 merits further investigation to improve both yield and range of example.

![Chemical structure diagram]

**Scheme 102**

### 3.3.1. Conclusion and future work

In conclusion, the catalytic cyclisation of propargyl amides and β-amidoketones using 2-iodoanisole as a catalyst to provide 2-oxazolines is reported. The catalytic enantioselective cyclisation reaction of β-amidoketones was also investigated with various chiral iodoarenes but, unfortunately the enantiomeric excess for the corresponding 2-oxazolines was very low and the highest enantioselectivity obtained was 14% ee by employing ester precatalyst 120b.

The future work will be the continuation of our investigation into developing enantioselective conditions for the cyclisation of β-amidoketone substrate 172s by preparing different chiral iodoarenes.
Experimental

General experimental

$^1$H NMR spectra were recorded at 400 MHz in CDCl$_3$ unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity ($s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $br$ = broad, $m$ = multiplet), and coupling constants (Hz). $^{13}$C NMR was recorded at 100 MHz in CDCl$_3$ unless otherwise stated with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl$_3$: 77.4 ppm). Mass spectrometry (m/z) was performed in ESI mode, with only molecular ions being reported. Infrared (IR) spectra $\nu_{\text{max}}$ are reported in cm$^{-1}$. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Melting points were determined on a Stuart SMP10. All purchased reagents were used as received without further purification. Petroleum ether refers to the fraction boiling at 40-60 °C. The solvents used were hexane ethanol and 2-propanol (all of HPLC grade purity, Fisher Scientific). HPLC analysis was performed with analytical chiral columns Chiralpak IA and Chiralpak IB with UV detector at 254 nm.

Experimental for Tetrahydrofuranylation Reactions

Synthesis of but-3-en-1-yl 4-methoxybenzoate, 115b:

![Chemical Structure]

According to literature procedure reported by Harried et al. To a solution of 4-methoxybenzoyl chloride (3.0 g, 17.5 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.2 g,
1.75 mmol) in CH₂Cl₂ (30 mL), was added 3-butanol (1.5 mL, 17.5 mmol). The mixture was cooled to 0 °C and Et₃N (2.5 mL, 17.5 mmol) was added slowly. The resulting mixture was stirred overnight at room temperature. The resulting mixture was treated with 5% solution of HCl (20 mL) and NaHCO₃ (0.5 M, 20 mL) and washed with brine (10 mL) then extracted with CH₂Cl₂ (2 × 30 mL). The organic layers were dried over anhydrous MgSO₄ and the solvent removed under vacuum to give the product as a yellow oil (3.39 g, 93% yield).

IR: 2961 (w), 1707 (m), 1605 (m), 1510 (m), 1248 (m) cm⁻¹

¹H NMR: δ 2.45 (2H, q, J = 6.4 Hz), 3.78 (3H, s), 4.28 (2H, t, J = 6.9 Hz), 5.04 (1H, dd, J = 1.4, 10 Hz), 5.11 (1H, dd, J = 1.6, 17 Hz), 5.75-5.87 (1H, m), 6.85 (2H, d, J = 8.7 Hz), 7.93 (2H, d, J = 8.7 Hz).

¹³C NMR: δ 33.4, 55.5, 63.8, 113.8 (2C), 117.4, 122.9, 131.7 (2C), 134.4, 163.5, 166.4.

HRMS: m/z calc'd for [M+H]⁺ C₁₂H₁₅NO₃⁺ 207.1016, found 207.1017.

**Synthesis of (S)-tetrahydrofuran-3-yl 4-methoxybenzoate, 116b:**

![Synthesis diagram]

To a stirred solution of **115b** (0.1 g, 0.48 mmol) and **123b** (0.03g, 0.05 mmol) in a 2:1 mixture of methanol/acetonitrile (3 mL) was added Selectfluor (0.34 g, 0.97 mmol) followed by bis(trifluoromethane)sulfonamide (0.27 g, 0.97 mmol) and water (0.04 mL, 2.42 mmol). The reaction was allowed to stir at room temperature overnight. The mixture was washed with water (2 × 5 mL) and brine then extracted with EtOAc (2 × 10 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed under vacuum. The residue
was purified by flash chromatography on silica gel (eluent: petroleum ether 40-60/EtOAc 20:1 to 5:1) to give 125a as a colourless oil (0.04g, 35% yield, 57% ee).

HPLC: The ee was determined on a Chiralpak IA 254 nm hexane/ethanol gradient (97:3 as eluent, 1 ml/min). Retention times were 17.9 min and 18.7 min.

IR: 2931 (w), 1707 (m), 1604 (m), 1511 (m), 1252 (s) cm$^{-1}$

$^1$H NMR: $\delta$ 2.09-2.19 (1H, m), 2.21-2.32 (1H, m), 3.86 (3H, s), 3.88-4.05 (4H, m), 5.48-5.55 (1H, m), 6.91 (2H, d, $J = 9.0$ Hz), 7.99 (2H, d, $J = 9.0$ Hz).

$^{13}$C NMR: $\delta$ 33.3, 55.8, 67.5, 73.6, 75.4, 113.9 (2C), 122.7, 132.0 (2C), 163.5, 166.1.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{12}$H$_{15}$O$_4$+ 223.0965, found 223.0965.

**Procedure for preparation of chiral iodoarenes:**

2-Iodobenzene-1,3-diol, 118$^{68}$

According to literature procedure reported by Tsujiyama and coauthors.$^{68}$ Resorcinol 117 (5.50 g, 49.9 mmol) was added to deionised water (30 mL). The solution was placed in an ice bath and iodine (19.0 g, 74.9 mmol) and NaHCO$_3$ (6.70 g, 79.9 mmol) were added in one portion. The resulting mixture was stirred at room temperature for half an hour. The precipitate was filtered and the filtrate was extracted twice with diethyl ether (2 $\times$ 50 mL), dried over MgSO$_4$, and concentrated to give 118 as a white solid (4.7 g, 40% yield), m.p 106-109 ºC (lit.$^{89}$ m.p. 107-109 ºC).

$^1$H NMR: $\delta = 5.45$ (2H, s), 6.55 (2H, d, $J = 8.0$ Hz), 7.10 (1H, t, $J = 8.0$ Hz).
$^{13}$C NMR: $\delta$ 77.5, 107.5 (2C), 130.5, 155.9 (2C).

HRMS (m/z): [M]$^+$ calcd for C$_6$H$_5$IO$_2$ $^+$ 235.9334, found, 235.9333.

$((2R,2'R)$-Diethyl 2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropanoate, 120a$^{27}$

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

A solution of 118 (0.50 g, 2.12 mmol) was dissolved in THF (20 mL) with PPh$_3$ (1.4 g, 5.3 mmol) and (-)-ethyl lactate (0.6 mL, 5.3 mmol) in an ice bath (0 °C) under N$_2$. Diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 1.04 mL, 5.3 mmol) was added slowly, and the mixture was stirred for 1h in ice bath. The mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum and purified by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/EtOAc) which afforded 120a as a colourless oil (1.27 g, 73% yield).

IR: 2984 (w), 1749 (m), 1586 (w), 1458 (m), 1248 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.20 (6H, t, $J = 7.3$ Hz), 1.65 (6H, d, $J = 6.8$ Hz), 4.13–4.23 (4H, m), 4.71 (2H, q, $J = 6.9$ Hz), 6.33 (2H, d, $J = 8.3$ Hz), 7.09 (1H, t, $J = 8.3$ Hz).

$^{13}$C NMR: $\delta$ 14.3 (2C), 18.8 (2C), 61.5 (2C), 74.4 (2C), 80.8, 107.1 (2C), 129.7, 158.4 (2C), 171.8 (2C).

HRMS: m/z calc'd for [M+H]$^+$ C$_{16}$H$_{22}$IO$_6$ $^+$ 437.0456, found 437.0454.

$((2R,2'R)$-Di-tert-butyl 2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropanoate, 120b$^{27}$

112
This compound was prepared according to the procedure for 120a using (+)-t-butyl lactate (1.5 g, 10.6 mmol) providing 120b as a colourless oil (1.29 g, 61% yield).

IR: 2984 (w), 1727 (s), 1581 (w), 1455 (s), 1235 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta 1.41 (18\text{H}, \text{s}), 1.66 (6\text{H}, \text{d, } J = 6.8 \text{ Hz}), 4.64 (2\text{H}, \text{q, } J = 7.2 \text{ Hz}), 6.35 (2\text{H}, \text{d, } J = 8.0 \text{ Hz}), 7.11 (1\text{H}, \text{t, } J = 8.0 \text{ Hz})\).

\(^13\)C NMR: \(\delta 18.8 (2\text{C}), 28.2 (6\text{C}), 74.8 (2\text{C}), 80.7, 82.3 (2\text{C}), 106.8 (2\text{C}), 129.6, 158.6 (2\text{C}), 171.2 (2\text{C})\).

HRMS: \(m/z\) calc’d for [M+H]\(^+\) C\(_{20}\)H\(_{30}\)I\(_6\)O\(_6\)\(^+\) 493.1009, found 493.1042.

\(((2R,2'R)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy))dipropanoic acid, (121)\)\(^{27}\)

To a solution of 120a (1.1 g, 2.5 mmol) in THF (7 mL) and MeOH (7 mL) was added 2 M NaOH (7 mL) and left to stir at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with HCl (1M, 20 mL) and extracted with EtOAc (\(3 \times 30 \text{ mL}\)). The organic layers were dried over anhydrous MgSO\(_4\) and the solvents were removed in vacuum to give analytically pure 121 as a white solid (3.4 g, 97% yield).

\(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta 1.58 (6\text{H}, \text{d, } J = 6.7 \text{ Hz}), 4.88 (2\text{H}, \text{q, } J = 6.8 \text{ Hz}), 6.42 (2\text{H}, \text{d, } J = 8.8 \text{ Hz}), 7.24 (1\text{H}, \text{t, } J = 8.1 \text{ Hz})\).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ 19.3 (2C), 73.7 (2C), 80.5, 106.8 (2C), 130.6, 158.7 (2C), 173.6 (2C).

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{16}$H$_{22}$IO$_6^+$ 380.9757, found 380.9755.

$$\text{(2R,2'R)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy))bis(N,N dimethylpropanamide), 123a:}$$

![Chemical Structure](image)

To a solution of 121 (0.87 g, 2.29 mmol) in CH$_2$Cl$_2$ (10 mL) and 1 drop of DMF was added oxalyl chloride (1.57 mL, 18.3 mmol) and the mixture was stirred overnight under N$_2$. The resulting mixture was concentrated under vacuum. The residue was dissolved in CH$_2$Cl$_2$ (6 mL) at 0 °C and dimethylamine hydrochloride (0.34 g, 4.17 mmol) was added. After 0.5 h, Et$_3$N (1.16 mL, 8.34 mmol) was added. After stirring overnight, the reaction mixture was poured into HCl (1 M, 20 mL) and extracted with brine and CH$_2$Cl$_2$ (25 mL). The organic layers were dried with MgSO$_4$ and the solvent was removed in vacuum to give the pure product as a white solid (0.54 g, 59% yield).

Melting point: 195-197 ºC

IR: 2939 (w), 1650 (m), 1587 (m), 1460 (m), 1345 (w) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.70 (6H, d, $J$ = 6.6 Hz), 2.92 (6H, s), 3.11(6H, s), 4.95 (2H, q, $J$ = 6.8 Hz), 6.46 (2H, d, $J$ = 8.4 Hz), 7.16 (1H, t, $J$ = 8.3 Hz).

$^{13}$C NMR: $\delta$ 18.0 (2C), 36.8 (2C), 37.2 (2C), 76.6 (2C), 78.9, 106.4 (2C), 130.7, 157.9 (2C), 170.9 (2C).

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{16}$H$_{24}$IN$_2$O$_4^+$ 435.0775, found 435.0796.
(2R,2′R)-2,2′-((2-Iodo-1,3-phenylene)bis(oxy))bis(N,N-diisopropylpropanamide), 123b:

This compound was prepared according to the procedure for 123a using diisopropyl amine (0.26 mL, 1.82 mmol) providing 123b as a yellow solid (0.38 g, 76% yield).

Melting point: 125-128 °C.

IR: 2967 (w), 1642 (m), 1622 (s), 1584(m), 1128 (m) cm⁻¹.

¹H NMR: δ 0.90 (6H, d, J = 6.4 Hz), 1.18 (6H, d, J = 6.8 Hz), 1.28 (6H, d, J = 6.8 Hz), 1.40 (6H, d, J = 6.8 Hz), 1.66 (6H, d, J = 6.8 Hz), 3.23-3.35 (2H, m), 4.46-4.59 (2H, m), 4.82 (2H, q, J = 6.8 Hz), 6.52 (2H, d, J = 8.6 Hz), 7.08-7.16 (1H, m).

¹³C NMR: δ 18.3 (2C), 20.2 (2C), 20.9 (2C), 21.0 (2C), 21.3 (2C), 46.8 (2C), 48.0 (2C), 78.3 (2C), 78.9, 106.3 (2C), 130.3, 158.0 (2C), 169.9 (2C).

HRMS: m/z calc'd for [M+H]⁺ C₂₄H₄₀IN₂O₄⁺ 547.2027, found 547.2024.

Experimental for Amide Cyclisation Reactions

Synthesis of N-(but-3-en-1-yl)benzamide, 128a:

According to literature procedure reported by Dvořák,⁶⁹ a solution of 1-amino-3-butene hydrochloride (0.5 g, 4.7 mmol) and triethylamine (1.3 mL, 9.3 mmol) in CH₂Cl₂ (10 mL) was cooled to 0 °C, then benzoyl chloride (0.6 mL, 5.11 mmol) was added dropwise and the
mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and filtered. The solvent from the filtrate was removed under vacuum, and the residue was dissolved in ether (20 mL) and again filtered and concentrated under vacuum. To the crude product NaOH (3 M, 20 mL) was added and the resulting mixture was stirred overnight at room temperature. The resulting mixture was extracted with diethyl ether twice (2 × 30 mL). The organic layers were dried over anhydrous MgSO₄ and the solvents were removed under vacuum to give 128a as a light yellow oil (0.65 g, 80% yield).

IR: 3314 (br), 3077 (w), 2978 (w), 2931 (w), 1640 (s), 1541 (s) cm⁻¹.

¹H NMR: δ 2.36 (2H, q, J = 6.2 Hz), 3.51 (2H, q, J = 6.2 Hz), 5.09 (1H, d, J = 9.5 Hz), 5.14 (1H, d, J = 16 Hz), 5.74-5.88 (1H, m), 6.34 (1H, br), 7.39 (2H, t, J = 7.2 Hz), 7.46 (1H, t, J = 7.2 Hz), 7.73 (2H, d, J = 7.2 Hz).

¹³C NMR: δ 34.0, 39.2, 117.4, 127.1 (2C), 127.2 (2C), 128.7, 131.6, 134.9, 167.9.

HRMS: m/z calc'd for [M+Na]⁺ C₁₁H₁₃NONa⁺ 198.0889, found 198.0905.

Synthesis of N-(but-3-en-1-yl)-p-methoxybenzamide, 128b:

This compound was prepared according to the procedure for 128a using p-methoxy benzoyl chloride (0.70 mL, 5.11 mmol) giving 128b as a yellow wax (0.84 g, 64% yield).

Melting point: 63-65 °C

IR: 3312 (br), 3081 (w), 2836 (w), 1629 (m), 1606 (s), 1502 (m) cm⁻¹.
$^1$H NMR: $\delta$ 2.36 (2H, q, $J = 6.6$ Hz), 3.49 (2H, q, $J = 6.4$ Hz), 3.82 (3H, s), 5.06-5.19 (2H, m), 5.75-5.88 (1H, m), 6.26 (1H, br), 6.89 (2H, d, $J = 8.8$ Hz), 7.71 (2H, d, $J = 8.8$ Hz).

$^{13}$C NMR: $\delta$ 34.1, 39.1, 55.5, 114.1 (2C), 117.3, 127.3, 129.0 (2C), 135.8, 162.4, 167.3.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{12}$H$_{16}$NO$_2^+$ 206.1176, found 206.1176.

**Synthesis of $N$-(but-3-en-1-yl)-$p$-nitrobenzamide, 128c:**

This compound was prepared according to the procedure for 128a using $p$-nitrobenzoyl chloride (0.95 g, 5.11 mmol) giving 128c as a light yellow solid (0.65 g, 64% yield).

Melting point: 94-96 °C.

IR: 3284 (br), 3112 (w), 2940 (w), 1633 (m), 1596 (w), 1509 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 2.41 (2H, q, $J = 6.8$ Hz), 3.56 (2H, q, $J = 6.3$ Hz), 5.12-5.23 (2H, m), 5.77-5.91 (1H, m), 6.26 (1H, br), 7.90 (2H, d, $J = 8.7$ Hz) 8.28 (2H, d, $J = 8.7$ Hz).

$^{13}$C NMR: $\delta$ 33.9, 39.4, 118.2, 124.2 (2C), 128.4 (2C), 135.3, 140.6, 149.9, 165.9.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{13}$N$_2$O$_3^+$ 221.0921, found 221.0920.

**Synthesis of $N$-(but-3-en-1-yl)-$p$-chlorobenzamide, 128d:**

![Chemical structure](image)
This compound was prepared according to the procedure for 128a using p-chloro benzoyl chloride (0.7 mL, 5.11 mmol) giving 128d as a white solid (0.41g, 91% yield).

Melting point: 73-74 °C.

IR: 3298 (br), 3022 (w), 2945 (w), 1636 (s), 1538 (s), 1277 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 2.37 (2H, q, $J = 7.2$ Hz), 3.51 (2H, q, $J = 6.5$ Hz), 5.12 (1H, d, $J = 10$ Hz), 5.14 (1H, d, $J = 17$ Hz), 5.74-5.89 (1H, m), 6.14 (1H, br), 7.38 (2H, d, $J = 8.2$ Hz), 7.67 (2H, d, $J = 8.2$ Hz).

$^{13}$C NMR: $\delta$ 34.1, 39.2, 117.9, 128.6 (2C), 129.2 (2C), 133.4, 135.6, 138.0, 166.8.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{13}$Cl$_3$NO$_2^+$  210.0680, found 210.0675.

**Synthesis of N-(but-3-en-1-yl)furan-2-carboxamide, 128e:**

This compound was prepared according to the procedure for 128a using p-methoxy benzoyl chloride (0.5 mL, 5.11 mmol) giving 128e as a colourless oil (0.48 g, 63% yield).

IR: 3297 (br), 2980 (w), 1639 (m), 1592 (m), 1300 (m) cm$^{-1}$.

$^1$H NMR: 2.29 (2H, q, $J = 7.1$ Hz), 3.43 (2H, q, $J = 6.4$ Hz), 5.01 (1H, d, $J = 9.6$ Hz), 5.05 (1H, d, $J = 17$ Hz), 5.66-5.79 (1H, m), 6.41 (1H, dd, $J = 1.7$, 3.4 Hz), 6.59 (1H, br), 7.03 (1H, d, $J = 6.4$ Hz), 7.36 (1H, s).

$^{13}$C NMR: $\delta$ 33.8, 38.3, 112.0, 114.0, 117.2, 135.2, 144.0, 148.1, 158.6.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_9$H$_{12}$NO$_2^+$  166.0863, found 166.0860.

**Synthesis of N-(but-3-en-1-yl)acetamide, 128f:**

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This compound was prepared according to the procedure for 128a using \( p \)-methoxy benzoyl chloride (0.4 mL, 5.12 mmol) giving 128f as a brown oil (0.57g, 97% yield).

IR: 3289 (br), 3079 (w), 2929 (w), 1633 (m), 1552 (m) cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 1.86 (3H, s), 2.08–2.24 (2H, m), 3.11-3.29 (2H, m), 4.92 (1H, d, \( J = 10 \) Hz), 4.96 (1H, d, \( J = 17 \) Hz), 5.57-5.74 (1H, m), 6.85 (1H, br).

\(^13\)C NMR: \( \delta \) 23.2, 33.7, 38.9, 117.1, 135.4, 170.9.

HRMS: \( m/z \) calc'd for \([\text{M+H}]^+\) C\(_6\)H\(_{12}\)NO\(^+\) 114.0913, found 114.0916.

**Preparation of 2-(but-3-en-2-yl)isoindoline-1,3-dione, 140j:**\(^\text{91}\)

Prepared a ccording to a literature procedure reported by Minakata and coauthors.\(^\text{70}\) To a stirred solution of potassium phthalimide (2.6 g, 14.1 mmol) and potassium carbonate (0.50 g, 3.64 mmol) in dry DMF (25 mL) at room temperature was added 3-chloro-1-butene (1.84 mL, 18.2 mmol). The flash was fitted with a reflux condenser and heated to 140 °C overnight under N\(_2\) atmosphere. The mixture was cooled to room temperature and ice cold water was poured into the mixture with rapid stirring. The resulting white precipitate was collected by filtration and rinsed with cold water giving 140j as a white solid (1.7 g, 61% yield), m.p 87-88 °C (lit. m.p. 86-87 °C).
IR: 3460 (br), 1769 (m), 1698 (s), 1469 (m), 1383 (s), 1139 (m), 715 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.57 (3H, d, $J = 7.2$ Hz), 4.92 (1H, pentet, $J = 7.0$ Hz), 5.15 (1H, d, $J = 10$ Hz), 5.22 (1H, d, $J = 17$ Hz), 6.18 (1H, ddd, $J = 17$, 10, 6.7 Hz), 7.69 (2H, dd, $J = 5.3$, 3.1 Hz), 7.81 (2H, dd, $J = 5.4$, 3.1 Hz).

$^{13}$C NMR: $\delta$ 18.6, 49.3, 116.7, 123.5 (3C), 132.4, 134.2 (2C), 137.2, 167.7 (2C).

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{12}$H$_{12}$NO$_2^+$ 202.0863, found 202.0866.

Synthesis of 2-(3-methylbut-2-en-1-yl)isoindoline-1,3-dione, 140k.$^{92}$

![Chemical structure](image)

This compound was prepared according to the procedure for 140j using 3,3-dimethylallyl bromide (2.1 mL, 1.8 mmol) giving 140k as a light brown solid (2.8 g, 93% yield), m.p 101-103 °C (lit. m.p. 100-102 °C).

IR: 3034 (br), 2902 (w), 1765 (m), 1697 (s), 1425 (m), 1382 (s), 718 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.68 (3H, s), 1.80 (3H, s), 4.24 (2H, d, $J = 7.5$ Hz), 5.25 (1H, t, $J = 7.3$ Hz), 7.64-7.70 (2H, m), 7.78-7.82 (2H, m).

$^{13}$C NMR: $\delta$ 18.3, 25.9, 36.1, 118.6, 123.4 (3C), 132.6, 134.1 (2C), 137.5, 167.7 (2C).

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{13}$H$_{14}$NO$_2^+$ 216.1019, found 216.1022.

$N$-(But-3-en-2-yl)benzamide, 137j.$^{91}$
According to literature procedure reported by Trost et al.\textsuperscript{71} To a solution of $140j$ (1.0 g, 4.9 mmol) in ethanol (16 mL) was added ethylenediamine (0.7 mL, 9.9 mmol) and the solution was heated to reflux for 4 h. The resulting mixture was cooled to room temperature and the solid was removed by filtration through a pad of celite. The solid was washed with ethanol (20 mL) and the combined washings were washed with water (10 mL) then brine (10 mL) then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layers were dried over anhydrous MgSO$_4$ and were used immediately to prepare $137j$ which was prepared according to the procedure for $128a$ using benzoyl chloride (0.64 mL, 5.47 mmol) to yield $137j$ a white solid (0.26 g, 29\% yield), m.p 87-88 °C (lit. m.p. 86-87 °C).

IR: 3296 (br), 2972 (w), 1632 (m), 1537 (s), 692 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.35 (3H, d, $J = 6.8$ Hz), 4.74-4.86 (1H, m), 5.13 (1H, d, $J = 10$ Hz), 5.23 (1H, d, $J = 17$ Hz), 5.87-5.99 (1H, m), 6.06 (1H, br), 7.43 (2H, t, $J = 7.2$ Hz), 7.49 (1H, t, $J = 7.2$ Hz), 7.78 (2H, d, $J = 7.3$ Hz).

$^{13}$C NMR: $\delta$ 20.7, 47.5, 114.8, 127.2 (2C), 128.9 (2C), 131.8, 135.0, 139.8, 167.0.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{14}$NO$^+$ 176.1070, found 176.1075.

$N$-(3-Methylbut-2-en-1-yl)benzamide, $137k$: 

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}
This compound was prepared according to the procedure for 137j using 140k (2.0 g, 9.3 mmol) and benzoyl chloride (1.19 mL, 1.02 mmol) giving 137k as a light yellow oil (0.84 g, 48% yield).

IR: 3303 (br), 1633 (s), 1533 (s), 1488 (m), 1289 (m), 1050 (m), 692 (s) cm⁻¹.

¹H NMR: δ 1.68 (6H, d, J = 11 Hz), 3.99 (2H, t, J = 6.3 Hz), 5.26 (1H, t, J = 6.7 Hz), 6.47 (1H, br), 7.36 (2H, t, J = 7.3 Hz), 7.44 (1H, t, J = 7.3 Hz), 7.76 (2H, d, J = 7.8 Hz).

¹³C NMR: δ 18.2, 25.9, 38.4, 120.4, 127.2 (2C), 128.7 (2C), 130.1, 134.9, 136.9, 167.7.

HRMS: m/z calc'd for [M+H]⁺ C₁₂H₁₆NO⁺ 190.1226, found 190.1228.

**Synthesis of 2-(pent-4-en-1-yl)isoindoline-1,3-dione, 142:**

![Structure of 142](image)

Prepared according to the literature procedure reported by Michael and Cochran.⁷² To a solution of triphenylphosphine (6.0 g, 23.2 mmol) in THF (25 mL), diethyl azodicarboxylate (DIAD) (4.6 mL, 25 mmol) was added dropwise at 0 °C under a N₂ atmosphere and stirred for 5 min. Then, 4-penten-1-ol (2.40 mL, 23.2 mmol) was added dropwise and stirred for 5 min. Lastly, phthalimide (3.4 g, 23.2 mmol) was added in one portion and the ice bath was removed. The mixture was stirred overnight. Then n-hexane was added and the reaction mixture was filtered. The filtrate was dried over MgSO₄ and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/ EtOAc) gave 142 as a colourless oil (4.09 g, 83% yield).

IR: 2939 (w), 1772 (m), 1702 (s), 1640 (m), 1437 (m), 1393 (s), 1071 (m), 716 (s) cm⁻¹.
$^1$H NMR: $\delta$ 1.74 (2H, pent, $J = 7.3$ Hz), 2.07 (2H, q, $J = 7.4$ Hz), 3.65 (2H, t, $J = 7.3$ Hz), 4.93 (1H, dd, $J = 10$, 1.5 Hz), 5.02 (1H, ddd, $J = 17$, 3.4, 1.6 Hz), 5.77 (1H, ddt, $J = 17$, 10, 6.6 Hz), 7.67 (2H, dd, $J = 5.5$, 2.9 Hz), 7.79 (2H, dd, $J = 5.5$, 2.9 Hz).

$^{13}$C NMR: $\delta$ 27.9, 31.3, 37.8, 115.6, 123.4 (3C), 132.4, 134.2 (2C), 137.6, 168.7 (2C).

HRMS: m/z calc’d for [M+H]$^+$ C$_{13}$H$_{14}$NO$_2^+$ 216.1019, found 216.1020.

**Synthesis of 2-(Hex-5-en-1-yl)isoindoline-1,3-dione, 143**

This compound was prepared according to the procedure for 142 using hex-5-en-1-ol (3.0 mL, 25 mmol) giving 143 as a colourless oil (2.05 g, 36% yield).

IR: 2936 (w), 1771 (m), 1703 (s), 1640 (w), 1466 (m), 1394 (s), 1039 (w), 717 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.37 (2H, pent, $J = 7.6$ Hz), 1.59 (2H, pent, $J = 7.6$ Hz), 1.99 (2H, q, $J = 7.4$ Hz), 3.58 (2H, t, $J = 7.4$ Hz), 4.83 (1H, d, $J = 10$ Hz), 4.90 (1H, dd, $J = 17$, 1.6 Hz), 5.67 (1H, ddt, $J = 17$, 10, 6.5 Hz), 7.61 (2H, dd, $J = 5.5$, 3.1 Hz), 7.72 (2H, dd, $J = 5.5$, 3.1 Hz).

$^{13}$C NMR: $\delta$ 26.2, 28.1, 33.4, 37.9, 114.9, 123.4 (3C), 132.3, 133.9 (2C), 138.4, 168.7 (2C).

HRMS: m/z calc’d for [M+H]$^+$ C$_{14}$H$_{16}$NO$_2^+$ 230.1176, found 230.1179.

**Synthesis of N-(pent-4-en-1-yl)benzamide, 144**

This compound was prepared according to the procedure for 142 using hex-5-en-1-ol (3.0 mL, 25 mmol) giving 143 as a colourless oil (2.05 g, 36% yield).

IR: 2936 (w), 1771 (m), 1703 (s), 1640 (w), 1466 (m), 1394 (s), 1039 (w), 717 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.37 (2H, pent, $J = 7.6$ Hz), 1.59 (2H, pent, $J = 7.6$ Hz), 1.99 (2H, q, $J = 7.4$ Hz), 3.58 (2H, t, $J = 7.4$ Hz), 4.83 (1H, d, $J = 10$ Hz), 4.90 (1H, dd, $J = 17$, 1.6 Hz), 5.67 (1H, ddt, $J = 17$, 10, 6.5 Hz), 7.61 (2H, dd, $J = 5.5$, 3.1 Hz), 7.72 (2H, dd, $J = 5.5$, 3.1 Hz).

$^{13}$C NMR: $\delta$ 26.2, 28.1, 33.4, 37.9, 114.9, 123.4 (3C), 132.3, 133.9 (2C), 138.4, 168.7 (2C).

HRMS: m/z calc’d for [M+H]$^+$ C$_{14}$H$_{16}$NO$_2^+$ 230.1176, found 230.1179.
This compound was prepared according to the procedure for 137j using 142 (1.0 g, 9.3 mmol) and benzoyl chloride (1.19 mL, 1.02 mmol) giving 144 as a yellow wax (0.21 g, 12% yield).

^1H NMR: 6 1.68 (2H, pent, J = 7.3 Hz), 2.10 (2H, q, J = 7.4 Hz), 3.41 (2H, q, J = 6.9 Hz), 4.96 (1H, d, J = 10 Hz), 5.02 (1H, dd, J = 17, 1.7 Hz), 5.73-5.85 (1H, m), 6.78 (1H, br), 7.36 (2H, t, J = 7.5 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.74 (2H, d, J = 7.4 Hz).

^13C NMR: 6 29.0, 31.6, 39.9, 115.6, 127.2 (2C), 128.8 (2C), 131.7, 135.0, 138.2, 167.9.

HRMS: m/z calc'd for [M+H]^+ C12H16NO+ 190.1226, found 190.1228.

Synthesis of N-(hex-5-en-1-yl)benzamide, 145:86

This compound was prepared according to the procedure for 137j using 143 (1 g, 4.37 mmol) and benzoyl chloride (0.56 mL, 4.80 mmol) giving 145 as yellow oil (0.45 g, 48% yield).

IR: 3298 (br), 3064 (w), 2929 (w), 1632 (s), 1539 (s) cm⁻¹.

^1H NMR: 6 1.42-1.53 (2H, m), 1.57-1.67 (2H, m), 2.09 (2H, q, J = 6.7 Hz), 3.44 (2H, q, J = 6.8 Hz), 4.95 (1H, d, J = 10 Hz), 5.01 (1H, dd, J = 17, 1.6 Hz), 5.73-5.86 (1H, m), 6.26 (1H, br), 7.41 (2H, t, J = 7.4 Hz), 7.48 (1H, t, J = 7.2 Hz), 7.75 (2H, d, J = 7.3 Hz).


HRMS: m/z calc'd for [M+H]^+ C13H18NO+ 204.1383, found 204.1391

Representative procedure for 2-idoanisole-catalysed cyclisation: Synthesis of (2-phenyl-5, 6-dihydro-4H-1, 3-oxazin-6-yl) methanol, 134a:77
To a stirred solution of 128a (0.1 g, 0.57 mmol) and 2-iodoanisole (1.5 μL, 0.11 mmol) in acetonitrile (4 mL) was added Selectfluor (0.41 g, 1.14 mmol), followed by TFA (9.1 μL, 1.14 mmol). The reaction was stirred overnight at room temperature. The mixture was washed with NaOH (2 M, 5 mL) and extracted with CH₂Cl₂ (2 × 10 mL). The organic layers were dried over anhydrous MgSO₄ and the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel (eluent: 4:1 EtOAc/petroleum ether 40-60) to give 134a as a colourless oil (0.06 g, 48% yield).

IR: 3220 (br), 2931 (w), 2860 (w), 1648 (s), 1352 (m) cm⁻¹.

1H NMR: δ 1.68-1.90 (2H, m), 3.50 (1H, br), 3.51 (1H, ddd, J = 17, 11, 5.3 Hz), 3.64 (1H, ddd, J = 17, 5.3, 2.5 Hz), 3.71 (1H, dd, J = 12, 5.7 Hz), 3.77 (1H, dd, J = 12, 4.0 Hz), 4.20-4.28 (1H, m), 7.33 (2H, t, J = 7.4 Hz), 7.39 (1H, t, J = 7.4 Hz), 7.86 (2H, d, J = 7.4 Hz),

13C NMR: δ 23.4, 42.8, 65.3, 75.8, 127.3 (2C), 128.4 (2C), 130.8, 134.0, 156.1.

HRMS: m/z calc'd for [M+H]+ C₁₁H₁₄NO₂⁺ 192.1019, found 192.1029.

Synthesis of (2-(p-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazin-6-yl)methanol, 134b:

This compound was prepared according to the procedure for 134a using 128b (0.1 g, 0.52 mmol) giving 134b as a yellow oil (0.07 g, 58% yield).
IR: 3155 (br), 2933 (w), 2858 (w), 1646 (m), 1511 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.78-1.93 (2H, m), 2.42 (1H, br), 3.55 (1H, ddd, $J = 17, 11, 5.2$ Hz), 3.67 (1H ddd, $J = 17, 5.2, 2.8$ Hz), 3.76 (1H, dd, $J = 12, 5.6$ Hz), 3.81 (3H, s), 3.86 (1H, dd, $J = 12, 3.4$ Hz), 4.29-4.35 (1H, m), 6.86 (2H, d, $J = 9.1$ Hz), 7.83 (2H, d, $J = 9.1$ Hz).

$^{13}$C NMR: $\delta$ 23.5, 42.8, 55.7, 65.7, 75.7, 113.7 (2C), 126.5, 128.9, (2C), 155.6, 161.8.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{12}$H$_{16}$NO$_3$ $^+$ 222.1125, found 222.1126.

Synthesis of (2-($p$-nitrophenyl)-5,6-dihydro-$4H$-1,3-oxazin-6-yl)methanol, 134c:

This compound was prepared according to the procedure for 134a using 128c (0.1 g, 0.45 mmol) giving 134c as a white solid (0.07 g, 65% yield).

Melting point: 148-150 °C.

IR: 3264 (br), 3107 (w), 2865 (w), 1651 (m), 1513 (m), 1337 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.86-2.01 (2H, m), 3.65 (1H, ddd, $J = 17, 11, 5.4$ Hz), 3.72-3.96 (3H, m), 4.36-4.44 (1H, m), 8.08 (2H, d, $J = 8.7$ Hz), 8.22 (2H, d, $J = 8.7$ Hz).

$^{13}$C NMR: $\delta$ 23.8, 42.9, 65.9, 75.9, 123.8 (2C), 129.6 (2C), 140.4, 149.2, 153.9.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{13}$N$_2$O$_4$ $^+$ 237.0870, found 237.0877.

Synthesis of (2-($p$-chlorophenyl)-5,6-dihydro-$4H$-1,3-oxazin-6-yl)methanol, 134d:
This compound was prepared according to the procedure for \textbf{134a} using \textbf{128d} (0.1 g, 0.48 mmol) giving \textbf{134d} as a colourless oil (0.072 g, 68% yield).

IR: 3189 (br), 2982 (w), 2859 (w), 1723 (w), 1645 (m), 1275 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.76-1.87 (2H, m), 2.70 (1H, br), 3.55 (1H, ddd, $J = 17$, 11, 5.6 Hz), 3.67 (1H, ddd, $J = 17$, 5.3, 2.5 Hz), 3.75 (1H, dd, $J = 12$, 5.7 Hz), 3.84 (1H, dd, $J = 12$, 3.7 Hz), 4.26-4.36 (1H, m), 7.31 (2H, d, $J = 8.5$ Hz), 7.81 (2H, d, $J = 8.5$ Hz).

$^{13}$C NMR: $\delta$ 23.3, 42.8, 65.2, 75.9, 128.6 (2C), 128.7 (2C), 132.4, 136.9, 155.8.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{13}$N$_3$ClO$_2$ $^+$ 226.0629, found 226.0639.

\textbf{4.2.11 Synthesis of (2-(furan-2-yl)-5,6-dihydro-4H-1,3-oxazin-6-yl)methanol, 134e:}$^{77}$

This compound was prepared according to the procedure for \textbf{134a} using \textbf{128e} (0.1 g, 0.61 mmol) giving \textbf{134e} as a colourless oil (0.07 g, 62% yield).

IR: 3078 (br), 2994 (w), 1664 (m), 1570 (m), 1481 (m), 1288 (m) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.74-2.00 (1H, m), 3.22 (1H, br), 3.54 (1H, ddd, $J = 17$, 11, 5.3 Hz), 3.65 (1H, ddd, $J = 17$, 5.3, 2.7 Hz), 3.75 (1H, d, $J = 4.9$ Hz), 3.85 (1H, s), 4.19 (1H, br), 4.24-4.34 (1H, m), 6.41 (1H, s), 6.80 (1H, s), 7.45 (1H, s).

$^{13}$C NMR: $\delta$ 23.7, 42.5, 65.4, 75.8, 111.5, 112.0, 144.6, 147.4, 149.4.
Synthesis of (4-methyl-2-phenyl-4,5-dihydrooxazol-5-yl)methanol, 134j:

This compound was prepared according to the procedure for 134a using 137j (0.1 g 0.57 mmol). The residue was purified by flash chromatography on silica gel (eluent: 2:1 EtOAc/petroleum ether 40-60) to give 134j as a yellow oil (0.08 g 74% yield).

IR: 3231 (br), 2926 (w), 2361 (w), 1643 (m), 693 (s) cm$^{-1}$.

$^1$H NMR (major isomer): $\delta$ 1.38 (3H, d, $J = 6.7$ Hz), 3.73 (1H, dd, $J = 12, 6.0$ Hz), 3.81-3.91 (1H, m), 4.08 (1H, pentet, $J = 7.0$ Hz), 4.28-4.34 (1H, m), 7.39 (2H, t, $J = 7.4$ Hz), 7.48 (1H, t, $J = 7.4$ Hz), 7.94 (2H, d, $J = 7.7$ Hz).

$^{13}$C NMR (major isomer): $\delta$ 21.6, 62.8, 63.8, 87.3, 127.8, 128.5 (2C), 128.6 (2C), 131.8, 163.3.

$^1$H NMR (minor isomer): $\delta$ 1.31 (3H, d, $J = 7.1$ Hz), 3.73-3.91 (2H, m), 4.39-4.49 (1H, m), 4.73-4.81 (1H, m), 7.39 (2H t, $J = 7.4$ Hz), 7.48 (1H t, $J = 7.4$ Hz), 7.94 (2H, d, $J = 7.7$ Hz).

$^{13}$C NMR (minor isomer): $\delta$ 15.6, 61.3, 63.7, 82.9, 127.8, 128.5 (2C), 128.6 (2C), 131.8, 163.2.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{11}$H$_{14}$NO$_2^+$ 192.1019, found 192.1026.
\textbf{N-}(3-Acetamido-2-fluoro-3-methylbutyl)benzamide, 141:

\begin{center}
\includegraphics[width=0.2\textwidth]{chemical_formula}
\end{center}

This compound was prepared according to the procedure for 134a using 137k (0.1 g 0.53 mmol). The residue was purified by flash chromatography on silica gel (eluent: 10:1 EtOAc/petroleum ether 40-60) to give 141 as a yellow wax (0.05 g 33% yield).

IR: 3297 (br), 1643 (s), 1552 (s), 1471 (m), 1287 (m), 1024 (m), 695 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.42 (2×3H, s), 1.94 (3H, s), 3.40-3.54 (1H, m), 3.96 (1H, dddd, J = 33, 14, 6.9, 2.8 Hz), 4.99 (1H, ddd, J = 49, 8.6, 2.8 Hz), 5.72 (1H, s), 6.70 (1H, t, J = 7.4 Hz), 7.50 (1H, t, J = 7.4 Hz), 7.78 (2H, d, J = 7.8 Hz).

$^{13}$C NMR: $\delta$ 23.1 (d, J = 4.0 Hz), 23.3 (d, J = 3.2 Hz), 24.7, 40.9 (d, J = 22 Hz), 55.7 (d, J = 20 Hz), 95.1 (d, J = 177 Hz), 127.3 (2C), 128.9 (2C), 132.1, 134.3, 168.1, 170.7.

$^{19}$F NMR: $\delta$ -194.13 ppm.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{14}$H$_{20}$FN$_2$O$_2$ $^+$ 267.1503, found 267.1506.

\textbf{Synthesis of (2-phenyl-4,5,6,7-tetrahydro-1,3-oxazepin-7-yl)methanol, 146:}$^{77}$

\begin{center}
\includegraphics[width=0.2\textwidth]{chemical_formula}
\end{center}

This compound was prepared according to the procedure for 134a using 144 (50 mg, 0.29 mmol) giving 146 as a yellow oil (0.024 g 30% yield).

IR: 3374 (br), 2945 (w), 2875 (w), 1598 (s), 1428 (m) cm$^{-1}$. 

129
$^1$H NMR: $\delta$ 1.52-1.95 (4H, m), 2.16 (1H, br), 3.42-3.55 (2H, m), 3.66-3.83 (2H, m), 4.35-4.44 (1H, m), 7.35-7.44 (3H, m), 7.49 (2H, d, $J = 6.7$ Hz).

$^{13}$C NMR: $\delta$ 25.4, 28.9, 51.5, 61.9, 67.6, 127.4 (2C), 128.7 (2C), 130.6, 136.9, 172.6.

HRMS: $m/z$ calc'd for [M+H]$^+$ $\text{C}_{12}\text{H}_{16}\text{NO}_2^+$ 206.1176, found 206.1180.

**Representative procedure for chiral iodoarene-catalysed cyclisation**

Amide 128a (1 equiv) was dissolved in solvent and chiral iodoarene (0.1 equiv) was added, followed by trifluoroacetic acid (2 equiv) and Selectfluor (2 equiv). The mixture was stirred overnight at room temperature, then aqueous NaOH solution (2 M) was added and the mixture extracted with CH$_2$Cl$_2$. The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/EtOAc) to furnish 134a or 148.

**(2-Phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)methanol, 134a:**

![Chemical structure](attachment:image.png)

HPLC: chiralpak IA 254 nm hexane/EtOH gradient (100:0 to 80:20 over 25 min), 1 mL/min.
6-(Methoxymethyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazine, 148.\textsuperscript{77}

![Chemical structure image]

Up to 0.12 g, 99%. Colourless oil.

IR: 2927 (br), 2860 (w), 1651 (s), 1346 (w), 1274 (m) cm\(^{-1}\).
$^1$H NMR: δ 1.74-1.86 (1H, m), 1.90-2.04 (1H, m), 3.46 (3H, s), 3.53-3.77 (4H, m), 4.37-4.46 (1H, m), 7.32-7.44 (3H, m), 7.91 (1H, d, $J$ = 7.5 Hz).

$^{13}$C NMR: δ 24.2, 42.6, 59.9, 74.1, 75.3, 127.3 (2C), 128.3 (2C), 130.7, 134.2, 155.9.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{12}$H$_{15}$NO$_2^+$ 206.1176, found 206.1185

HPLC: chiralpak IA 254 nm hexane/EtOH gradient (100:0 to 80:20 over 25 min), 1 mL/min.
(Z)-3-Iodobut-2-enoic acid, 150:\(^{97}\)

\[
\begin{align*}
\text{O} & \quad \text{OH} \quad \text{H} \\
\text{I} & \\
\end{align*}
\]

Following the literature procedure reported by Wirth and coauthors,\(^{73}\) a 47% aq. HI solution (3.65 mL, 22.8 mmol) was added dropwise to 2-butynoic acid 149 (1.5 g, 17.8 mmol). The solution was heated at 90 °C with stirring for 2 h. After cooling to r.t, a 5% aq. Na\(_2\)S\(_2\)O\(_3\) (6 mL) solution was added. The organic phase was separated, and the aqueous phase was extracted with (2 × 30 mL) Et\(_2\)O. The combined organic phases were washed with brine (20 mL) and dried over MgSO\(_4\), filtered and concentrated under reduced pressure to give 150 as a white solid (2.69 g, 71% yield), m.p 100-102 °C (lit. m.p. 111 °C).

IR: 2246 (w), 1671 (m), 1613 (s), 1428 (m), 1216 (s), 1084 (m), 861 (s) cm\(^{-1}\).

\(^1\)H NMR: δ 2.78 (3H, s), 6.37 (1H, s), 11.6 (1H, br).

\(^{13}\)C NMR: δ 37.4, 117.2, 125.5, 169.7.

HRMS: m/z calc’d for [M+H]\(^+\) C\(_4\)H\(_6\)IO\(_2\)\(^+\) 212.9407, found 212.9407.

(S,Z)-Methyl 2-(3-iodobut-2-enamido)-3-phenylpropanoate, 152

\[
\begin{align*}
\text{H} & \quad \text{NH} \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

1-Propanephosphonic acid anhydride solution (T\(_3\)P; 50% in DMF, 2.07 mL, 7.08 mmol, 3 equiv) was dissolved in CH\(_2\)Cl\(_2\) (40 mL) and cooled to 0 °C. Triethylamine (1.97 mL, 14.2
mmol, 6 equiv) and (Z)-3-iodobut-2-enoic acid 150 (0.50 g, 2.36 mmol, 1 equiv) were added. The reaction mixture was left to stir at 0 °C for 0.5 h, then (L)-methyl 2-amino-3-phenylpropanoate hydrochloride (0.51 g, 2.36 mmol, 1 equiv) was added. After stirring overnight at room temperature, the reaction was quenched with H2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organics were dried (MgSO4), filtered and concentrated under vacuum. The crude product was purified by flash chromatography (1:1 petroleum ether/EtOAc) to provide 152 as a yellow oil (0.35 g, 40% yield).

IR: 2980 (br), 2970 (m), 1745 (m), 1667 (s), 1539 (m), 1211 (s), 700 (s) cm⁻¹.

¹H NMR: δ 2.66 (3H, d, J = 1.5 Hz), 3.16 (2H, ddd, J = 19, 14, 5.6 Hz), 3.72 (3H, s), 4.96 (1H, dt, J = 7.8, 5.9 Hz), 6.20-6.24 (2H, m), 7.11 (2H, d, J = 7.3 Hz), 7.21-7.31 (3H, m).

¹³C NMR: δ 36.4, 38.1, 52.7, 53.5, 108.1, 127.5, 128.1, 128.9 (2C), 129.7 (2C), 136.1, 164.1, 172.2.

HRMS: m/z calc'd for [M+H]⁺ C₁₄H₁₇INO₃⁺ 374.0248, found 374.0244.

1-Ethoxy-1-oxopropan-2-yl but-2-ynoate, 153:

Following the literature procedure reported by Kennedy and Hall,75 a solution of 2-butynoic acid (1.0 g, 1.2 mmol, 1 equiv), L-ethyllactate (1.4 mL, 1.2 mmol, 1.1 equiv), DIC (2.2 mL, 1.4 mmol, 1.2 equiv) and DMAP (0.2 g, 0.2 mmol, 0.2 equiv) in CH₂Cl₂ (20 mL) were stirred at room temperature under N₂ for two days. The resulting mixture was diluted with water (120 mL), the layers separated and the aqueous layers subsequently extracted with CH₂Cl₂ (3 x 30 mL). The organic layers were washed with aq. NaHCO₃ (2 x 30 mL), and brine (60 mL)
then dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 petroleum ether/EtOAc) to provide 153 as a yellow oil (0.63 g, 29% yield).

IR: 2981 (br), 2241 (m), 1743 (m), 1711 (s), 1448 (w), 1250 (s), 746 (m) cm⁻¹.

¹H NMR: δ 1.23 (3H, t, J = 7.2 Hz), 1.47 (3H, d, J = 7.1 Hz), 1.96 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 5.06 (1H, q, J = 7.1 Hz).

¹³C NMR: δ 4.11, 14.3, 17.1, 61.8, 69.9, 72.1, 87.3, 153.0, 170.2.

HRMS: m/z calc’d for [M+H]+ C₉H₁₃O₄+ 185.0808, found 185.0813.

(Z)-1-Ethoxy-1-oxopropan-2-yl 3-iodobut-2-enoate, 154

Following the literature procedure reported by Piers and coauthors, a flask was charged with a mixture of 153 (0.20 g, 1.09 mmol, 1 equiv), NaI (0.26 g, 1.74 mmol, 1.6 equiv) and glacial acetic acid (0.46 mL, 7.27 mmol, 6.7 equiv) under N₂. The mixture was stirred at 115 °C for 2 h. The mixture was cooled down to room temperature, quenched with water (20 mL) and subsequently extracted with Et₂O (3 x 10 mL). The organic layers were washed with 5% solution of Na₂CO₃ (15 mL), saturated solution of Na₂S₂O₃ (5 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 petroleum ether/EtOAc) to provide 154 as a yellow oil (0.19 g, 58% yield).

IR: 3358 (br), 2968 (m), 1731 (s), 1625 (m), 1377 (w), 1189 (s), 950 (m) cm⁻¹.
$^1$H NMR: $\delta$ 1.26 (3H, t, $J = 7.2$ Hz), 1.50 (3H, d, $J = 7.1$ Hz), 2.74 (3H, s), 4.19 (2H, qd, $J = 7.0$, 2.2 Hz), 5.15 (1H, q, $J = 7.1$ Hz), 6.40 (1H, s).

$^{13}$C NMR: $\delta$ 14.5, 17.4, 37.1, 61.8, 69.0, 115.7, 125.1, 163.8, 170.9.

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_9$H$_{14}$IO$_4$ $^+$ 312.9931, found 312.9937.

(E)-N$_2$N'-((hex-3-ene-1,6-diyl)dibenzamide, 155

![Chemical structure of (E)-N$_2$N'-((hex-3-ene-1,6-diyl)dibenzamide)](image)

Second generation Grubbs catalyst, (0.024 g, 0.029 mmol, 0.05 equiv) was add to a stirring solution of 128a (0.1 g, 1.71 mmol, 1 equiv) in dry CH$_2$Cl$_2$ (5 mL). The mixture was refluxed for overnight at 42 °C under N$_2$. The resulting mixture was filtrate through ped of cilete and washed by CH$_2$Cl$_2$ (10 mL). The filtrate was dried over anhydrous MgSO$_4$ and the solvents were removed under vacuum. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to provide 155 as a light brown solid (0.082 g, 44% yield).

IR: 3324 (br), 2359 (w), 1632 (s), 1536 (s), 1488 (m), 1294 (m), 692 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 2.31 (3H, d, $J = 6.1$ Hz), 2.41 (1H, q, $J = 6.7$ Hz), 3.44-3.59 (4H, m), 5.54-5.59 (2H, m), 6.36 (1H, br), 6.44 (1H, br), 7.38-7.51 (6 H, m), 7.72-7.79 (4H, m).

$^{13}$C NMR: $\delta$ 33.2 (2C), 39.7 (2C), 127.3 (4C), 128.9 (4C), 130.1 (2C), 131.8 (2C), 134.9 (2C), 167.9 (2C).

HRMS: $m/z$ calc'd for [M+H]$^+$ C$_{20}$H$_{23}$N$_2$O$_2$ $^+$ 323.1754, found 323.1753.

2,2'-Diphenyl-5,5',6,6'-tetrahydro-4H,4'H-6,6'-bi(1,3-oxazine), 156
To a stirred solution of 155 (0.05 g, 0.16 mmol) and 2-iodoanisole (0.0041 mL, 0.062 mmol) in acetonitrile (2 mL) was added Selectfluor (0.110 g, 0.62 mmol), followed by TFA (0.025 mL, 0.62 mmol). The reaction was allowed to stir at room temperature overnight. The mixture was washed with 2 M NaOH (2 × 5 mL) and extracted with CH₂Cl₂ (2 × 10 mL). The organic layers were dried over anhydrous MgSO₄ and the solvents were removed under vacuum. The residue was purified by flash chromatography (1:3 petroleum ether/EtOAc) to give 156 as light yellow wax (0.0341 g, 69% yield).

IR: 2859 (br), 2359 (w), 1651 (s), 1445 (m), 1344 (m), 1111 (s), 699 (s) cm⁻¹.

¹H NMR: δ 1.99-2.15 (4H, m), 3.66 (2H, ddd, J = 17, 11, 5.4 Hz), 3.81 (2H, ddd, J = 17, 5.2, 2.1 Hz), 4.39-4.45 (2H, m), 7.34-7.44 (6H, m), 7.93 (2 × 2H, d, J = 8.6 Hz).

¹³C NMR: δ 23.2 (2C), 43.2 (2C), 76.1 (2C), 127.3 (4C), 128.4 (4C), 130.9 (2C), 133.9 (2C), 155.8 (2C).

HRMS: m/z calc’d for [M+H]+ C₂₀H₂₁N₂O₂⁺ 321.1598, found 321.1599.

**Representative procedure: Preparation of 4-chloro-N-(3-phenylprop-2-yn-1-yl)benzamide, 160a:**

![Chemical structure](image)
Following the literature procedure reported by Rominger and coauthors, benzoyl chloride (0.23 mL, 1.8 mmol) was added dropwise to an ice cooled solution of 3-phenyl-2-propyn-1-amine.HCl (0.30 g, 1.8 mmol) and triethylamine (0.50 mL, 3.6 mmol) in CH2Cl2 (10 mL) and the mixture was stirred overnight at room temperature. The mixture was washed with water and extracted with CH2Cl2 (3 × 10 mL). The organic layers were dried over anhydrous MgSO4 and the solvents were removed under vacuum to give 160 as a white solid (0.31 g, 73% yield), m.p 102-104 ºC (lit. m.p. 102-103 ºC).

IR: 3308 (br), 3053 (w), 1639 (s), 1529 (s), 1486 (m), 1323 (m), 757 (s) cm⁻¹.

1H NMR: δ 4.44 (2H, d, J = 5.1 Hz), 6.44 (1H, br), 7.27-7.35 (3H, m), 7.40-7.48 (4H, m), 7.52 (1H, t, J = 7.3 Hz), 7.82 (2H, d, J = 7.6 Hz)

13C NMR: δ 31.0, 84.1, 85.1, 122.8, 127.4 (2C), 128.7 (2C), 128.9 (2C), 129.0, 132.1, 132.2 (2C), 134.3, 167.4.

HRMS: m/z calc'd for [M+H]+ C16H14NO+ 236.1071, found 236.1070.

4-Methoxy-N-(3-phenylprop-2-yn-1-yl)benzamide, 160b

This compound was prepared according to the procedure for 160a using 4-methoxybenzoyl chloride (0.24 mL, 1.79 mmol) giving 160b as a white solid (0.29 g, 63% yield), m.p 156-157 ºC (lit. m.p. 155-156 ºC).

IR: 3246 (br), 1630 (m), 1606 (s), 1552 (s), 1299 (s), 1252 (m), 1025 (s), 692 (s) cm⁻¹.
$^1$H NMR: $\delta$ 3.85 (3H, s), 4.84 (2H, $d$, $J = 5.1$ Hz), 6.44 (1H, br), 6.93 (2H, $d$, $J = 8.8$ Hz), 7.29-7.34 (3H, m), 7.42-7.47 (2H, m), 7.79 (2H, $d$, $J = 8.8$ Hz)

$^{13}$C NMR: $\delta$ 30.9, 55.8, 84.0, 85.3, 114.2 (2C), 122.9, 126.5, 128.9 (2C), 129.0, 129.2 (2C), 132.1 (2C), 162.8, 166.9.

HRMS: m/z calc’d for [M+H]$^+$ C$_{17}$H$_{16}$NO$_2^+$ 266.1176, found 266.1181.

4-Chloro-$$N$$-(3-phenylprop-2-yn-1-yl)benzamide, 160c:

This compound was prepared according to the procedure for 160a using 4-chlorobenzoyl chloride (0.23 mL, 1.79 mmol) giving 160c as a white solid (0.48 g, 99% yield), m.p 157-158°C.

IR: 3257 (br), 3073 (w), 1633 (s), 1545 (s), 1487 (s), 1299 (m), 1093 (m), 751 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 4.48 (2H, $d$, $J = 5.1$ Hz), 6.37 (1H, br), 7.28-7.35 (3H, m), 7.40-7.46 (4H, m), 7.76 (2H, $d$, $J = 8.2$ Hz).

$^{13}$C NMR: $\delta$ 31.1, 84.3, 84.8, 122.7, 128.7 (2C), 128.9 (2C), 129.0, 129.3 (2C), 132.1 (2C), 132.6, 138.4, 166.4.

HRMS: m/z calc’d for [M+H]$^+$ C$_{16}$H$_{13}$ClNO$^+$ 270.0680, found 270.0680.

4-Nitro-$$N$$-(3-phenylprop-2-yn-1-yl)benzamide, 160d:$^{98}$
This compound was prepared according to the procedure for 160a using 4-nitrobenzoyl chloride (0.33 g, 1.79 mmol) giving 160d as a light yellow solid (0.42 g, 84% yield), m.p 132-134 ºC (lit. m.p. 131-132 ºC).

IR: 3288 (br), 3059 (w), 1639 (s), 1602 (w), 1537 (s), 1487 (m), 1262 (m), 626 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta\) 4.52 (2H, d, \(J = 5.1\) Hz), 6.52 (1H, br), 7.28-7.37 (3H, m), 7.41-7.46 (2H, m), 7.99 (2H, d, \(J = 8.8\) Hz), 8.30 (2H, d, \(J = 8.8\) Hz).

\(^13\)C NMR: \(\delta\) 31.3, 84.3, 84.6, 122.6, 124.2 (2C), 128.7 (3C), 128.8, 129.1, 132.1 (2C), 139.7, 150.1, 165.5.

HRMS: m/z calc’d for [M+H]\(^+\) C\(_{16}\)H\(_{13}\)N\(_2\)O\(_3\)\(^+\) 281.0921, found 281.0921.

2,4,6-Trimethyl-N-(3-phenylprop-2-yn-1-yl)benzamide, 160e:

This compound was prepared according to the procedure for 160a using 2,4,6-trimethyl benzoyl chloride (0.30 mL, 1.79 mmol) giving 160e as a white solid (0.31 g, 63% yield), m.p 113-114 ºC.

IR: 3255 (br), 1630 (s), 1537 (s), 1442 (w), 1287 (s), 845 (s), 756 (s) cm\(^{-1}\).
$^1$H NMR: δ 2.47 (3H, s), 2.31 (6H, s), 4.46 (2H, d, $J = 5.3$ Hz), 5.89 (1H, br), 6.84 (2H, s), 7.29-7.34 (3H, m), 7.39-7.43 (2H, m)

$^{13}$C NMR: δ 19.4 (2C), 21.5, 30.5, 83.9, 84.9, 128.6 (2C), 128.7 (2C), 128.8 (3C), 132.0, 134.5(2C), 134.7, 139.1, 170.7.

HRMS: m/z calc’d for [M+H]$^+$ C$_{19}$H$_{20}$NO$^+$ 278.1539, found 278.1532.

$N$-(3-phenylprop-2-yn-1-yl)furan-2-carboxamide, 160f:

This compound was prepared according to the procedure for 160a using 2-furoyl chloride (0.18 mL, 1.79 mmol) giving 160f as a brown solid (0.41 g, 98% yield), m.p 90-92 °C (lit. m.p. 92.4 °C).

IR: 3205 (br), 3059 (w), 1640 (m), 1574 (s), 1419 (m), 1487 (m), 1323 (s), 754 (s) cm$^{-1}$.

$^1$H NMR: δ 4.44 (2H, d, $J = 5.4$ Hz), 6.47 (1H, dd, $J = 3.5$, 1.7 Hz), 6.78 (1H, br), 7.15 (1H, d, $J = 3.7$ Hz), 7.28-7.33 (3H, m), 7.38-7.46 (3H, m)

$^{13}$C NMR: δ 29.9, 83.8, 84.9, 112.5, 115.0, 122.8, 128.6 (2C), 128.8, 132.0 (2C), 144.5, 147.8, 158.3.

HRMS: m/z calc’d for [M+H]$^+$ C$_{14}$H$_{12}$N$_2$O$_3$$^+$ 281.0921, found 281.0921.

General procedure for the Sonogashira-coupling of aryl iodides with propargylamides.
Prepared according to the procedure reported by Cikotiene and coauthors.\textsuperscript{81} \(N\)-(Prop-2-yn-1-yl)benzamide (0.7 g, 6.28 mmol) was added under N\(_2\) to a mixture of the corresponding aryl iodide (3.99 mmol), \(\text{PdCl}_2(\text{PPh}_3)_2\) (0.62 g, 0.88 mmol) and Et\(_3\)N (1.84 mL, 13.2 mmol) in THF (10 mL). The mixture was left to stir for 5 min at room temperature followed by addition of CuI (0.08 g, 0.44 mmol). After stirring overnight at room temperature the solvent was removed by rotary evaporation, and the crude product was purified by flash column chromatography (5:1 petroleum ether/EtOAc).

**Synthesis of \(N\)-(prop-2-yn-1-yl)benzamide, 164:\textsuperscript{100}**

According to literature procedure reported by Ouerghui and coauthors.\textsuperscript{100} Propargylamine (4.7 mL, 72.6 mmol), triethylamine (1.3 mL, 9.29 mmol) and DMAP (0.88 g, 7.26 mmol) were dissolved in CH\(_2\)Cl\(_2\) (25 mL). The mixture was cooled in an ice bath, then benzoyl chloride (8.4 mL, 72.6 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The mixture was then extracted with 0.1 M aqueous solutions of HCl (2 × 10 mL) and NaOH (2 × 10 mL), washed with water (3 × 20 mL), dried over MgSO\(_4\), filtered and the solvent removed under vacuum to give 164 as a white solid (11.1 g, 96% yield), m.p 107-109 °C (lit. m.p. 106 °C).

IR: 3288 (br), 3058 (w), 2930 (w), 1639 (s), 1537 (s), 1448 (m), 1047 (m) cm\(^{-1}\).
**N-(3-(P-Tolyl)prop-2-yn-1-yl)benzamide, 160g:**

This compound was prepared according to the procedure A using 4-iodotoluene (0.87 g, 3.99 mmol) giving 160g as a light brown solid (0.36 g, 34% yield), m.p 139-140 °C (lit. m.p. 149-150 °C).

**IR:** 3294 (br), 1627 (s), 1577 (m), 1522 (s), 1486 (m), 1282 (s), 848 (s), 689 (s) cm$^{-1}$.

$^1$H NMR: δ 2.35 (3H, s), 4.48 (2H, d, $J = 4.8$ Hz), 6.33 (1H, br), 7.12 (2H, d, $J = 8.0$ Hz), 7.33 (2H, d, $J = 8.4$ Hz), 7.45 (2H, t, $J = 7.6$ Hz), 7.52 (1H, t, $J = 7.5$ Hz), 7.81 (2H, d, $J = 8.0$ Hz).

$^{13}$C NMR: δ 21.8, 31.1, 84.2, 84.3, 119.7, 127.4 (2C), 128.9 (2C), 129.5 (2C), 132.0 (2C), 132.1, 134.3, 139.0, 167.4.

HRMS: m/z calc'd for [M+H]$^+$ C$_{17}$H$_{16}$NO$^+$ 250.1226, found 250.1226.

**N-(3-(3,5-dimethylphenyl)prop-2-yn-1-yl)benzamide, 160h:**
This compound was prepared according to the procedure A using iodo-\textit{m}-xylene (0.58 mL, 4.0 mmol) giving 160\textbf{h} as a brown oil (0.57 g, 49\% yield).

IR: 3295 (br), 2915 (w), 1639 (s), 1525(s), 1484 (m), 1286 (w), 689 (s) cm\textsuperscript{-1}.

\textsuperscript{1}H NMR: \(\delta\) 2.28 (6H, s), 4.47 (2H, \(d, J = 5.1\) Hz), 6.51 (1H, br), 7.29-7.40 (3H, m), 7.41-7.47 (2H, m), 7.51 (1H, t, \(J = 7.1\) Hz), 7.82 (2H, \(d, J = 7.6\) Hz).

\textsuperscript{13}C NMR: \(\delta\) 21.3, 30.8, 84.0, 84.5, 122.5, 127.4 (2C), 128.7 (2C), 129.7 (2C), 130.6, 132.3 (2C), 134.2, 138.0, 141.8, 167.4.

HRMS: m/z calc'd for [M+H]\textsuperscript{+} \text{C}_{18}\text{H}_{18}\text{NO}\textsuperscript{+} 264.1383, found 264.1380.

\textit{N-(3-(4-Chlorophenyl)prop-2-yn-1-yl)benzamide, 160\textbf{i}:}\textsuperscript{81}

This compound was prepared according to the procedure A using 1-chloro-4-iodobenzene (0.95 g, 3.99 mmol) giving 160\textbf{i} as a yellow solid (0.56 g, 47\% yield), m.p 175-177 °C (lit. m.p. 177-178 °C).

IR: 3271 (br), 1650 (m), 1539 (s), 1486 (s), 1305 (m), 1086 (m), 821 (s) cm\textsuperscript{-1}.  

144
$^1$H NMR: δ 4.48 (2H, d, $J = 5.2$ Hz), 6.36 (1H, br), 7.28 (2H, d, $J = 8.6$ Hz), 7.36 (2H, d, $J = 8.6$ Hz), 7.45 (2H, t, $J = 7.5$ Hz), 7.53 (1H, t, $J = 7.3$ Hz), 7.81 (2H, d, $J = 8.2$ Hz).

$^{13}$C NMR: δ 30.9, 84.9, 86.1, 121.3, 127.4 (2C), 129.0 (2C), 129.1 (2C), 132.2, 133.4 (2C), 134.2, 135.0, 167.4.

HRMS: m/z calc’d for [M+H]$^+$ C$_{16}$H$_{13}$ClNO$^+$ 270.0680, found 270.0682.

$N$-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)benzamide, 160j:

This compound was prepared according to the procedure A using 4-iodoanisole (0.94 g, 3.99 mmol) giving 160j as a yellow solid (0.42 g, 37% yield), m.p 116-117 °C (lit. m.p. 116.5 °C).

IR: 3311 (br), 1639 (m), 1601 (m), 1542 (s), 1240 (s), 1034 (s), 685 (s) cm$^{-1}$.

$^1$H NMR: δ 3.78 (3H, s), 4.45 (2H, d, $J = 4.8$ Hz), 6.66 (1H, br), 6.81 (2H, d, $J = 8.8$ Hz), 7.36 (2H, d, $J = 8.8$ Hz), 7.41 (2H, t, $J = 7.6$ Hz), 7.49 (1H, t, $J = 7.6$ Hz), 7.82 (2H, d, $J = 7.8$ Hz).

$^{13}$C NMR: δ 31.0, 55.6, 83.7, 83.8, 114.2 (2C), 114.9, 127.4 (2C), 128.9 (2C), 131.9, 133.5 (2C), 134.2, 160.0, 167.5.

HRMS: m/z calc’d for [M+H]$^+$ C$_{17}$H$_{16}$NO$_2$$^+$ 266.1176, found 266.1176.

$N$-(3-(3-Methoxyphenyl)prop-2-yn-1-yl)benzamide, 160k
This compound was prepared according to the procedure A using 3-iodoanisole (0.48 mL, 3.99 mmol) giving **160k** as a yellow wax (0.48 g, 41% yield).

IR: 3308 (br), 3062 (w), 1639 (s), 1526 (s), 1484 (m), 1286 (s), 686 (s) cm\(^{-1}\).

\(^1\)H NMR: δ 3.74 (3H, s), 4.45 (2H, d, \(J = 5.2\) Hz), 6.85 (2H, d, \(J = 8.2\) Hz), 6.94 (1H, br), 7.00 (1H, d, \(J = 7.4\) Hz), 7.18 (1H, t, \(J = 7.9\) Hz), 7.39 (2H, t, \(J = 7.6\) Hz), 7.47 (1H, t, \(J = 7.2\) Hz), 7.82 (2H, d, \(J = 7.6\) Hz).

\(^13\)C NMR: δ 30.8, 55.5, 83.6, 85.1, 115.3 (2C), 116.9, 123.8, 124.6, 127.4 (2C), 128.8 (2C), 132.0, 134.1, 159.5, 167.5.

HRMS: m/z calc'd for [M+H]\(^+\) C\(_{17}\)H\(_{16}\)NO\(_2\)\(^+\) 266.1176, found 266.1175.

\(N\)-(3-(3-Nitrophenyl)prop-2-yn-1-yl)benzamide, 160l:

This compound was prepared according to the procedure A using 1-iodo-3-nitrobenzene (0.99 g, 3.99 mmol) giving **160l** as a light brown solid (0.63 g, 36% yield), m.p 99-101 °C.

IR: 3376 (br), 3062 (w), 1642 (w), 1514 (s), 1386 (s), 1124 (m), 967 (s) cm\(^{-1}\).

\(^1\)H NMR: δ 4.49 (2H, d, \(J = 5.5\) Hz), 6.82 (1H, br), 7.39-7.54 (4H, m), 7.68 (1H, d, \(J = 7.7\) Hz), 7.84 (2H, d, \(J = 7.5\) Hz), 8.13 (1H, d, \(J = 8.9\) Hz), 8.21 (1H, s).
$^{13}$C NMR: δ 30.7, 81.3, 88.2, 123.5, 124.7, 126.9, 127.4 (2C), 129.0 (2C), 129.7, 132.2, 134.0, 137.8, 148.3, 167.6.

HRMS: m/z calc’d for [M+H]$^+$ C$_{16}$H$_{13}$N$_2$O$_3$ $^+$ 281.0921, found 281.0920.

$N$-(3-(Naphthalen-2-yl)prop-2-yn-1-yl)benzamide, 160m:

This compound was prepared according to the procedure A using 2-iodonaphthalene (0.58 mL, 4.0 mmol) giving 160m as a yellow solid (0.51 g, 41% yield), m. p. 103-105°C (lit. m.p. 105.2 °C).

IR: 3385 (br), 2967 (m), 1629 (s), 1530 (m), 1284 (w), 1130 (m), 666 (s) cm$^{-1}$.

$^1$H NMR: δ 4.65 (2H, d, $J = 5.2$ Hz), 6.56 (1H, br), 7.39-7.48 (3H, m), 7.49-7.61 (3H, m), 7.68 (1H, d, $J = 7.2$ Hz), 7.81-7.88 (4H, m), 8.32 (1H, d, $J = 8.4$ Hz).

$^{13}$C NMR: δ 31.2, 82.2, 89.9, 120.5, 125.5, 126.4, 126.8, 127.2, 127.4 (2C), 128.6, 129.0 (2C), 129.6, 131.1, 132.1, 133.5, 133.7, 134.3, 167.5.

HRMS: m/z calc’d for [M+H]$^+$ C$_{20}$H$_{16}$NO $^+$ 286.1226, found 286.1232.

$N$-(3-((1,1'-Biphenyl)-2-yl)prop-2-yn-1-yl)benzamide, 160n:
This compound was prepared according to the procedure A using 2-iodobiphenyl (0.70 mL, 4.0 mmol) giving 160n as a light brown solid (0.48 g, 24% yield), m. p. 113-115°C.

IR: 3290 (br), 1630 (s), 1525 (s), 1301 (m), 1077 (w), 690 (s) cm\(^{-1}\).

\(^1\)H NMR: δ 4.35 (2H, d, \(J = 5.0 \) Hz), 6.10 (1H, br), 7.28-7.34 (2H, m), 7.35-7.41 (4H, m), 7.44 (2H, t, \(J = 7.5 \) Hz), 7.50-7.60 (4H, m), 7.72 (2H, d, \(J = 7.8 \) Hz).

\(^{13}\)C NMR: δ 31.2, 84.0, 87.8, 121.2, 127.3 (2C), 127.4, 127.9, 128.3 (2C), 128.9 (2C), 129.1, 129.6 (2C), 129.8, 132.1, 133.2, 134.2, 140.9, 144.4, 167.3.

HRMS: m/z calc’d for [M+H]\(^+\) \(\text{C}_{22}\text{H}_{18}\text{NO}^+\) 312.1383, found 312.1392.

\(N\)-(3-(thiophen-2-yl)prop-2-yn-1-yl)benzamide, 160o:

This compound was prepared according to the procedure A using 2-iodothiophene (0.44 mL, 3.99 mmol) giving 160o as a brown solid (0.10 g, 9% yield), m. p. 107-109°C (lit. m.p. 108.9 °C).

IR: 3332 (br), 2967 (w), 1657 (s), 1601 (m), 1581 (s), 1486 (m), 1292 (s) cm\(^{-1}\).

\(^1\)H NMR: δ 4.51 (2H, d, \(J = 5.2 \) Hz), 6.36 (1H, br), 6.97 (1H, dd, \(J = 5.5, 3.8 \) Hz), 7.22 (1H, dd, \(J = 3.7, 1.1 \) Hz), 7.25 (1H, d, \(J = 4.6 \) Hz), 7.45 (2H, t, \(J = 7.4 \) Hz), 7.52 (1H, t, \(J = 7.2 \) Hz), 7.81 (2H, d, \(J = 7.5 \) Hz).

\(^{13}\)C NMR: δ 31.2, 77.1, 89.0, 122.5, 127.3, 127.4 (2C), 127.7, 129.0 (2C), 132.2, 132.8, 134.2, 167.4.
General procedure for the synthesis of starting material (β-amidoketones).

**Ethyl 2-(benzamidomethyl)-2-methyl-3-oxopentanoate, 169a:**

Following the literature procedure reported by Wang and coauthors, a mixture of N-(hydroxylmethyl)benzamide (3 g, 19.8 mmol, 1 equiv) and ethyl benzoyl acetoacetate (3.42 mL, 19.8 mmol) was cooled to 0 °C and BF₃.OEt₂ solution (5.0 mL, 39.7 mmol, 2 equiv) was added slowly with stirring. The reaction mixture was left to stir at room temperature for 2 h. The resulting mixture was added to a solution of sodium acetate (6 g) in water (15 mL) mixed well and allowed to separate. The aqueous layer was extracted twice with CH₂Cl₂ (10 mL). The organic layers were dried over anhydrous MgSO₄ and the solvents were removed under vacuum giving 169a as a yellow oil (12.2 g, 96% yield).

IR: 3339 (br), 2980 (w), 2360 (w), 1732 (m), 1530 (m), 689 (s) cm⁻¹.

¹H NMR: δ 1.17 (3H, t, J = 7.2 Hz), 3.89-3.98 (1H, m), 4.07-4.23 (3H, m), 4.89 (1H, t, J = 6.5), 6.97 (1H, br), 7.40 (2H, t, J = 7.6 Hz), 7.45-7.53 (3H, m), 7.59 (1H, t, J = 7.3 Hz), 7.74 (2H, d, J = 8.1 Hz), 8.01 (2H, d, J = 8.1 Hz).

¹³C NMR: δ 14.2, 39.3, 53.6, 61.9, 127.2 (2C), 128.8 (2C), 129.1 (3C), 129.2, 131.9, 134.1, 134.3, 135.9, 168.1, 169.3, 194.9.

HRMS: m/z calc'd for [M+H]⁺ C₁₉H₂₀NO₄⁺ 326.1387, found 326.1387.
Ethyl 2-((4-methoxybenzamido)methyl)-3-oxo-3-phenylpropanoate, 169b:

This compound was prepared according to the procedure for 169a using N-(hydroxymethyl)-4-methoxybenzamide (2.0 g, 11 mmol, 1 equiv) and ethyl benzoylacetoacetate (1.9 mL, 11 mmol, 1 equiv) giving 169b as a yellow wax (3.7 g, 94% yield).

IR: 3341 (br), 2979 (w), 2931 (w), 1731 (m), 1636 (m), 1499 (s) cm$^{-1}$.

$^1$H NMR: δ 1.15 (3H, t, $J = 7.1$ Hz), 3.80 (3H, s), 3.85-3.94 (1H, m), 4.04-4.19 (3H, m), 4.89 (1H, t, $J = 6.7$ Hz), 6.85-6.94 (3H, m), 7.48 (2H, t, $J = 7.5$ Hz), 7.58 (1H, t, $J = 7.5$ Hz), 7.71 (2H, d, $J = 8.8$ Hz), 8.09 (2H, d, $J = 7.5$ Hz).

$^{13}$C NMR: δ 14.0, 30.9, 39.3, 53.6, 55.4, 61.8, 113.8 (2C), 126.3, 128.9 (2C), 129.0 (3C), 134.1, 135.8, 162.4, 167.6, 169.2, 194.9.

HRMS: m/z calc'd for [M+H]$^+$ C$_{20}$H$_{22}$NO$_5$ $^+$ 356.1492, found 356.1498.

Ethyl 2-((4-nitrobenzamido)methyl)-3-oxo-3-phenylpropanoate, 169d:

This compound was prepared according to the procedure for 169a using N-(hydroxymethyl)-4-nitrobenzamide (1.8 g, 9.0 mmol, 1 equiv) and ethyl benzoylacetoacetate (1.6 mL, 9.0 mmol, 1 equiv) giving 169d as a white solid (1.33 g, 39% yield), m. p. 141-144 °C.
IR: 3376 (m), 3064 (w), 1725 (s), 1666 (m), 1520 (s), 1198 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.19 (3H, t, $J = 7.1$ Hz), 3.94-4.03 (1H, m), 4.10-4.25 (3H, m), 4.83 (1H, t, $J = 6.0$), 7.05 (1H, br), 7.52 (2H, t, $J = 8.1$ Hz), 7.63 (1H, t, $J = 8.1$ Hz), 7.90 (2H, d, $J = 8.6$ Hz), 8.06 (2H, d, $J = 7.8$ Hz), 8.26 (2H, d, $J = 8.6$ Hz).

$^{13}$C NMR: $\delta$ 14.2, 39.4, 53.4, 62.4, 124.2 (2C), 128.6 (2C), 129.2 (2C), 129.3 (2C), 134.6, 135.8, 139.9, 150.0, 166.1, 169.2, 194.9.

HRMS: m/z calc'd for [M+H]$^+$ C$_{19}$H$_{19}$N$_2$O$_6$+ 371.1238, found 371.1250.

**Ethyl 2-(benzamidomethyl)-3-(4-chlorophenyl)-3-oxopropanoate, 169i:**

This compound was prepared according to the procedure for 169a using $N$-(hydroxymethyl)benzamide (1.6 g, 11 mmol, 1 equiv) and ethyl 3-(4-chlorophenyl)-3-oxopropanoate (2.0 mL, 11 mmol, 1 equiv) giving 169i as a colourless oil (3.1 g, 81% yield).

IR: 3342 (br), 3067 (w), 1729 (s), 1639 (s), 1525 (m), 1091 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 1.11 (3H, t, $J = 7.1$ Hz), 3.90 (1H, ddd, $J = 14, 7.2, 6.4$ Hz), 4.02 (1H, dd, $J = 13, 6.6$ Hz), 4.09 (2H, dq, $J = 7.1, 2.5$ Hz), 4.89 (1H, t, $J = 6.7$), 7.26-7.45 (6H, m), 7.72 (2H, t, $J = 8.1$ Hz), 7.99 (2H, d, $J = 8.5$ Hz).

$^{13}$C NMR: $\delta$ 14.1, 39.3, 53.5, 62.0, 127.2 (2C), 128.7 (2C), 129.3 (2C), 130.5 (2C), 131.9, 133.9, 134.2, 140.7, 168.2, 168.9, 193.8.

HRMS: m/z calc'd for [M+H]$^+$ C$_{19}$H$_{19}$ClNO$_4$+ 360.0997, found 360.0991.
Ethyl 2-(benzamidomethyl)-3-(4-methoxyphenyl)-3-oxopropanoate, 169j:

This compound was prepared according to the procedure for 169a using ethyl-3-(4-methoxyphenyl)-3-oxopropanoate giving 169j as a yellowish wax (4.3 g, 92% yield).

IR: 3399 (br), 2979 (w), 1724 (s), 1653 (m), 1530 (m), 1181 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta 1.17 (3\text{H, t, } J = 7.2 \text{ Hz})\), 3.85 (3\text{H, s}), 3.87-3.96 (1\text{H, m}), 4.05-4.22 (3\text{H, m}), 4.81-4.88 (1\text{H, m}), 6.95 (3\text{H, d, } J = 8.8 \text{ Hz}), 7.39 (2\text{H, t, } J = 7.5 \text{ Hz}), 7.47 (1\text{H, t, } J = 7.5 \text{ Hz}), 7.74 (2\text{H, d, } J = 8.1 \text{ Hz}), 8.08 (2\text{H, d, } J = 8.8 \text{ Hz}).

\(^{13}\)C NMR: \(\delta 14.3, 39.5, 53.5, 62.0, 114.4 (2\text{C}), 127.3 (2\text{C}), 128.8 (2\text{C}), 128.9, 131.7 (2\text{C}), 131.9 (2\text{C}), 134.3, 164.6, 168.0, 169.6, 193.3.\)

HRMS: m/z calc'd for [M+H]\(^+\) \(C_{20}H_{22}NO_5^+\) 356.1492, found 356.1498.

Ethyl 2-(benzamidomethyl)-3-(furan-2-yl)-3-oxopropanoate, 169p:

This compound was prepared according to the procedure for 169a using \(N\)-(hydroxylmethyl)benzamide (1.3 g, 8.2 mmol, 1 equiv) and ethyl-3-(2-furyl)-3-oxopropanoate (1.5 g, 8.2 mmol, 1 equiv) giving 169p as a white solid (1.2 g, 46% yield), m.p. 110-112 °C.
IR: 3364 (br), 3133 (w), 2979 (w), 1723 (m), 1639 (s), 1275 cm$^{-1}$.

$^1$H NMR δ 1.12 (3H, t, $J = 7.1$ Hz), 3.98 (1H, ddd, $J = 14, 7.3, 6.4$ Hz), 4.04 (1H, ddd, $J = 14, 7.3, 6.4$ Hz), 4.19 (2H, dq, $J = 7.3, 1.4$ Hz), 4.61 (1H, t, $J = 6.4$ Hz), 6.58 (1H, dd, $J = 3.7, 1.6$ Hz), 6.86 (1H, br), 7.38-7.46 (3H, m), 7.46-7.52 (1H, m), 7.63-7.66 (1H, m), 7.70-7.76 (2H, m).

$^{13}$C NMR: δ 14.3, 38.9, 53.6, 62.2, 113.2, 120.2, 127.3 (2C), 128.9 (2C), 131.9, 134.3, 148.0, 151.9, 167.9, 168.9, 183.1.

HRMS: m/z calc'd for [M+H]$^+$ C$_{17}$H$_{18}$NO$_5^+$ 316.1179, found 316.1179.

**methyl 2-(benzamidomethyl)-3-oxobutanoate, 169q:**

![Chemical structure](image)

This compound was prepared according to the procedure for 169a using methyl acetoacetate giving 169q as a light yellow oil (3.92 g, 48% yield).

IR: 3308 (br), 1743 (s), 1708 (m), 1635 (s), 1530 (s), 1370 (m), 817 (m) cm$^{-1}$.

$^1$H NMR: δ 2.33 (3H, s), 3.84-3.95 (3H, m), 3.95-4.01 (3H, m), 6.81 (1H, br), 7.41 (2H, t, $J = 7.2$ Hz), 7.47-7.53 (1H, m), 7.72 (2H, d, $J = 7.1$ Hz).

$^{13}$C NMR: δ 30.2, 38.0, 53.0, 58.0, 127.3 (2C), 128.9 (2C), 131.9, 134.2, 167.9, 169.4, 202.8.

HRMS: m/z calc'd for [M+H]$^+$ C$_{13}$H$_{16}$NO$_4^+$ 250.1074, found 250.1079.

**Ethyl 2-(benzamidomethyl)-3-oxopentanoate, 169r:**
This compound was prepared according to the procedure for 169a using N-(hydroxymethyl)benzamide (2.0 g, 13 mmol, 1 equiv) and ethyl propionylacetate (1.9 mL, 13 mmol, 1 equiv) giving 169r as a white wax (2.2 g, 55% yield).

IR: 3363 (br), 2939 (w), 1736 (s), 1630 (m), 1524 (s), 717 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 0.98 (3H, t, $J = 7.3$ Hz), 1.17 (3H, t, $J = 7.3$ Hz), 2.46-2.67 (2H, m), 3.82 (2H, dt, $J = 6.2$, 2.0 Hz), 3.96 (1H, t, $J = 6.3$ Hz), 4.10 (2H, q, $J = 7.1$ Hz), 7.13 (1H, br), 7.31 (2H, t, $J = 7.6$ Hz), 7.40 (1H, t, $J = 7.3$ Hz), 7.68 (2H, d, $J = 8.1$ Hz).

$^{13}$C NMR: $\delta$ 7.7, 14.2, 36.3, 38.2, 57.4, 61.8, 127.2 (2C), 128.7 (2C), 131.7, 134.2, 167.8, 168.9, 205.6.

HRMS: m/z calc'd for [M+H]$^+$ C$_{15}$H$_{20}$NO$_4$ $^+$ 278.1387, found 278.1391.

Ethyl 2-(benzamidomethyl)-2-methyl-3-oxopentanoate, 169s:

This compound was prepared according to the procedure for 169a using ethyl methyl acetoacetate (1.9 mL, 13 mmol, 1 equiv) giving 169s as a light yellow oil (3.0 g, 82% yield).

IR: 3345 (br), 2985 (w), 1735 (s), 1645 (m), 1525 (m), 1242 (s) cm$^{-1}$.
$^1$H NMR: $\delta$ 1.06 (3H, $t$, $J = 7.1$ Hz), 1.28 (3H, s), 2.05 (3H, s), 3.63-3.77 (2H, m), 3.97-4.01 (2H, m), 6.99 (1H, br), 7.21 (2H, $t$, $J = 6.3$ Hz), 7.29 (1H, $t$, $J = 7.6$ Hz), 7.56 (2H, d, $J = 7.4$ Hz).

$^{13}$C NMR: $\delta$ 13.8, 17.9, 26.2, 43.3, 60.3, 61.7, 126.9 (2C), 128.4 (2C), 134.2, 167.6, 171.7, 205.7.

HRMS: m/z calc'd for [M+H]$^+$ C$_{14}$H$_{20}$NO$_4^+$ 278.1348, found 278.1392.

General procedure for the decarboxylation reaction.

$N$-(3-oxo-3-phenylpropyl)benzamide, 172a:

According to the literature procedure reported by Kaku et al., a flask was charged with 169a (0.40 g, 1.22 mmol, 1 equiv), LiCl (0.12 g, 2.82 mmol), H$_2$O (1.7 mL) and DMSO (22 mL) at room temperature. The solution was stirred overnight at 160 °C. The resulting solution was cooled to room temperature and diluted with water (20 mL). The mixture was extracted with diethyl ether (20 mL × 3). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to provide a 170a as a white solid (0.15 g, 50% yield).

Melting point: 90-92 °C.

IR: 3239 (br), 3066 (w), 1669 (m), 1553 (m), 1323 (s), 1203 (w), 684 (s) cm$^{-1}$.  

155
1H NMR: δ 3.35 (2H, t, J = 5.5 Hz), 3.89 (2H, q, J = 5.8 Hz), 6.95 (1H, br), 7.41 (2H, t, J = 7.4 Hz), 7.47 (3H, t, J = 7.5 Hz), 7.58 (1H, t, J = 7.1 Hz), 7.76 (2H, d, J = 7.5 Hz), 7.97 (2H, d, J = 7.5 Hz).

13C NMR: δ 35.2, 38.6, 127.3 (2C), 128.4 (2C), 128.9 (2C), 129.1 (2C), 131.8, 133.9, 135.2, 136.8, 167.7, 200.2.

HRMS: m/z calc'd for [M+H]+ C16H16NO+ 254.1176, found 254.1174.

4-Methoxy-N-(3-oxo-3-phenylpropyl)benzamide, 172b:

![Chemical structure](image)

This compound was prepared according to the procedure for 172a using 169b (1.8 g, 4.7 mmol, 1 equiv) giving 172b as a yellow solid (0.54 g, 41% yield).

Melting point: 110-114 °C.

IR: 3395 (br), 2932 (w), 1678 (m), 1503 (m), 1176 (s), 845 (m) cm⁻¹.

1H NMR: δ 3.34 (2H, t, J = 5.5 Hz), 3.83 (3H, s), 3.87 (2H, q, J = 5.6 Hz), 6.84-6.92 (3H, m), 7.47 (2H, t, J = 7.5 Hz), 7.58 (1H, t, J = 7.5 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.97 (2H, d, J = 8.4 Hz).

13C NMR: δ 35.1, 38.5, 55.6, 113.9 (2C), 126.9, 128.3 (2C), 128.9 (2C), 129.0 (2C), 133.7, 136.7, 162.3, 167.3, 199.9.

HRMS: m/z calc'd for [M+H]+ C17H18NO3+ 284.1281, found 284.1280.

4-Nitro-N-(3-oxo-3-phenylpropyl)benzamide, 172d:
This compound was prepared according to the procedure for 172a using 169d (0.29 g, 0.78 mmol, 1 equiv) giving 172d as a white solid (0.17 g, 41% yield).

Melting point: 135-138 °C.

IR: 3364 (br), 2929 (w), 1673 (m), 1518 (s), 1345 (s), 1213 (m), 781 (s) cm$^{-1}$.

$^1$H NMR: δ 3.37 (2H, t, $J = 5.4$ Hz), 3.92 (2H, q, $J = 5.9$ Hz), 7.10 (1H, br), 7.49 (2H, t, $J = 7.7$ Hz), 7.61 (1H, t, $J = 7.4$ Hz), 7.91 (2H, d, $J = 8.7$ Hz), 7.97 (2H, d, $J = 8.5$ Hz), 8.27 (2H, d, $J = 8.5$ Hz).

$^{13}$C NMR: δ 35.5, 38.2, 124.1 (2C), 128.4 (2C), 128.5 (2C), 129.2 (2C), 134.2, 136.7, 140.3, 149.9, 165.7, 200.2.

HRMS: m/z calc'd for [M+H]$^+$ C$_{16}$H$_{15}$N$_2$O$_4$+ 299.1026, found 299.1025.

$N$-(3-(4-Chlorophenyl)-3-oxopropyl)benzamide, 172i:

This compound was prepared according to the procedure for 172a using 169i (0.89 g, 2.46 mmol, 1 equiv) giving 172i as a white solid (0.21 g, 29% yield).

Melting point: 119-122 °C.

IR: 3237 (br), 2924 (w), 1673 (m), 1297 (m), 1104 (s), 692 (s) cm$^{-1}$. 
$^1$H NMR: δ 3.28 (2H, t, $J = 5.5$ Hz), 3.84 (2H, q, $J = 5.7$ Hz), 7.06 (1H, br), 7.33-7.48 (5H, m), 7.74 (2H, d, $J = 7.7$ Hz), 7.86 (2H, d, $J = 7.7$ Hz).

$^{13}$C NMR: δ 35.2, 38.5, 127.2 (2C), 128.8 (2C), 129.3 (2C), 129.8 (2C), 131.2, 134.6, 135.0, 140.3, 167.8, 198.7.

HRMS: m/z calc'd for [M+H]$^+$ C$_{16}$H$_{15}$ClNO$_2$+ 288.0786, found 288.0781.

$N$-(3-(4-Methoxyphenyl)-3-oxopropyl)benzamide, 172j:

This compound was prepared according to the procedure for 172a using 169j (1.0 g, 2.8 mmol, 1 equiv) giving 172j as a yellowish wax (0.67 g, 85% yield).

IR: 3363 (br), 2935 (w), 1676 (m), 1599 (m), 1171 (s), 1302 (m), 831 (s) cm$^{-1}$.

$^1$H NMR: δ 3.28 (2H, t, $J = 5.4$ Hz), 3.80-3.86 (5H, m), 6.92 (2H, d, $J = 8.8$ Hz), 7.07 (1H, br), 7.39 (2H, t, $J = 7.6$ Hz), 7.46 (1H, t, $J = 7.3$ Hz), 7.75 (2H, d, $J = 7.7$ Hz), 7.93 (2H, d, $J = 8.8$ Hz).

$^{13}$C NMR: δ 35.2, 38.0, 55.8, 114.1 (2C), 127.2 (2C), 128.7 (2C), 129.4, 130.7 (2C), 131.7, 134.7, 164.1, 167.7, 198.5.

HRMS: m/z calc'd for [M+H]$^+$ C$_{17}$H$_{18}$NO$_3$+ 284.1281, found 284.1279.

$N$-(3-(Furan-2-yl)-3-oxopropyl)benzamide, 172p:
This compound was prepared according to the procedure for 172a using 169p (0.47 g, 1.49 mmol, 1 equiv) giving 172p as a light yellow solid (0.21 g, 54% yield).

Melting point: 92-96 °C.

IR: 3362 (br), 2928 (w), 1627 (s), 1522 (s), 1281 (m), 688 (s) cm\(^{-1}\).

\[^1\text{H}\] NMR: \(\delta\) 3.19 (2H, t, \(J = 5.7\) Hz), 3.85 (2H, q, \(J = 5.8\) Hz), 6.53 (1H, dd, \(J = 3.7, 1.6\) Hz), 6.97 (1H, br), 7.22 (1H, d, \(J = 3.7\) Hz), 7.39 (2H, t, \(J = 7.6\) Hz), 7.47 (1H, t, \(J = 7.6\) Hz), 7.59 (1H, s), 7.74 (2H, d, \(J = 8.1\) Hz).

\[^{13}\text{C}\] NMR: \(\delta\) 34.9, 38.2, 112.7, 118.2, 127.3 (2C), 128.9 (2C), 131.8, 134.7, 147.2, 152.6, 167.7, 188.9.

HRMS: m/z calc'd for [M+H\(^+\)]\(^+\) C\(_{14}\)H\(_{14}\)NO\(_3\)\(^+\) 244.0929, found 244.0969.

\(N\)-(3-oxobutyl)benzamide, 172q:\(^{104}\)

\[\text{O} \quad \text{N} \quad \text{O} \]

This compound was prepared according to the procedure for 172a using 169q (0.41 g, 1.61 mmol, 1 equiv) giving 172q as a colourless oil (0.20 g, 65% yield).

IR: 3332 (br), 2926 (w), 1708 (m), 1637 (s), 1536 (s), 1294 (m), 692 (s) cm\(^{-1}\).

\[^1\text{H}\] NMR: \(\delta\) 2.17 (3H, s), 2.80 (2H, t, \(J = 5.6\) Hz), 3.67 (2H, q, \(J = 5.8\) Hz), 6.85 (1H, br), 7.41 (2H, t, \(J = 7.3\) Hz), 7.46 (1H, t, \(J = 6.9\) Hz), 7.74 (2H, d, \(J = 7.6\) Hz).

\[^{13}\text{C}\] NMR: \(\delta\) 30.5, 34.8, 43.2, 127.2 (2C), 128.8 (2C), 128.9, 134.6, 167.7, 209.1.

HRMS: m/z calc'd for [M+H\(^+\)]\(^+\) C\(_{11}\)H\(_{14}\)NO\(^\circ\) 192.1019, found 192.10120.
N-(3-Oxopentyl)benzamide, 172r:

![Chemical structure of N-(3-Oxopentyl)benzamide]

This compound was prepared according to the procedure for 172a using 169r (0.71g, 2.69 mmol, 1 equiv) giving 172r as a yellow wax (0.17 g, 31% yield).

IR: 3306 (br), 2935.8 (w), 1711 (s), 1633 (s), 1537 (s), 1115 (m) cm⁻¹.

¹H NMR: δ 1.03 (3H, t, J = 7.4 Hz), 2.42 (2H, q, J = 7.6 Hz), 2.74 (2H, t, J = 5.8 Hz), 3.66 (2H, q, J = 6.2 Hz), 6.97 (1H, br), 7.38 (2H, t, J = 7.2 Hz), 7.45 (1H, t, J = 7.2 Hz), 7.73 (2H, d, J = 7.6 Hz).

¹³C NMR: δ 7.98, 34.9, 36.5, 41.8, 127.2 (2C), 128.9 (2C), 131.8, 134.7, 167.6, 211.9.

HRMS: m/z calc'd for [M+H]^+ C_{12}H_{16}NO_2^+ 206.1176, found 206.1177.

N-(2-Methyl-3-oxobutyl)benzamide, 172s:

![Chemical structure of N-(2-Methyl-3-oxobutyl)benzamide]

This compound was prepared according to the procedure for 172a using 169s (7.21g, 26.1 mmol, 1 equiv) giving 172s as a yellow oil (2.68 g, 50% yield).

IR: 3359 (br), 2362 (w), 1707 (s), 1645 (m), 1358 (s), 1220 (s) cm⁻¹.

¹H NMR: δ 1.17 (3H, d, J = 2.5 Hz), 2.15 (3H, s), 2.86-2.96 (1H, m), 3.42-5.51 (1H, m), 3.56-3.65 (1H, m), 6.89 (1H, br), 7.37 (2H, t, J = 7.3 Hz), 7.44 (1H, t, J = 7.3 Hz), 7.72 (2H, d, J = 7.7 Hz).
Synthesis of **N-(4-oxo-4-phenylbutan-2-yl)benzamide, 172t:**

This compound was prepared according to the literature procedure reported by Taskasu, Kiyosei and coauthors. A mixture of benzamide (0.66 g, 5.47 mmol, 1 equiv), 1-phenylbut-2-en-1-one (0.80 g, 5.47 mmol, 1 equiv) and Pd(PhCN)₂Cl₂ (3.57 mL, 33.1 mmol) was heated to 60 °C for 24 h. The resulting mixture was diluted with CHCl₃ and filtered off. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (5:1 petroleum ether/EtOAc) to give **172t** as a yellow solid (0.67 g, 46% yield).

Melting point: 140-142 °C (lit. m.p. 145-146 °C).

IR: 3308 (br), 3169 (w), 1683 (m), 1634 (m), 1546 (s), 1293 (m), 802 (s) cm⁻¹.

¹H NMR: δ 1.41 (3H, d, J = 6.9 Hz), 3.20 (1H, dd, J = 17, 5.9 Hz), 3.48 (1H, dd, J = 17, 4.2 Hz), 4.64-4.76 (1H, m), 7.05 (1H, d, J = 7.2 Hz), 7.39-7.53 (5H, m), 7.59 (1H, t, J = 7.4 Hz), 7.78 (2H, d, J = 7.7 Hz), 7.99 (2H, d, J = 7.7 Hz).

¹³C NMR: δ 20.5, 43.3, 43.6, 127.2 (2C), 128.5 (2C), 128.9 (2C), 129.1 (2C), 131.8, 133.9, 135.0, 137.3, 167.0, 200.1.

HRMS: m/z calc'd for [M+H]⁺ C₁₇H₁₈NO₂⁺ 268.1332, found 268.1333

Synthesis of **N-(3-oxo-1,3-diphenylpropyl)benzamide, 172u:**
Following the literature procedure reported by Khan and coauthors,\textsuperscript{86} to a stirred solution of benzaldehyde (0.88 g, 8.32 mmol), acetyl chloride (0.89 mL, 12.5 mmol), and acetophenone (0.97 mL, 8.32 mmol) in acetonitrile (20 mL) was added FeCl$_3$ (1.35 g, 8.32 mmol). The reaction was stirred at room temperature overnight, then quenched with water (50 mL) and extracted with EtOAc (3 × 70 mL). The organic layer was dried over anhydrous MgSO$_4$ and purified by flash chromatography (2:1 petroleum ether/EtOAc) to give 172u as a white solid (0.98 g, 44%). m.p 104-106 °C (lit. m.p. 103-105 °C).

IR: 3323 (br), 2931 (w), 1660 (w), 1378 (m), 1128 (s), 950 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 2.03 (3H, s), 3.44 (1H, dd, $J = 17$, 6.2 Hz), 3.76 (1H, dd, $J = 17$, 5.1 Hz), 5.54-5.60 (1H, m), 6.71 (1H, br), 7.23 (1H, t, $J = 7.4$ Hz), 7.27-7.36 (4H, m), 7.45 (2H, t, $J = 7.9$ Hz), 7.56 (1H, t, $J = 7.6$ Hz), 7.90 (2H, d, $J = 8.0$ Hz).

$^{13}$C NMR: $\delta$ 23.9, 43.5, 50.3, 126.8 (2C), 127.8, 128.5 (2C), 129.0 (2C), 129.1 (2C), 133.9, 136.9, 141.2, 169.8, 199.0.

HRMS: m/z calc'd for [M+H]$^+$ C$_{17}$H$_{18}$NO$_2^+$ 268.1332, found 268.1335.

$N$-(3-oxo-1,3-diphenylpropyl)benzamide, 172v,\textsuperscript{105}
This compound was prepared according to the procedure for \textbf{172u} using benzonitrile giving \textbf{172v} as a white solid (0.95 g, 35% yield), m.p 153-155 ºC (lit. m.p. 153-154 ºC).

IR: 3361 (br), 3165 (w), 3064 (w), 1625 (s), 1577 (m), 1402 (m) 684 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 3.54 (1H, dd, $J = 17$, 5.4 Hz), 3.89 (1H, dd, $J = 17$, 4.9 Hz), 5.74-5.81 (1H, m), 7.23 (1H, t, $J = 7.3$ Hz), 7.32 (2H, t, $J = 7.3$ Hz), 7.38-7.53 (7H, m), 7.57 (1H, t, $J = 7.3$ Hz), 7.63 (1H, d, $J = 8.0$ Hz), 7.85 (2H, d, $J = 7.8$ Hz), 7.93 (2H, d, $J = 7.8$ Hz).

$^{13}$C NMR: $\delta$ 43.3, 50.7, 126.8 (2C), 127.4 (2C), 127.8, 128.5 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 131.9, 133.9, 134.6, 137.0, 141.3, 167.0, 199.5.

HRMS: m/z calc'd for [M+Na]$^+$ C$_{22}$H$_{19}$NO$_2$Na$^+$ 352.1308, found 352.1304.

\textbf{Representative procedure for 2-iodoanisole-catalysed cyclisation: synthesis of} 

\textit{Phenyl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161a:}

\begin{center}
\includegraphics[width=0.2\textwidth]{160.png}
\end{center}

\textbf{160} (0.10 g, 0.43 mmol, 1 equiv) was dissolved in acetonitrile (3 mL) and 2-iodoanisole (11 \textmu L, 0.09 mmol, 0.2 equiv) was added, followed by \textit{m}CBPA (0.29 g, 1.28 mmol, 3 equiv) and \textit{p}-TsOH.H$_2$O (0.24 g, 1.28 mmol, 3 equiv). The mixture was stirred overnight at room temperature, then aqueous Na$_2$SO$_4$ solution (5 mL) and saturated aqueous NaHCO$_3$ solution (5 mL) were added and the mixture extracted with CH$_2$Cl$_2$ (10 mL $\times$ 2). The organic layers were combined and dried with MgSO$_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether/EtOAc) to provide \textbf{161a} as a bright yellow solid (0.076 g, 77% yield).
Melting point: 104-108 °C.

IR: 2922 (br), 2355 (w), 1702 (m), 1650 (s), 1596 (w), 685 (s) cm$^{-1}$.

$^1$H NMR: δ 4.28 (1H, dd, $J = 15, 7.6$ Hz), 4.46 (1H, dd, $J = 15, 11$ Hz), 5.86 (1H, dd, $J = 11, 7.7$ Hz), 7.42 (2H, t, $J = 7.5$ Hz), 7.45-7.56 (3H, m), 7.63 (1H, t, $J = 7.3$ Hz) 7.99 (4H, d, $J = 7.7$ Hz).

$^{13}$C NMR: δ 58.8, 79.9, 127.3, 128.8 (3C), 129.1 (2C), 129.3 (2C), 132.0 (2C), 134.3, 134.4, 164.5, 195.2.

HRMS: m/z calc'd for [M+H]$^+$ C$_{16}$H$_{14}$NO$_2^+$ 252.0980, found 252.1026.

(2-(4-Methoxyphenyl)-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161b:

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\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}
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This compound was prepared according to the procedure for 161a using 172b (0.10g, 0.35 mmol, 1 equiv) giving 161b as a yellow solid (0.073 g, 77% yield).

Melting point: 134-137 °C.

IR: 2924 (br), 2849 (w), 1694 (m), 1604 (m), 1378 (m), 1301 (s), 688 (s) cm$^{-1}$.

$^1$H NMR: δ 3.85 (3H, s), 4.24 (1H, dd, $J = 15, 7.7$ Hz), 4.44 (1H, dd, $J = 15, 11$ Hz), 5.82 (1H, dd, $J = 11, 7.7$ Hz), 6.92 (2H, d, $J = 8.7$ Hz), 7.52 (2H, t, $J = 7.7$ Hz), 7.64 (1H, t, $J = 7.6$ Hz), 7.93 (2H, d, $J = 8.8$ Hz), 7.99 (2H, d, $J = 7.7$ Hz).

$^{13}$C NMR: δ 55.7, 58.9, 79.9, 114.1 (2C), 119.9, 129.1 (2C), 129.3 (2C), 130.5 (2C), 134.3, 134.5, 162.7, 164.3, 195.5.
HRMS: m/z calc'd for [M+H]^+ C_{17}H_{16}NO_3^+ 282.1085, found 282.1123.

(2-(4-Chlorophenyl)-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161c:

This compound was prepared according to the procedure for 161a using 160c (0.10 g, 0.37 mmol, 1 equiv) giving 161c as a white solid (0.079 g, 75% yield).

Melting point: 103-107 °C.

IR: 2927 (br), 1702 (m), 1649 (m), 1488 (m), 1089 (s), 850 (s) cm$^{-1}$.

$^1$H NMR: δ 4.26 (1H, dd, $J$ = 15, 7.5 Hz), 4.46 (1H, dd, $J$ = 15, 11 Hz), 5.87 (1H, dd, $J$ = 11, 7.5 Hz), 7.39 (2H, t, $J$ = 8.4 Hz), 7.52 (2H, d, $J$ = 7.7 Hz), 7.64 (1H, t, $J$ = 7.3 Hz), 7.92 (2H, d, $J$ = 8.3 Hz), 7.98 (2H, d, $J$ = 8.3 Hz).

$^{13}$C NMR: δ 58.9, 80.0, 125.8, 129.0 (3C), 129.1 (2C), 129.3 (2C), 130.1, 134.3, 134.4, 138.3, 163.7, 195.0.

HRMS: m/z calc'd for [M+H]^+ C_{16}H_{13}^{35}ClNO_2^+ 286.0629, found 286.0643.

(2-(Furan-2-yl)-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161f:
This compound was prepared according to the procedure for 161a using 160f (0.10g, 0.44 mmol, 1 equiv) giving 161f as a yellow solid (0.071 g, 66% yield).

Melting point: 76-79 °C.

IR: 3111 (br), 2924 (s), 1700 (s), 1672 (s), 1479 (m), 1097 (s) cm⁻¹.

¹H NMR: δ 4.24 (1H, dd, J = 15, 7.7 Hz), 4.47 (1H, dd, J = 15, 11 Hz), 5.84 (1H, dd, J = 11, 7.7 Hz), 6.51 (1H, s), 7.05 (1H, d, J = 3.7 Hz), 7.52 (2H, t, J = 7.7 Hz), 7.57 (1H, s), 7.64 (1H, t, J = 7.9 Hz), 7.97 (2H, d, J = 7.9 Hz).

¹³C NMR: δ 58.9, 79.9, 111.9, 115.5, 129.1 (2C), 129.3 (2C), 134.3, 134.4, 142.6, 145.9, 156.7, 194.8.

HRMS: m/z calc’d for [M+H]+ C14H12NO3+ 242.0812, found 242.0818.

(2-Phenyl-4,5-dihydrooxazol-5-yl)(p-tolyl)methanone, 161g:

This compound was prepared according to the procedure for 161a using 160g (0.10g, 0.40 mmol, 1 equiv) giving 161g as a yellow solid (0.037 g, 35% yield).

Melting point: 119-122 °C.

IR: 2924 (br), 1722 (w), 1689 (w), 1577 (w), 1247 (s), 709 (s) cm⁻¹.

¹H NMR: δ 2.44 (3H, m), 4.26 (1H, dd, J = 15, 7.7 Hz), 4.45 (1H, dd, J = 15, 11 Hz), 5.84 (1H, dd, J = 11, 7.7 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.42 (2H, t, J = 7.7 Hz), 7.49 (1H, t, J = 7.4 Hz), 7.89 (2H, d, J = 8.1 Hz), 7.99 (2H, d, J = 8.1 Hz).
$^{13}$C NMR: $\delta$ 22.2, 58.9, 79.9, 127.4, 128.7 (4C), 128.8 (2C), 129.2 (2C), 130.0, 132.0, 145.4, 164.5, 194.9.

HRMS: m/z calc'd for [M+H]$^+$ C$_{17}$H$_{16}$NO$_2^+$ 266.1176, found 266.1176.

(3,5-Dimethylphenyl)(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161h:

This compound was prepared according to the procedure for 161a using 160h (0.10g, 0.38 mmol, 1 equiv).

The characterisation data could not be obtained due to the low conversion of the compound 161h

(4-Chlorophenyl)(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161i:

This compound was prepared according to the procedure for 161a using 172i (0.10g, 0.35 mmol, 1 equiv) giving 161i as a yellow solid (0.083 g, 84% yield).

Melting point: 106-108 °C.

IR: 3063 (br), 2848 (w), 1693 (m), 1586 (m), 1362 (m), 1058 (m), 710 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 4.31 (1H, dd, $J$ = 15, 7.5 Hz), 4.44 (1H, dd, $J$ = 15, 11 Hz), 5.78 (1H, dd, $J$ = 11, 7.5 Hz), 7.42 (2H, t, $J$ = 7.6 Hz), 7.47-7.53 (3H, m), 7.93-7.99 (4H, m).
$^{13}$C NMR: $\delta$ 58.6, 79.9, 127.3, 128.7 (2C), 128.8 (2C), 129.7 (2C), 130.6 (2C), 132.1, 132.9, 140.9, 164.2, 194.4.

HRMS: m/z calc'd for [M+H]$^+$ $C_{16}H_{13}^{35}$ClNO$_2$$^+$ 286.0629, found 286.6020.

(4-Methoxyphenyl)(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161j:

![Chemical structure](image)

This compound was prepared according to the procedure for 161a using 160j (0.10g, 0.35 mmol, 1 equiv) giving 161j as a yellowish wax (0.052 g, 52% yield).

IR: 3324 (br), 2924 (w), 2836 (w), 1740 (m), 1646 (m), 1598 (s), 1169 (m), 695 (s) cm$^{-1}$.

$^1$H NMR: $\delta$ 3.89 (3H, s), 4.29 (1H, dd, $J = 15, 7.7$ Hz), 4.45 (1H, dd, $J = 15, 11$ Hz), 5.82 (1H, dd, $J = 11, 7.7$ Hz), 6.99 (2H, d, $J = 8.9$ Hz), 7.42 (2H, t, $J = 7.7$ Hz), 7.49 (1H, t, $J = 7.4$ Hz), 7.99 (2 x 2H, d, $J = 7.8$ Hz).

$^{13}$C NMR: $\delta$ 55.9, 58.8, 79.9, 114.5 (2C), 127.4, 127.5, 128.8 (5C), 131.5 (2C), 132.0, 164.5, 193.7.

HRMS: m/z calc'd for [M+H]$^+$ $C_{17}H_{16}$NO$_3$$^+$ 282.1125, found 282.1134.

(3-methoxyphenyl)(2-phenyl-4,5-dihydrooxazol-5-yl)methanone 161k:

![Chemical structure](image)

This compound was prepared according to the procedure for 161a using 160k (0.05g, 0.19 mmol, 1 equiv) giving 161k as a Yellowish wax (0.0073 g, 14% yield).
IR: 3326 (br), 2935 (w), 2838 (w), 1744 (m), 1646 (m), 1593 (s), 1170 (m), 695 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta\) 3.87 (3H, s), 4.29 (1H, dd, \(J = 15, 7.6\) Hz), 4.46 (1H, dd, \(J = 15, 11\) Hz), 5.84 (1H, dd, \(J = 11, 7.6\) Hz), 7.18 (1H, dd, \(J = 8.3, 2.5\) Hz), 7.40-7.47 (3H, m), 7.49 (3H, m), 7.99 (2H, d, \(J = 7.3\) Hz).

\(^13\)C NMR: \(\delta\) 55.9, 59.0, 80.0, 113.4 (2C), 120.9, 121.6, 128.8 (5C), 130.3 (2C), 132.1, 160.4, 193.5.

HRMS: m/z calc'd for [M+H]\(^+\) C\(_{17}\)H\(_{16}\)NO\(_3\)\(^+\) 282.1125, found 282.1134.

Naphthalen-2-yl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, \(\text{161m}\):

\[
\text{N} \quad \text{O} \\
\text{O} \\
\text{N} \\
\text{O}
\]

This compound was prepared according to the procedure for \(\text{161a}\) using \(\text{160m}\) (0.083 g, 0.29 mmol, 1 equiv) giving \(\text{161m}\) as a light yellow oil (0.072 g, 82% yield).

IR: 3339 (br), 2968 (m), 1694 (w), 1650 (m), 1508 (s), 950 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta\) 4.30 (1H, dd, \(J = 15, 7.4\) Hz), 4.43 (1H, dd, \(J = 15, 11\) Hz), 5.93 (1H, dd, \(J = 11, 7.4\) Hz), 7.41 (2H, t, \(J = 7.5\) Hz), 7.49 (1H, t, \(J = 7.5\) Hz), 7.52-7.65 (3H, m), 7.91 (2H, t, \(J = 8.7\) Hz), 7.97 (2H, d, \(J = 7.7\) Hz), 8.06 (1H, d, \(J = 8.1\) Hz), 8.64 (1H, d, \(J = 8.5\) Hz).

\(^13\)C NMR: \(\delta\) 59.3, 81.1, 124.6, 125.9, 127.2, 127.4, 128.7 (2C), 128.7 (2C), 128.8, 128.8, 128.9, 131.1, 132.0, 132.6, 134.1, 134.3, 164.6, 199.4.

HRMS: m/z calc'd for [M+H]\(^+\) C\(_{20}\)H\(_{16}\)NO\(_2\)\(^+\) 302.1176, found 302.1193.

\([1,1'\text{-Biphenyl}]\text{-2-yl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, \(\text{161n}\):}\)

169
This compound was prepared according to the procedure for 161a using 160n (0.080g, 0.25 mmol, 1 equiv) giving 161n as a yellow wax (0.078 g, 75% yield).

IR: 3055 (br), 2926 (w), 2871 (w), 1698 (m), 1646 (m), 1252 (m) cm$^{-1}$.

$^1$H NMR: δ 3.90 (1H, dd, $J = 15$, 11 Hz), 3.99 (1H, dd, $J = 15$, 7.4 Hz), 4.81 (1H, dd, 11, 7.4 Hz), 7.33-7.41 (4H, m), 7.42-7.50 (6H, m), 7.52-7.61 (2H, m), 7.76 (2H, d, $J = 8.1$ Hz).

$^{13}$C NMR: δ 59.2, 81.4, 127.3, 128.0, 128.6 (5C), 129.0, 129.3 (2C), 129.4 (2C), 130.5, 131.8, 131.9, 137.8, 140.4, 141.2, 164.3, 205.9.

HRMS: m/z calc'd for [M+H]$^+$ C$_{22}$H$_{18}$NO$_2^+$ 328.1332, found 328.1329.

Furan-2-yl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161p:

This compound was prepared according to the procedure for 161a using 172p (0.05g, 0.21 mmol, 1 equiv) giving 161p as a brown solid (0.095 g, 95% yield).

Melting point: 75-77 °C.

IR: 3335 (br), 2969 (s), 1466 (w), 1378 (m), 1127 (m), 950 (s) cm$^{-1}$.
H NMR: δ 4.25 (1H, dd, \(J = 15, 7.8 \text{ Hz}\)), 4.47 (1H, dd, \(J = 15, 11 \text{ Hz}\)), 5.61 (1H, dd, \(J = 11, 7.8 \text{ Hz}\)), 6.58 (1H, dd, \(J = 3.8, 1.8 \text{ Hz}\)), 7.41 (1H, t, \(J = 3.9 \text{ Hz}\)), 7.45 (2H, d, \(J = 7.9 \text{ Hz}\)), 7.51 (1H, t, \(J = 7.3 \text{ Hz}\)), 7.71 (1H, s), 8.00 (2H, d, \(J = 7.7 \text{ Hz}\)).

\(^{13}\)C NMR: δ 59.2, 80.1, 113.0, 120.1, 127.4, 128.8 (2C), 128.8 (2C), 132.1, 147.9, 150.7, 164.3, 185.0.

HRMS: \(m/z\) calc’d for [M+H]\(^{+}\) \(C_{14}H_{12}NO_{3}\)^{+} 242.0812, found 242.0804.

1-(2-Phenyl-4,5-dihydrooxazol-5-yl)ethan-1-one, 161q:

This compound was prepared according to the procedure for 161a using 172q (0.10g, 0.52 mmol, 1 equiv) giving 161q as a yellow oil (0.062 g, 63% yield).

IR: 2937 (br), 1717 (s), 1651 (s), 1254 (m), 1058 (s), 778 (m) cm\(^{-1}\).

\(^{1}\)H NMR: δ 2.28 (3H, s), 4.09 (1H, dd, \(J = 15, 7.3 \text{ Hz}\)), 4.33 (1H, dd, \(J = 15, 11 \text{ Hz}\)), 4.96 (1H, dd, \(J = 11, 7.3 \text{ Hz}\)), 7.45 (2H, t, \(J = 7.6 \text{ Hz}\)), 7.53 (1H, t, \(J = 7.6 \text{ Hz}\)), 7.99 (2H, d, \(J = 7.3 \text{ Hz}\)).

\(^{13}\)C NMR: δ 26.3, 59.0, 82.8, 127.3, 128.6 (2C), 128.9 (2C), 132.2, 164.2, 208.1.

HRMS: \(m/z\) calc’d for [M+H]\(^{+}\) \(C_{11}H_{12}NO_{2}\)^{+} 190.0863, found 190.0866.

1-(2-Phenyl-4,5-dihydrooxazol-5-yl)propan-1-one, 161r:
This compound was prepared according to the procedure for \textbf{161a} using \textbf{172r} (0.10g, 0.48 mmol, 1 equiv) giving \textbf{161r} as a colourless oil (0.055 g, 56\% yield).

IR: 2969 (br), 1717 (m), 1643 (w), 1451 (w), 1264 (m), 711 (s) \text{cm}^{-1}.

$^1$H NMR: $\delta$ 1.09 (3H, t, $J = 7.3$ Hz), 2.52-2.64 (1H, m), 2.67-2.79 (1H, m), 4.08 (1H, dd, $J = 15$, 7.2 Hz), 4.33 (1H, dd, $J = 15$, 11 Hz), 4.99 (1H, dd, $J = 11$, 7.2 Hz), 7.45 (2H, t, $J = 7.4$ Hz), 7.53 (1H, t, $J = 7.4$ Hz), 7.99 (2H, d, $J = 7.8$ Hz).

$^{13}$C NMR: $\delta$ 7.2, 32.2, 59.3, 82.6, 127.4, 128.6 (2C), 128.9 (2C), 132.2, 164.3, 210.8.

HRMS: m/z calc'd for $[\text{M+NH}_4]^+$ C$_{12}$H$_{17}$N$_2$O$_2$+ 221.1285, found 221.1284.

\textbf{1-(5-Methyl-2-phenyl-4,5-dihydrooxazol-5-yl)ethanone, 161s:}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure}
\end{center}

This compound was prepared according to the procedure for \textbf{161a} using \textbf{172s} (0.10g, 0.49 mmol, 1 equiv) giving \textbf{161s} as a colourless oil (0.075 g, 75\% yield).

IR: 3335 (br), 2969 (m), 2928 (w), 2359 (m), 1713 (m), 1646 (m), 950 (s) \text{cm}^{-1}.

$^1$H NMR: $\delta$ 1.58 (3H, s), 2.29 (3H, s), 3.85 (1H, d, $J = 15$ Hz), 4.21 (1H, d, $J = 15$ Hz), 7.44 (2H, t, $J = 7.5$ Hz), 7.52 (1H, t, $J = 7.5$ Hz), 7.99 (2H, d, $J = 7.3$ Hz).

$^{13}$C NMR: $\delta$ 23.1, 25.5, 65.1, 89.8, 127.7, 128.5 (2C), 128.8 (2C), 132.0, 163.5, 209.9.

HRMS: m/z calc'd for $[\text{M+H}]^+$ C$_{12}$H$_{14}$NO$_2$+ 204.1019, found 204.1012.

\textbf{((syn)-4-Methyl-2-phenyl-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161t:}
This compound was prepared according to the procedure for 161a using 172t (0.10g, 0.37 mmol, 1 equiv) giving 161t as a yellow wax (0.053 g, 54% yield).

IR: 2925 (br), 1698 (m), 1448 (m), 1218 (s), 687 (s) cm\(^{-1}\).

\(^1\)H NMR: \(\delta\) 1.09 (3H, d, \(J = 7.0\) Hz), 4.89 (1H, dq, \(J = 10, 6.9\) Hz), 6.00 (1H, d, \(J = 10\) Hz), 7.44 (2H, t, \(J = 7.6\) Hz), 7.49-7.56 (3H, m), 7.64 (1H, t, \(J = 7.3\) Hz), 7.95 (2H, d, \(J = 8.2\) Hz), 8.03 (2H, d, \(J = 8.2\) Hz).

\(^13\)C NMR: \(\delta\) 17.8, 65.5, 83.6, 127.4, 128.4 (2C), 128.8 (2C), 128.9 (2C), 129.4 (2C), 132.1, 134.3, 135.8, 163.7, 194.7.

HRMS: m/z calc'd for [M+H]\(^+\) C\(_{17}\)H\(_{16}\)NO\(_2\)\(^+\) 266.1176, found 266.1167.

((anti)-4-Methyl-2-phenyl-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161t:

This compound was prepared according to the procedure for 161a using 160t (0.10g, 0.37 mmol, 1 equiv) giving 161t as a yellow solid (0.034 g, 34% yield).

Melting point: 71-73 °C.

IR: 2925 (br), 1698 (m), 1647 (m), 1448 (m), 1218 (s), 687 (s) cm\(^{-1}\).
1H NMR: δ 1.54 (3H, d, J = 6.7 Hz), 4.52 (1H, pent, J = 6.6 Hz), 5.39 (1H, d, J = 6.7 Hz), 7.42 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.8 Hz), 7.52 (2H, t, J = 7.8 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.99 (2 x 2H, d, J = 7.8 Hz).

13C NMR: δ 22.0, 66.5, 86.4, 127.5, 128.7 (2C), 128.8 (2C), 129.1 (2C), 129.2 (2C), 132.0, 134.3, 134.8, 163.0, 195.7.

HRMS: m/z calc’d for [M+H]+ C17H16NO2+ 266.1176, found 266.1167.

=((syn)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161v:

This compound was prepared according to the procedure for 161a using 172v (0.10g, 0.42 mmol, 1 equiv) giving 161v as a yellow oil (0.025 g, 18% yield).

IR: 2918 (br), 1700 (m), 1644 (s), 1447 (m), 1238 (m), 1068 (m) cm⁻¹.

1H NMR: δ 5.83 (1H, d, J = 11 Hz), 6.29 (1H, d, J = 11 Hz), 6.93 (2H, dd, J = 7.5, 1.8 Hz), 6.98-7.05 (3H, m), 7.31 (2H, t, J = 7.7 Hz), 7.43-7.60 (6H, m), 8.06 (2H, d, J = 8.1 Hz).

13C NMR: δ 74.5, 84.8, 127.3, 128.1 (2C), 128.3 (3C), 128.6 (2C), 128.8 (2C), 128.9 (2C), 129.2 (2C), 132.4, 133.6, 136.2, 136.7, 165.5, 194.7.

HRMS: m/z calc’d for [M+H]+ C22H18NO2+ 328.1331, found 328.1330.

((anti)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161v:
This compound was prepared according to the procedure for 161a using 172v (0.10g, 0.42 mmol, 1 equiv) giving 161v as a yellow oil (0.041 g, 28% yield).

IR: 2918 (br), 1700 (m), 1644 (s), 1447 (m), 1238 (m), 1068 (m) cm\(^{-1}\).

\(^1\)H NMR: δ 5.53 (1H, d, \(J = 6.6\) Hz), 5.71 (1H, d, \(J = 6.6\) Hz), 7.29-7.40 (5H, m), 7.45-7.57 (5H, m), 7.63 (1H, t, \(J = 7.5\) Hz), 7.94 (2H, t, \(J = 7.2\) Hz), 8.09 (2H, d, \(J = 7.3\) Hz).

\(^13\)C NMR: δ 74.0, 87.1, 127.3, 127.4 (2C), 128.6, 128.8 (2C), 129.1 (3C), 129.2 (2C), 129.4 (2C), 129.5 (2C), 132.3, 134.4, 141.4, 164.2, 194.8.

HRMS: m/z calc'd for [M+H]\(^+\) C\(_{22}\)H\(_{18}\)NO\(_2\)\(^+\) 328.1331, found 328.1330.

\(N\)-(2-Hydroxy-3-oxo-3-phenylpropyl)-4-nitrobenzamide, 175:

This compound was prepared according to the procedure for 161a using 172d (0.10g, 0.31 mmol, 1 equiv) giving 175 as a light yellow solid (0.069 g, 66% yield).

Melting point: 75-77 °C.

IR: 3405 (br), 2969 (m), 1667 (m), 1535 (m), 1368 (w), 1124 (m), 950 (s) cm\(^{-1}\).
^1^H NMR: δ 3.33 (1H, ddd, \( J = 13, 8.3, 5.5 \) Hz), 4.09 (1H, br), 4.24 (1H, ddd, \( J = 10, 6.8, 3.2 \) Hz), 5.34 (1H, dd, \( J = 7.7, 2.8 \) Hz), 6.87 (1H, br), 7.57 (2H, t, \( J = 7.7 \) Hz), 7.68 (1H, t, \( J = 7.7, 8.7 \) Hz), 7.95 (2H, d, \( J = 8.7 \) Hz), 8.12 (2H, d, \( J = 8.2 \) Hz), 8.29 (2H, d, \( J = 8.7 \) Hz).

^1^3^C NMR: δ 45.7, 72.8, 124.2 (2C), 128.6 (2C), 129.2 (2C), 129.6 (2C), 133.3, 135.2, 139.8, 150.1, 166.3, 199.4.

HRMS: m/z calc'd for [M+H]^+ \( \text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_5^+ \) 315.0936, found 315.0972.

\( N^-\)-((1\( R \),2\( S \))-1-Hydroxy-1-phenylpropan-2-yl)-2-iodo-\( N \),3-dimethylbenzamide, 185: ^3^8

\[
\begin{array}{c}
\text{I} \\
\text{O} \\
\text{N} \\
\text{H}
\end{array}
\]

Prepared following the literature procedure reported by Moran and Rodriguez. ^3^7 2-iodo-3-methylbenzoic acid (0.5 g, 1.9 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (19 mL) at room temperature and oxalyl chloride (0.32 mL, 3.9 mmol) and DMF (0.01 mL) were added sequentially. The reaction mixture was stirred overnight, then concentrated under vacuum. The residue was dissolved in THF (10 mL) and added dropwise to a solution of (1\( S \),2\( S \))-pseudoephedrine hydrochloride (0.31 g, 1.6 mmol) and triethylamine (0.5 mL, 3.6 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight and then quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL), dried (\( \text{MgSO}_4 \)), filtered and concentrated. Purification by flash chromatography (silica gel; 1:1 petroleum ether/EtOAc) provided 185 as a white solid (0.35 g, 45% yield), m.p: 182-186 °C (lit. m.p. 181-185 °C).

185 Exists as four amide rotamers A, B, C, and D. Only NMR data specified for the two major rotamers A and B.

IR (neat): 3330 (br), 2856 (w), 1607 (s), 1412 (m), 1038 (m) cm\(^{-1}\).
1^H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 0.97 (3H<sub>A</sub>, d, J = 6.8 Hz), 1.03 (3H<sub>B</sub>, d, J = 6.9 Hz), 2.36 (3H<sub>A</sub>, s), 2.37 (3H<sub>B</sub>, s), 2.62 (3H<sub>B</sub>, s), 2.97 (3H<sub>A</sub>, s), 3.36-3.44 (1H<sub>A</sub>, m), 4.46 (1H<sub>A</sub>, dd, J = 8.2, 3.6 Hz), 4.66 (1H<sub>B</sub>, dd, J = 7.5, 4.6 Hz), 4.82-4.90 (1H<sub>B</sub>, m), 5.51 (1H<sub>B</sub>, d, J = 4.5 Hz), 5.61 (1H<sub>A</sub>, d, J = 3.6 Hz), 6.61-6.66 (1H<sub>B</sub>, m), 6.76-6.82 (1H<sub>A</sub>, m), 7.07 (2H<sub>A</sub>, d, J = 6.7 Hz), 7.20-7.44 (5H<sub>A</sub>, m; 7H<sub>B</sub>, m).

13C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 13.7<sup>B</sup>, 15.5<sup>A</sup>, 26.9<sup>A</sup>, 28.4<sup>B</sup>, 28.7<sup>A</sup>, 31.1<sup>B</sup>, 52.9<sup>B</sup>, 60.0<sup>A</sup>, 73.9<sup>B</sup>, 74.1<sup>A</sup>, 99.6<sup>B</sup>, 100.1<sup>A</sup>, 124.0<sup>B</sup>, 126.4<sup>A</sup>, 127.0<sup>B</sup> (2C), 127.1<sup>A</sup> (2C), 127.4<sup>B</sup>, 127.7<sup>A</sup>, 128.0<sup>B</sup>, 128.4<sup>B</sup> (2C), 128.8<sup>A</sup> (2C), 129.3<sup>B</sup>, 129.3<sup>A</sup>, 129.4<sup>B</sup>, 141.8<sup>A</sup>, 142.1<sup>B</sup>, 143.6<sup>A</sup>, 143.7<sup>B</sup>, 144.6<sup>A</sup>, 144.8<sup>B</sup>, 170.6<sup>B</sup>, 171.2<sup>A</sup>.

HRMS: m/z calc’d for [M+H]+ C<sub>18</sub>H<sub>21</sub>INO<sub>2</sub> 410.0611, found 410.0611.

N<sup>1</sup>,N<sup>3</sup>-bis((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-2-ido-N<sup>1</sup>,N<sup>3</sup>-dimethylisophthalamide, 188:

Prepared following the literature procedure reported by Moran and Rodriguez.\textsuperscript{37} using 2-iodoisophthalic acid (0.5 g, 1.7 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at room temperature and oxalyl chloride (0.59 mL, 6.85 mmol) and DMF (0.02 mL) were added sequentially. The reaction mixture was stirred overnight, and then concentrated under vacuum. The residue was dissolved in THF (10 mL) and added dropwise to a solution of (1S,2S)-pseudoephedrine hydrochloride (0.56 g, 2.8 mmol) and triethylamine (1.8 mL, 12.6 mmol) in THF (18 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight and then quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL), dried (MgSO<sub>4</sub>), filtered and
concentrated. Purification by flash chromatography (silica gel; 1:10 petroleum ether/EtOAc) provided 188 as a white solid (0.48g, 48% yield), m.p 197-200 °C.

188 Exists as sixteen amide rotamers only 1H NMR data specified for the major rotamers.

IR: 3390 (br), 1611 (s), 1402 (m), 1109 (m), 1046 (m), 699 (s) cm⁻¹.

1H NMR (400 MHz, DMSO-d⁶): δ 0.89-1.14 (6H, m), 2.95 (3H, s), 3.34 (3H, s), 4.39-4.55 (1H, m), 4.58-4.70 (1H, m), 4.77-4.91 (1H, m), 5.45-5.57 (1H, m), 5.59-5.71 (1H, m), 6.77-7.55 (14H, m).

13C NMR data specified for the two rotamers (A) major and (B) minor

13C NMR (100 MHz, DMSO-d⁶): δ 16.4B, 16.6A, 27.9B, 28.1A, 31.8B, 32.1A, 60.4A, 60.6B, 74.8B, 75.1A, 92.8B, 92.9A, 128.0B (4C), 128.1A (4C), 128.5A, 128.7B, 128.8A (2C), 128.9B (2C), 129.3A (2C), 129.3B (2C), 129.4B (4C), 129.5A (4C), 144.5A (2C), 144.6B (2C), 145.4A, 145.8B, 171.0B, 170.2A, 171.6B, 171.7A.

HRMS: m/z calc’d for [M+H]+ C₂₈H₃₂IN₂O₄ 587.1401, found 587.1400.

(R)-2,2'-Diiodo-1,1'-binaphthyl, 190:⁸⁷

Prepared according to the literature procedure.⁸⁷ A mixture of commercial (R)-(+)−2,2'-diamino-1,1'-binaphthyl (1 g, 3.52 mmol), potassium iodide (5.87 g, 35 mmol), and sodium nitrite (1.69 g, 28 mmol) were placed in flask charged with N₂. The solids were dissolved in DMSO (60 mL) in a room temperature water bath. Then, 47% aqueous HBr (4.8 mL) was
added dropwise with intense stirring which led to darkening and visible gas evolution. Then, the water bath was removed and the mixture was stirred for 2 h. The resulting mixture was poured into 50% aqueous sat. NaHCO₃ (60 mL) and extracted with CH₂Cl₂ (60 mL). The combined organic extracts were washed with 10% aq. Na₂S₂O₃ (2 x 30 mL), water (2 x 30 mL), brine (15 mL), and dried over MgSO₄. Then, the solvent was removed under vacuum and the residue purified by flash column chromatography on silica gel (eluent: petroleum ether 40-60) which afforded 190 as a white solid (0.83 g, 47% yield), m.p 116-117 °C (lit. m.p. 116.5 °C).

IR: 2970 (br), 1573 (m), 1497 (w), 1265 (m), 1097 (m), 827 (s) cm⁻¹.

¹H NMR: δ 7.08 (2H, d, J = 8.6 Hz), 7.25-7.33 (2H, m), 7.48-7.54 (2H, m), 7.72 (2H, d, J = 8.7 Hz), 7.93 (2H, d, J = 8.1 Hz), 8.06 (2H, d, J = 8.8 Hz).

¹³C NMR: δ 100.1 (2C), 126.7 (3C), 126.9 (2C), 127.7 (2C), 128.6 (2C), 130.0 (2C), 133.3 (2C), 136.0 (3C), 145.1 (2C).

HRMS: m/z calc’d for [M-I]⁺ C₂₀H₁₂I⁺ 378.9978, found 378.9974

N-(3-Hydroxy-3-phenylpropyl)benzamide, 192:¹⁰⁸

![Structure of N-(3-Hydroxy-3-phenylpropyl)benzamide]

Following the literature procedure reported by Legault,⁴⁰ a solution of diisopropylamine (0.17 mL, 1.2 mmol) in THF (5 mL) under an argon atmosphere at −78 °C was slowly add n-Butyllithium 2.5M (4.7 mL, 1.2 mmol). The mixture was stirred for 30 min, and then N-(3-oxo-3-phenylpropyl)benzamide (0.25 g, 0.99 mmol) was added. The resulting mixture was stirred for 45 min, and then acetic anhydride (0.19 mL, 1.97 mmol) was added. The reaction
was stirred 30 min at −78 °C and another 30 min at room temperature. The mixture was poured into saturated NaHCO₃ (5 mL), and extracted twice with EtOAc (10 mL). The combined organic layers were washed with brine and dried over MgSO₄, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1:10 petroleum ether/EtOAc to EtOAc) to provide **192** as a yellow oil (0.06 g, 24% yield).

IR: 3332 (br), 1466 (w), 1378 (m), 1159 (m), 950 (s), 816 (m) cm⁻¹.

¹H NMR: δ 1.92-2.00 (2H, m), 3.39-3.47 (1H, m), 3.69-3.77 (1H, br), 3.77-3.88 (1H, m), 4.81 (2H, dd, J = 8.5, 4.4 Hz), 7.09 (1H, br), 7.24-7.28 (1H, m), 7.32-7.36 (4H, m), 7.37-7.43 (2H, m), 7.48 (1H, t, J = 7.4 Hz), 7.75 (2H, d, J = 7.8 Hz).

¹³C NMR: δ 37.9, 38.9, 73.0, 125.9 (2C), 127.9 (2C), 128.8, 128.9 (4C), 131.9, 134.6, 144.5, 168.5.

HRMS: m/z calc’d for [M+H]⁺ C₁₆H₁₈NO₂⁺ 256.1332, found 256.1338.

**Representative procedure for chiral iodoarene-catalysed cyclisation**

1-(5-Methyl-2-phenyl-4,5-dihydrooxazol-5-yl)ethanone **161s**

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{phenyl}
\end{array}
\]

Amide **172s** (1 equiv) was dissolved in solvent and chiral iodoarene (0.1 equiv) was added, followed by mCBPA (3 equiv) and p-TsOH.H₂O (3 equiv). The mixture was stirred overnight at room temperature, then aqueous Na₂SO₄ solution (5 mL) and saturated aqueous NaHCO₃ solution (5 mL) were added and the mixture extracted with CH₂Cl₂ (10 mL × 2). The organic layers were combined and dried with MgSO₄, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether/EtOAc) to provide **161s**.
ee: 14%, determined by HPLC analysis: chiralpak IB, hexane/IPA gradient (93:7), 1 mL/min.

254 nm; Retention Time (minor) = 5.3 min, Retention Time (major) = 5.8 min.
References


46. Koposov, A. Y.; Boyarskikih, V. V.; Zhdankin, V. V. Org. Lett. 2004, 6, 3613–3615.


