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Cyclisation of Propargyl and Allyl Amides: Syntheses of Oxazolines

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Abbreviations:

BQ: 1,4-benzoquinone.
Bn: benzyl.
Boc: tert-butyloxycarbonyl.
Cbz: benzyloxycarbonyl.

m-CPBA: m-chloroperoxybenzoic acid.
Cy: cyclohexyl.

DABCO: 1,4-diazabicyclo[2.2.2]octane.
DCE: dichloroethane.

DCM: dichloromethane.
DIAD: diisopropyl azodicarboxylate.

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.
DEAD: diethyl azodicarboxylate.

DMA: N,N-dimethylacetamide.
DMF: N,N-dimethylformamide.

DMP: Dess–Martin periodinane.
DMSO: dimethylsulfoxide.

DMEDA: N,N′-dimethylethylenediamine.

Fmoc: fluorenlymethyloxycarbonyl

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

HPBP: 2,2′,3,3′,5,5′-Hexaphenyl-(1,1′-biphenyl)-4,4′-diol.

HRMS: high resolution mass spectrometry.

h: hour.
IR: Infrared.
MW: microwave.
MS: mass spectrometry.
NMR: nuclear magnetic resonance spectroscopy.
o/n: overnight.
PIDA: phenyliodine(III) diacetate.
PIFA: [Bis(trifluoroacetoxy)iodo]benzene.
Pd(dba)$_2$: bis(dibenzylideneacetone)palladium(0).
PIDA: [bis(trifluoroacetoxy)iodo]benzene.
PTSA: $p$-toluenesulfonic acid monohydrate.
TFA: trifluoroacetic anhydride.
THF: tetrahydrofuran.
TBAB: tetra-$n$-butylammonium bromide.
TBAF: tetra-$n$-butylammonium fluoride.
rt: room temperature.
Abstract:

This thesis describes several approaches to the synthesis of dihydrooxazoles (oxazolines) by the cyclisation of unsaturated amides.

The first major approach to the synthesis of substituted dihydrooxazoles is the CuI-catalysed cycloisomerisation of terminal propargyl amides. The reaction has been shown to have good substrate scope and experiments to delineate the mechanism have been performed. Substrates containing a benzylic methylene were oxidised to the ketone under the reaction conditions.

\[
\begin{align*}
\text{R}^2 \text{R}^1 \text{N} & \quad \text{10 mol\% CuI} \\
\text{DCE, 80 °C} & \quad \text{DCM, rt}
\end{align*}
\]

The second major focus of this thesis is the cyclisation of \(N\)-alkenylamides catalysed by iodoarenes under oxidative conditions. Dihydrooxazoles were prepared by this route with a range of substitution patterns in good yields.

\[
\begin{align*}
\text{R}^1 \text{N} & \quad \text{20 mol\% 2-iodoanisole} \\
\text{TFA (1 equiv), Selectfluor (1 equiv), MeCN, rt}
\end{align*}
\]
Introduction:

A large number of oxazole, oxazoline and thiazole-containing natural products have been isolated from marine organisms, mainly sponges and ascidians, over the last two decades. The cytotoxic and antineoplastic activities that they exhibit, as well as the possibility of acting as metal ion chelating metabolites, have inspired a considerable amount of both structural and synthetic studies. In many cases, promising anti-tumour, antibacterial, anti-viral, anti-malaria and anthelmintic activities have been identified for these compounds. 1-5

As an example, the bistratamides (Figure 1) are a family of macrolactams isolated from Lissoclinum bistratum in the southern Philippines. 6-8 Their interesting biological activities led to total syntheses of bistratamide family members. 9,10 Bistratamides E to J (Figure 1) were isolated in the last few years and exhibit moderate cytotoxic activity against a human colon tumor (HCT-116) cell line. 5

There are several methods which can be used to form the oxazole ring or its derivatives. Hanzawa and co-workers have reported a method, where PIDA [phenyliodine(III) diacetate] (1.5 equiv) is used to form 2,5-disubstituted oxazoles via the oxidative cycloisomerisation of propargylamide derivatives (Scheme 1). Two sets of conditions were used in this reaction: AcOH as solvent at 90 °C, and HFIP (hexafluoroisopropanol) as solvent with the addition of AcOH (5 equiv) at room temperature. 11
Figure 1: Bistratamides E-J
When they tried their two sets of conditions with internal alkynes, the oxazole ring was obtained only with the AcOH at 90 °C (Scheme 2).

The mechanism of oxazole formation could proceed by two possible routes. Route a consists of (i) the cyclisation of 1 through the activation of the triple bond by PIDA, (ii) the formation of 6 by the deprotonation of 2 and the subsequent acetic acid elimination of 5, and (iii) the substitution of the phenyliodonium group in 6 by AcOH. In route b, the reaction of terminal alkynes with PIDA leads to the formation of the alkynyliodonium salts 3, which undergo ring closure to form intermediate 4. Proton transfer leads to 5 and the rest of the mechanism is the same as in route a (Scheme 3).
Propargylic alcohols and amides are used to produce oxazoles in the presence of PTSA (p-toluenesulfonic acid monohydrate) as a catalyst (Scheme 4). This reaction is a one-pot PTSA-catalysed propargylation/cycloisomerisation tandem reaction. PTSA acts as a bifunctional catalyst and effectively catalyses two reaction processes in a single reaction vessel under the same conditions. The reaction is completed rapidly under mild conditions and is tolerant of air, giving water as the only by-product.12
Another method to access oxazoles from propargylamides uses a Pd(II) catalyst in the presence of the oxidant 1,4-benzoquinone (BQ) (Scheme 5).\(^{13}\)

\[
\begin{align*}
\text{R}^1 &= \text{Ph, 1-naphthyl, 4-MeOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4 \\
\text{R}^2 &= \text{H, TMS, } n\text{-Bu.} \\
\text{R}^3 &= \text{Ph, 4-MeC}_6\text{H}_4, \text{HOC}_6\text{H}_4, \text{Me, } i\text{-pr, } n\text{-pr.}
\end{align*}
\]

Scheme 4

Beccalli et al. proposed the mechanism of this reaction to be an oxidative heterocyclisation (Scheme 6). The complexation of amide 7 with Pd(II) takes place on the C-C triple bond (intermediate 8) making it susceptible to nucleophilic attack. The role of the nucleophile is covered by the oxygen atom of the amide group, which gives rise to 5-\textit{exo}-dig cyclisation to produce the oxazole skeleton by formation of the $\sigma$-alkenylpalladium complex 9. Ligand exchange with water, followed by reductive elimination and tautomerisation gives rise to 10.
At this point the oxidising system intervenes with a double role, namely (i) to reoxidise the Pd(0) species, formed at the end of the catalytic cycle, to the active Pd(II) and (ii) to promote the dehydrogenation of 10 giving 11.

Scheme 6

Several groups have reported that gold catalysts can cyclise amides onto alkynes.\textsuperscript{11} One of these reports states that oxazoles can be obtained by using catalytic gold(III) chloride (Scheme 7).\textsuperscript{14}

\[ \text{Scheme 7} \]

\[ R = \text{alkyl, vinyl, aryl} \]
In this reaction, the C-C triple bond is activated by cationic Au(III) coordination. This can accept the attack of the amide oxygen to afford a vinylgold intermediate. Alkene isomerisation forms the aromatic heterocycle and protonation of the Au-C bonds leads to the final product (Scheme 8).\textsuperscript{15}

\begin{center}
\textbf{Scheme 8}
\end{center}

A one-pot reaction starting from propargyl amine to prepare oxazoles has been reported by Müller and Merkul (Scheme 9). In this case, amidation followed by Sonogashira cross-coupling and then acid mediated cycloisomerisation provides the products.\textsuperscript{16}

\begin{center}
\textbf{Scheme 9}
\end{center}
Black and Arndtson reported that Cu(I) and Zn(II) can be used to form secondary propargylamides from aldehydes, silylamide, acid chlorides, and alkynes (steps 1 and 2), but when catalytic NaH was added to the reaction mixture, cyclisation to the oxazole was effected (Scheme 10).\textsuperscript{17}

\[ \text{R}^1 = \text{Ph, } p-\text{Tol, } t-\text{Bu.} \]
\[ \text{R}^2 = \text{Ph, Vinyl, } t-\text{Bu, } p-\text{IC}_\text{6}H_4. \]
\[ \text{R}^3 = \text{Ph, } n-\text{Bu, } \text{CH}_2\text{OTMS.} \]

**Scheme 10**

Bartoli et al. have published a rapid and efficient MW-assisted synthesis of oxazoles via the 5-\textit{exo}-dig cyclisation of functionalised \( N \)-propargyl carboxamides. After a variety of conditions were tested, it was observed that the addition of iodine to the reaction mixture gave higher selectivity and increased the yields: the resulting monomeric CeCl\(_3\)-\textit{H}_2\text{O}-NaI-I\(_2\) complex is a strong Lewis acid (Scheme 11).\textsuperscript{18}

\[ \text{R}^1 = \text{H, Ph, CO}_2\text{Et.} \]
\[ \text{R}^2 = \text{H, Me, Ph.} \]
\[ \text{R}^3 = \text{Ph, Me, furan, } \text{CH}_2\text{CO}_2\text{Et} \]

**Scheme 11**

Hacksell and Nilsson prepared oxazoles by the cyclisation of \( \alpha \)-arylsubstituted propargyl amides using either sodium hydride (0.3-0.4 equiv) in tetrahydrofuran (method A) or powdered potassium carbonate (10 equiv) in acetonitrile (method B) (Scheme 12).\textsuperscript{19}
The proposed mechanisms for the two methods are shown in Scheme 1. In mechanism A, the acetylenes rearrange to allenes and the central allenic carbon is attacked by the nucleophilic amide oxygen. In mechanism B, an acetylenic carbon is the electrophilic species. The authors stated that, the reaction is most likely going through mechanism A, because $^1$H NMR experiment demonstrated the presence of an allenic intermediate.

Buchwald and Cheung reported a method for the synthesis of 2,5-disubstituted oxazoles via a stepwise Cu-catalysed sequence amidation of vinyl halides to form enamides, followed by a
Cu-catalysed oxidative cyclisation of the enamide intermediate promoted by potassium persulfate under ambient conditions (Scheme 14).²⁰

\[
\begin{align*}
R^1 & \quad + \quad H_2N\text{C}O\text{R}^2 \quad \xrightarrow{\text{Cul (10-20 mol\%) \ DEAD (20-60 mol\%) \ K}_2\text{CO}_3, \text{THF, 70-80 °C}} \quad \text{CuBr}_2 (7.5-15 \text{ mol\%) \ Pyridine ligand (15-60 mol\%)} \\
R^1, R^2 & = \text{aryl, vinyl, alkyl, heteroaryl} \quad \text{X= Br, I} \\
\end{align*}
\]

Scheme 14

CuBr₂ most likely serves as a single-electron oxidant, converting the electron-rich enamide 12 to an enamide radical cation (Scheme 15, transformation i), which then cyclises to radical intermediate 13 (transformation ii). Subsequent oxidation of 13 by CuBr₂ provides the oxazole (transformation iii). The reduced form of copper, CuBr, is then oxidised by K₂S₂O₈ and reacts with TBAB to regenerate the CuBr₂ catalyst (transformation iv).

Scheme 15
Stahl and Wendlandt prepared 2,5-disubstituted oxazoles by the cyclisation of enamides. The reaction required 2 equivalents of CuCl$_2$ and 2 equivalents of N-methylimidazole (NMI) in 1,4-dioxane under air at 140 °C (Scheme 16).$^{21}$

![Scheme 16](image)

The authors speculated that this reaction involves initial Cu$^{II}$-mediated one electron oxidation of the enamide followed by loss of two protons and another electron to provide the oxazole product (Scheme 17).

![Scheme 17](image)

Wang and co-workers reported a one-pot method to prepare oxazoles, where CuI was used as catalyst (0.3 equiv), from benzylamine and benzil derivatives. The optimised conditions for the reaction required the addition of molecular sieves (4Å) and N,N-dimethylacetamide as solvent open to air at room temperature (Scheme 18).$^{22}$
Scheme 18

A plausible mechanism for the reaction is described as follows (Scheme 18): First, \( \text{O}_2 \) activates the Cu and \( \text{14} \) is formed from the condensation of benzyl and benzylamine. Enolisation provides \( \text{15} \) which undergoes an intramolecular cyclisation via the oxygen atom attacking the imine double bond to give the intermediate \( \text{16} \). After proton transfer, \( \text{17} \) is formed which is oxidised to \( \text{18} \) and the final product is released (Scheme 19).

Scheme 19

Strand and co-workers showed that the reaction between \( \text{N-benzylpropargylamines} \) and acid chlorides at elevated temperature (150 °C) using microwave irradiation can produce oxazole rings. This reaction required no solvent and just 15 minutes for complete conversion. Also, di-
and tri-substituted oxazoles can be prepared by using appropriate starting materials (Scheme 20).²³

![Chemical Reaction](image)

Scheme 20

The mechanism of this reaction is illustrated in Scheme 21. First, the amide is formed and the proton lost from the nitrogen adds to the alkyne which enables the attack of oxygen of the amide to form the unstable five membered ring. Then, the benzyl is lost by the attack of Cl⁻ and the alkene isomerises into the ring to provide the observed product.

![Mechanism Diagram](image)

Scheme 21

The Wang group has developed the first example of ZnI₂ and FeCl₃ promoted cyclisation of acetylenic amides to selectively achieve oxazolines and oxazoles respectively via a C-O bond formation (Scheme 22).²⁴
A mechanism was proposed for the formation of oxazolines (23) and oxazoles (26) (Scheme 23). First, ZnI₂ coordinates with the triple bond of 19 which enhances the electrophilicity of the alkyne. Tautomerisation of the amido-imido intermediate 20 followed by regioselective intramolecular 5-exo-dig cyclisation via 21 gave the vinyl zinc intermediate 22 which on protonolysis with HI generated in situ, resulted in desired compound 23. In mechanism B, iron(III) is thought to acts as a Lewis acid that promotes the 5-exo-dig cyclisation of compound 19 via 24 to provide intermediate 25. Tautomerisation of intermediate 25 resulted in the formation of the required oxazole derivative 26.
Larock and Waldo have reported that methyl oximes can be cyclised to oxazoles via an electrophilic cyclisation strategy. They used iodine monochloride (ICl) in DCM at room temperature to effect this transformation (Scheme 24).\textsuperscript{25}

\textbf{Scheme 24}

A possible mechanism was postulated as shown in Scheme 25. Coordination of the carbon-carbon triple bond to the ICl or attack of the iodine cation on the triple bond can produce an iodonium intermediate. Nucleophilic attack of the oxygen of the methoxy group on to the activated iodonium intermediate can generate a five membered ring. Finally, facile removal of the methyl group via S\textsubscript{N}2 displacement by the chloride anion present in the reaction mixture can generate the final product and one equivalent of MeCl.\textsuperscript{26}
Boshun Wan and his group have developed the base-catalysed cyclisation of N-sulfonyl propargylamides 27 to furnish various 5-(sulfonylmethyl)oxazoles 30. A number of bases were tested in an attempt to promote this process (PPh$_3$, Et$_3$N, DBU, DMAP, DABCO, LiOH, t-BuOLi, K$_2$CO$_3$, Na$_2$CO$_3$, Li$_2$CO$_3$, NaOAc, KOAc, CsOAc, K$_3$PO$_4$) in CH$_3$CN. Among all the bases tested, only DBU selectively afforded the oxazole 30 after 7 hours using N-sulfonyl propargylamides 27 (Scheme 26).$^{27}$

\[ R^1, R^2 = \text{Ar}, R^3 = \text{Ar, Me, cyclopropyl, cyclobutyl, OBn.} \]
All of the other bases tested gave a mixture of the allenes 28 and the oxazoles or did not catalyse this rearrangement at all. Following this, they have shown that treating N-sulfonyl propargylamides with DABCO in DCM produce the corresponding allenylamides in high yields, and then reaction with DBU provides the oxazoles (Scheme 27).

A mechanistic rationale is proposed for this transformation (Scheme 28). First, base-catalysed 1,3-proton migration results in the formation of allenylamides 28, followed by nucleophilic attack of the oxygen at the allenyl carbon to give a zwitterionic intermediate 29. Finally rearrangement to oxazole 30 occurs via 1,4-sulfonyl shift.
As a continuation of their interest in the cyclisation of $N$-sulfonyl propargylamides, the Wan group tried a previous set of conditions (140 °C in DMF) to cyclise $N$-sulfonylpropargylamides to obtain 4-sulfonylmethyloxazoles, but the reaction did not work (Scheme 29).\textsuperscript{28}

The major reason for this failure they attributed to the [3,3]-rearrangement of propargylamides not occurring under thermal conditions. To overcome this issue, they reasoned that activation of the alkyne moiety by a transition-metal catalyst (AgBF$_4$) might promote the rearrangement of the propargylamide. In addition, they used a directing group (acyloxy) for its potential ability to coordinate with the transition-metal catalyst (Scheme 30).
They used different phenyl ring substituents (both electron-withdrawing and electron-donating) and the oxazole rings were successfully obtained in good to excellent yields, but when alkyl substituents was used there was no product isolated.

The authors postulated a mechanism for this reaction (Scheme 31). The first step is a π-complex 32 formed between the alkyne moiety 31 and Ag(I) cation. The acyloxy group can also coordinate with Ag(I) to facilitate the subsequent transformation. Then, intramolecular nucleophilic attack of the carbonyl oxygen on to the amide via 6-endo-dig mode can lead to the formation of intermediate 33, which can collapse to allene intermediate 34. Then, nucleophilic attack of the nitrogen at the allenyl carbon can give zwitterionic intermediate 35 which can rearrange to oxazole 36 via a sulfonyl shift by either intra- or intermolecular manner.

**Scheme 30**
Inspired by the above proposed mechanism, propargylamide was converted into allenylamide. Then, the same conditions were applied to the allenylamide, but no 4-sulfonylmethyloxazole product was formed. Instead, 5-vinylloxazole was isolated. In this transformation, the allene moiety was proposed to be activated by the Ag(I) cation, followed by the intramolecular nucleophilic attack of the oxygen atom at the amide moiety (Scheme 32). Elimination of both the sulfonyl and acyloxy groups generated the final vinylloxazole product.
Another example of $N$-allenyl amides cyclisation has been presented by the Ma group. Here $N$-propargylamides were converted into $N$-allenyl amides in good to excellent yields with wide substrate scope using a Cy$_2$NH/CuI protocol (Scheme 33).\textsuperscript{29}

In order to cyclise these $N$-allenylamides, they used a palladium catalyst and an aryl iodide in the presence of K$_2$CO$_3$ and DMF as solvent to form the oxazolines (Scheme 34). The mechanism of this reaction is proposed to proceed through the oxidative addition of palladium(0) to the aryl iodide 38 to form the organopalladium species 39 (Scheme 35). Reaction with $N$-allenyl amides gives intermediate 40 and oxygen attacks the allene to form the five-membered ring 41. Reductive elimination forms the desired product 42 and regenerates palladium catalyst 37.
Wan and co-workers reported a method for the cyclisation of N-sulfonyl propargylamides. They applied two sets of conditions both using N-iodosuccinimide (1.2 equiv) as an iodine source. They ran the first reaction in DCM at 40 °C to obtain polyfunctionalised oxazolidines which incorporated the succinimide. Whereas, running the reaction in DMF at room temperature led to formation of iodoalkylidene dihydrooxazoles instead (Scheme 36).
A plausible mechanism for the above two iodocyclisation reactions is depicted in Scheme 37. The reaction is initiated by the coordination of propargylamide with I$^+$, thereby enhancing the electrophilicity of the alkyne moiety to generate intermediate 43. The activated triple bond then undergoes nucleophilic attack by the carbonyl oxygen to form intermediate 44 via a 5-exo-dig cyclisation mode. Two different pathways are followed in the next reaction step on the basis of the choice of solvents. In DCM, the succinimide anion attacks the more electrophilic carbon of the iminium ion to furnish the final product (oxazolidine). In contrast, the succinimide anion traps the tosyl group of intermediate 44 to give the desired product (dihydrooxazole) when the reaction is carried out in the more polar solvent DMF.
These authors went on to demonstrate that iodoalkylidene dihydrooxazoles converted to oxazoles in the presence of one atmosphere of dioxygen (Scheme 38). This is the first report of the oxidation of iodoalkylidene dihydrooxazoles to the corresponding oxazoles.

Scheme 38

The mechanism of this oxidation is shown in the next scheme. The radical intermediate 44 and an iodine radical are formed by homolytic cleavage of the C−I bond upon heating. Intermediate 44 can then quickly react with oxygen to give the peroxyl radical species 45.
which can be converted to the radical 46 via a six-membered-ring transition state. Radical 46 can also be represented as its resonance structure 47, which is aromatic. Cleavage of the O-O bond leads to formation of the final product. The combination of iodine radicals and hydroxyl radicals results in the formation of HIO, which can easily decompose into oxygen, iodine, and water.

![Scheme 39](image)

On the basis of the above result, they combined the formation and oxidation of iodoalkylidene dihydrooxazole in one pot by adding dioxygen after the NIS-triggered cyclisation of propargylamides. Thus, the two-step one-pot reaction was accomplished successfully (Scheme 40).

![Scheme 40](image)
Harmata and Huang stated that propargylic amides can be cyclised to 5-methylenooxazolines in high yield at room temperature with a catalytic amount of silver hexafluoroantimonate (Scheme 41).

\[
\text{Propargylic Amide} \quad \text{AgSbF}_6 (5 \text{ mol\%}) \quad \text{DCM, r.t, 5-10 min} \quad \text{Oxazoline}
\]

\[R^1, R^2 = H, \text{Me, Et} \quad R^3 = \text{Me, Et, } t\text{-Bu} \quad p\text{-NO}_2\text{Ph, Ph.}\]

Scheme 41

The possible mechanism of this reaction is shown in Scheme 42. In this reaction, cationic Ag(I) is thought to coordinate with the C-C triple bond. This activates it to intermolecular attack by the amide to afford the five membered ring intermediate. Finally, protonation of the C-Ag bond occurs to generate the product.

Scheme 42

Oxazoline can be formed by treating \(N\)-allylamide with PhI(OAc)_2 (PIDA) in AcOH/\(\text{Ac}_2\text{O}\) (5:1) at 50 °C. When the reaction was left overnight some conversion to oxazoline had occurred, but there was still some starting material. By adding BF\(_3\)·OEt\(_2\) (1.2 equiv) to the reaction mixture and conducting the reaction at room temperature, more starting material was converted to the product but full conversion was not achieved (Scheme 43).
The expected mechanism for this transformation is shown in Scheme 44. It was suggested that BF₃·OEt₂ first converts PIDA to the more electrophilic aryliodonium ion 49. Then, iodonium ion 49 can interact with the alkene in 48 to generate either an activated olefin complex (50a) or a cyclic iodonium ion (50b). When R₂ = H, attack by the amide in a 5-exo fashion affords primary alkyl iodonane 51. Because of the superior leaving group ability of the iodine(III) nucleus, the nucleophilic attack by a second nucleophile (in this case acetic acid) is quite favorable. This Sₐ2-like, bimolecular reductive elimination forms the oxazoline and liberates acetate and iodobenzene. The cyclisation reaction conditions were attempted with internal alkenes substrates, but these efforts resulted in complex product mixtures. As they stated, this is the result of the formation of carbocations via unimolecular reductive fragmentation of iodonane 51 (R₂ ≠ H). This again mentions the extreme leaving group ability of the iodine(III) nucleus. The authors stated that this mechanism is still under study.
Minakata’s group prepared oxazolines directly from unfunctionalised olefins and readily accessible amides using tert-butyl hypoiodite as a reagent in the presence of NaI and MeCN as solvent at room temperature (Scheme 45).³³

A mechanism was proposed for oxazoline formation with t-BuOI, generated in situ, initially reacting with the amide, not the olefin, to give the diiodinated amide. This occurs because a Lewis acid or UV light is known to be required for olefins to react with t-BuOI.³⁴ When benzamide in CD₃CN was treated with t-BuOCl and NaI, the ¹H NMR spectrum showed a signal corresponding to the active hydrogens on the amide nitrogen that smoothly disappeared
and a signal corresponding to the tert-butyl group of t-BuOH appeared within one hour. From the NMR study, the generation of 52 might be suggested but there is no clear evidence at present. The active species 52 might function as an iodonium source, which reacts with 3-hexene to generate the cyclic iodonium intermediate 53, followed by the addition of the counter amide anion, yielding adduct 54 which cyclised to oxazoline (Scheme 46).

![Scheme 46]

Wuts and co-workers obtained oxazolines by the cyclisation of amido alcohols using the Vilsmeier reagent in pyridine at room temperature. For most amido alcohol substrates they obtained both the desired oxazolines 55 as well as the chloride 56 (Scheme 47). Although an inconvenience, the chloride is readily converted to the oxazoline upon treatment with DBU.35
Zhdankin and co-workers have reported the first hypervalent iodine catalysed synthesis of isoxazoline derivatives using 3,5-Me₂C₆H₃I (0.2 equiv) as catalyst. Oxone (2KHSO₅.KHSO₄.K₂SO₄) (3 equiv) was used as the oxidant, and the solvent was a mixture of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and MeOH and a small amount of water (10:10:1). The addition of a small amount of water is needed to increase the solubility of Oxone in the reaction mixture. They used alkenes (1.2 equiv) and aldoximes (1 equiv) as starting materials to get isoxazolines in moderate to excellent yields (Scheme 48).³⁶

After alkenes were successfully used, the authors tried to use alkynes instead of alkenes and applied the same conditions. The reaction worked to give isoxazoles in moderate to good yields (Scheme 49).
The proposed mechanism for this reaction is shown in scheme 50. First, the reaction of ArI with Oxone in aqueous HFIP generates the activate hypervalent iodine species hydroxyl(aryl)iodonium ion ArI(OH)\(^+\) 57, which reacts with aldoxime 58 to give hypervalent iodine species 59 through ligand exchange. Reductive elimination of ArI is taking place to generate nitrile oxide 60 which reacts with the alkene 61 or alkyne 62 to provide the corresponding isoxazoline 63 or isoxazole 64. The addition of HFIP to the reaction mixture is believed to generate the highly reactive electron-deficient hypervalent species 57, which speeds up the subsequent steps in the catalytic cycle, such as ligand exchange and oxidation of the aldoxime.
The Jin group established an efficient copper-catalysed cyclisation (10 mol% CuI) of steroidal acylaminoacetylenes to give the corresponding 11β-aryl-17,17-spiro[(4′H,5′-methylene)oxazole]-substituted steroids in moderate to good yields (Scheme 51). According to the report, the authors did not propose a mechanism for this reaction.

The authors stated that the yield is dependent on the solvents used in the reaction. For example, when benzene at 80 °C was used just 30-35% product was isolated, but when they used a mixture of benzene and Et₃N (1:1) at 90 °C 83-97% yield was obtained in 30 min.
Lowering the temperature to 40 °C gave the product in only 30-46% yield even after 24 h reaction time. Also, they tried the reaction with DMF and DMSO as solvents but there was no conversion in either case.

Hashmi et al. have reported the cyclisation of nonterminal propargylic amides with a substituent on the propargyl group using gold(I) catalysis. They found that TMS protected propargylamine was the perfect building block for this approach. Then, they tested alkyl-substituted propargylic amides, which were synthesised by deprotonation of \( N,N \)-bis(trimethylsilyl)propargylamine with \( n \)-butyllithium and reaction with alkyl iodide to yield the substituted propargylamines \( 65 \). After the reaction with acid chloride, propargylic amide \( 66 \) was obtained. Then, the gold catalyst and silver salt in THF were added to the propargylic amide \( 66 \) to produce a mixture of alkylideneoxazoline \( 67 \) (12-78%) and 1,3-oxazine \( 68 \) (10-35%) (Scheme 52).\(^{38}\)

![Scheme 52](image)

The oxazine \( 68 \) is formed via a 6-endo-dig cyclisation (path A), whereas the oxazoline \( 67 \) originates from the 5-exo-dig cyclisation (path B) (Scheme 53).
Tungsten hexacarbonyl and molybdenum hexacarbonyl in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) have been used to cyclise N-propargyl amides to form oxazolines and oxazines (Scheme 54).
Mechanistically, the alkynyl functionality of the propargylic amides 69 is activated by coordination with the W and Mo catalysts to generate π–alkyne complex 70, which is in equilibrium with the vinylidene complex 71 (Scheme 55). Intramolecular nucleophilic attack of the carbonyl oxygen on the amide of intermediate 70 via 5-exo or 6-endo mode followed by the protonation of the corresponding carbene compounds 72 or 73 produces oxazoline 74 or oxazine 75.

The Zhu group reported a route where 3,4,5-trisubstituted oxazolones can be synthesised by the reaction of N-alkynyl tert-butylxycarbamates with aryl halides or related electrophiles. This reaction requires a catalytic amount of bis(dibenzylideneacetone)palladium(0) [Pd(dba)_2]
and ligand (PPh₃ or Xphos) in the presence of K₂CO₃ (1.5 equiv) in DMF at 70 °C (Scheme 56).³⁰

![Chemical Reaction Scheme]

**Scheme 56**

The mechanism of this reaction is illustrated in the next scheme. The palladium intermediate 76 formed by the oxidative addition of Pd(0) to the carbon-halide bond of R³X activates the alkyne to intramolecular attack to give palladium species 77. In the final step, cleavage of the C-O bond of the tert-butyloxy group in intermediate 78 as well as reductive elimination results in the generation of 3,4,5-trisubstituted oxazolones with reformation of the palladium catalyst.
Ramesh et al. studied the effect of various bases and solvents on the cyclisation of \( O \)-propargylcarbamates to 2-oxazolidinones, and they found that LiOH in DMF gave the best results (Scheme 58). Oxazolidinones have been found to have a large range of applications in organic synthesis as potential intermediates, as chiral auxiliaries, and in the preparation of organometallic reagents. Also derivatives have been shown to have antibacterial properties and hence these heterocyclic compounds are widely used in the pharmaceutical chemistry.\(^{41}\)

First, deprotonation occurs by LiOH (base) to leave a nucleophilic nitrogen, which attacks the triple bond and forms the five membered ring (Scheme 59).
Sanjaya and Chiba have reported the Cu-catalysed aminoacetoxylation of \( N \)-alkenylamidines to form imidazoles using PhI(OAc)\(_2\) as the oxygen source in the presence of a nitrogen ligand and a base. They examined several reaction conditions using different nitrogen ligands and bases, and found that using copper acetate Cu(OAc)\(_2\) (15 mol\%) and 1,10-phenanthroline (15 mol\%) with K\(_2\)PO\(_4\) (1 equiv) and DMF at room temperature provided the best yields (Scheme 60).°

Their proposed catalytic cycle for this aminoacetoxylation is outlined in Scheme 61. This process might be initiated by the formation of higher valent \( N \)-Cu(III) species 80 generated
from amidine 79, Cu(OAc)₂, and PhI(OAc)₂. The resulting N-Cu(III) species 80 undergoes 5-
*exo* aminocupration onto the alkenyl moiety to give organocopper(III) species 81. The
subsequent reaction of 81 with an acetate ion, probably via an S₂N₂ type substitution reaction,
forms the C-O bond to afford 4-acetoxymethyl-4,5-dihydroimidazole 82 along with CuOAc
83 that could maintain further catalytic turnover with PhI(OAc)₂.

\[
\begin{align*}
\text{R}^1 & \text{N} = \text{N} \quad \text{R}^3 \quad \text{R}^2 \\
\text{OAc} & \quad \text{AcO}^- \quad \text{AcO}^- \\
\end{align*}
\]

Scheme 61

The Wu group prepared imidazoles from propargyl amidines in excellent yields which were
obtained under mild conditions by gold(I) catalysis via 5-*exo*-dig cyclisation. They envisioned
that 2-fluoroalkyl imidazoles can be obtained in one pot from fluorinated imidoyl chlorides.
With Ph₃PAuCl/AgSbF₆ as the catalyst and CH₃CN as the solvent, an optimised yield of 89%
was obtained when the reaction was carried out at 60 °C (Scheme 62).
Upon amidation the cationic Au(I) is thought to coordinate with the C-C triple bond and activate it to attack by the amidinonyl nitrogen to afford intermediate 84. Affected by the R_f group, 84 isomerises to the more stable imidazole 85 by a 1,3 proton shift. Finally, protonation of the C-Au bond leads to formation of the final product (Scheme 63).

Scheme 62

Upon amidation the cationic Au(I) is thought to coordinate with the C-C triple bond and activate it to attack by the amidinonyl nitrogen to afford intermediate 84. Affected by the R_f group, 84 isomerises to the more stable imidazole 85 by a 1,3 proton shift. Finally, protonation of the C-Au bond leads to formation of the final product (Scheme 63).

Scheme 63

Peng and co-workers reported a copper-catalysed method for intramolecular N-arylation which provides the benzimidazole ring system. In this reaction, Cu_2O (5 mol%) was used as
the catalyst, $N,N'$-dimethylethylenediamine (DMEDA) (10 mol%) as the ligand, and $K_2CO_3$ as the base in water at 100 °C (Scheme 64).\(^{43}\)

\[
\begin{align*}
\text{Scheme 64} \\
\text{A proposed reaction mechanism for this intramolecular C-N bond formation from amidines to benzimidazole derivatives is shown in Scheme 65. This transformation presumably occurs through coordination of the imine functional group of amidine 86 to the Cu(I) centre followed by an intramolecular oxidative addition to the aryl halide, affording an intermediate complex 87. The resulting complex 87 can react with base to form a Cu-N bond and afford the intermediate complex 88. This can undergo reductive elimination to form the coupled product 89 and regenerate the catalytic copper species (path A). However, an alternative pathway via Cu-N bond formation in the first instance followed by oxidative addition cannot be completely ruled out (path B).}
\end{align*}
\]
Ishihara and co-workers have developed an efficient molybdenum oxide catalysed dehydrative cyclisation of serine, threonine, and cysteine derivatives, which gives oxazolines and thiazolines in good yields. In particular, (NH₄)₆Mo₇O₂₄·4H₂O and (NH₄)₂MoO₄ showed excellent catalytic activities for the dehydrative cyclisation of serine and threonine derivatives (Scheme 66). This method can be applied to a wide range of complex substrates because the reaction proceeds under neutral conditions. The authors state that mechanistic studies and the application of this method to the synthesis of more complex natural products are in progress.⁴⁴
Sanz-Cervera and co-workers reported a simple and efficient method to prepare 1,3-oxazoles and 1,3-thiazoles using α-amido-β-ketoesters as starting materials (Scheme 67). This reaction was performed by treating the α-amido-β-ketoesters with triphenylphosphine, Ph₃P, in the presence of iodine and triethylamine in dichloromethane at room temperature to give 2,5-disubstituted oxazoles. Finally, the deprotection of the ester in position 4 of the oxazole ring through palladium-catalysed hydrogenolysis or hydrolysis with LiOH in THF/H₂O gave the final oxazole compounds.

![Reaction Scheme 67](image)

**Scheme 67**

Thiazoles are obtained from the same α-amido-β-ketoesters by reaction with Lawesson’s reagent in THF to produce 2,5-disubstituted thiazoles. Then the deprotection of the ester in position 4 of the thiazoles ring through palladium-catalysed hydrogenolysis or hydrolysis with LiOH in THF/H₂O gave the final thiazole compounds (Scheme 68).

![Reaction Scheme 68](image)

**Scheme 68**
Batey and Evindar have reported that the copper-catalysed cyclisation of *ortho*-haloanilides is a generally applicable approach to benzoxazole ring formation. A reaction using 5 mol% of copper(I) iodide could be achieved with either 1,10-phenanthroline or *N,N*-dimethylethylenediamine as ligands, but 1,10-phenanthroline in general, showed greater substrate tolerance. The approach is readily applied to the synthesis of substituted benzoxazoles through incorporation of appropriately positioned substituents on the *ortho*-haloanilide precursors. The reaction could also be adapted for benzothiazole formation using thioamide substrates (Scheme 69).

![Scheme 69](image)

The most likely mechanism for the reaction involves the coordination of the amide group of 90 with 91 to give 92, followed by an oxidative insertion to generate 93, and then a reductive elimination to release product 95 with concomitant regeneration of 91. The initial coordination to copper in 92 is supported by the lack of reactivity of the halo substituents at other positions in the ring under the copper catalysed conditions. The authors previous study on benzimidazole formation revealed similar selectivity for the copper-catalysed reactions, whereas the use of palladium catalysis led to competing debromination. The chelating 1,10-phenanthroline ligand may serve to avoid multiple coordination of Cu by the amide substrate in 94 (Scheme 70).
Batey and Joyce have established a Pd/Mn based catalyst system for 2-aminobenzothiazole formation via an oxidative C-H functionalisation (Scheme 71). They used tetrakis(triphenylphosphine)palladium(0) \([\text{Pd(PPh}_3\text{)}_4]\) as catalyst and manganese dioxide \((\text{MnO}_2)\) as co-oxidant under an oxygen atmosphere.\(^{48}\)

The mechanism of this cyclisation is still not fully understood, but they proposed a mechanism which suggests that a \(\sigma\)-bond metathesis mechanism occurs, wherein an anionic peroxy/peroxide-Pd bound ligand aids in proton abstraction (Scheme 72).
Bose and Idrees have reported a first preparation of benzothiazoles from thioformanilides by using Dess-Martin periodinane (DMP). This reaction is a one step process occurring in DCM at room temperature within 15 minutes (Scheme 73).\textsuperscript{49}

They proposed a plausible mechanism for this Dess-Martin periodinane promoted cyclisation reaction (Scheme 74). Arylthioformanilide \textbf{96} can exist as thioiminol \textbf{97}; the latter reacts with DMP to produce thyl radical \textbf{98} while iodine(V) is reduced to iodine(IV) at the same time. Subsequently, 1,5-homolytic radical cyclisation of \textbf{98} followed by aromatisation of radical \textbf{99} gives 2-arylbenzothiazole \textbf{100}. 
Previous work in the Moran group on the formation of carbocycles has shown that iodobenzene can catalyse the cyclisation of δ-alkynyl β-ketoesters under oxidative conditions to generate cyclopentane rings with high diastereoselectivity (Scheme 75). Under these conditions, iodobenzene is oxidised to an iodine(III) species which mediates this reaction. The products contain adjacent quaternary and tertiary stereocentres which are otherwise difficult to prepare.\textsuperscript{50}

Table 1 shows the derivatives which have been cyclised under these reaction conditions. The methyl and isopropyl ester derivatives of ethyl ester were cyclised, and the former resulted in a slightly diminished yield (entry 1, 54\%- entry 2, 61\%) whereas the latter only provided 37\% yield (entries 1 and 3 vs 2). More importantly, the presence of the isopropyl ester reduced the diastereomeric ratio from 14:1 to 5:1. The increased steric bulk of the isopropyl ester is presumed to make the cyclisation event more difficult and reduce the facial selectivity. The
success of the cyclisation reaction was also found to be dependent on the alkyne substituent, with alkyl substituted benzene derivatives cyclising in low yield but with superior diastereoselectivity (>20:1 dr) (entries 4 and 5). However, the p-chlorobenzene substrate cyclised in a superior 88% yield with 14:1 dr (entry 6).

A substrate with an ethyl ketone substituent cyclized in a diminished yield and diastereoselectivity (entry 7). Substrates bearing p-nitrophenyl or p-methoxyphenyl substituted alkynes cyclised in only trace amounts. The reason for this is unknown.
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield/%</th>
<th>dr</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>54</td>
<td>14:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>61</td>
<td>14:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>37</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>25</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
Two plausible mechanisms are proposed for this cyclisation (Scheme 76). Both involve oxidation of the iodobenzene to a phenyliodine(III) species, which then either coordinates to the alkyne of the substrate (pathway A) or forms a ketoester α-I(III) species (pathway B). The former can then undergo intramolecular cyclisation to form a cyclopentane ring and vinyliodine(III) moiety II. Alternatively, the latter can undergo alkyne insertion to generate II. This species loses iodobenzene, thus regenerating the catalyst, and producing a vinylic
carbocation. This is trapped by water, and the resulting enol tautomerises to the observed tricarbonyl compound.

Scheme 76
Aims and objectives:

The overall aim of this project is to develop iodoarene catalysed methods to prepare heterocycles.

Objective 1: To develop intramolecular amide-alkyne cyclisation reactions.

Objective 2: To develop intramolecular amide-alkene cyclisation reactions.
Results and discussion:

Building on the previous work using in-situ generated iodine(III) species to induce alkyne cyclisation processes (Scheme 75), the aim was to prepare alkynes bearing a pendant amide group and study the cyclisation of these compounds (Figure 2).

As shown, two possible amide isomers were envisaged, however the investigation commenced with amides derived from propargyl amine. In this way, it was surmised that oxazoline derivatives would be prepared. Accordingly, N-(prop-2-yn-1-yl)benzamide 101 was prepared from propargyl amine using a known procedure,\textsuperscript{51} and then N-(3-phenylprop-2-yn-1-yl)benzamide (102) was synthesised from that amide through Sonogashira coupling using standard conditions (Scheme 77).\textsuperscript{52}
The yield of isolated product was very low; however enough of compound 102 was in hand to attempt the desired cyclisation. In addition, it was assumed that modification of the Sonogashira coupling conditions would lead to superior yields in this process. In the event, treatment of amide 102 with the previously developed conditions did indeed lead to the desired ring formation (Scheme 78). Unfortunately, just 11% yield of isolated dihydrooxazole 103 was obtained.

In an attempt to increase the yield of dihydrooxazole produced, a different iodoarene catalyst 2,2'-diiodo-4,4',6,6'-tetramethylbiphenyl was prepared according to the method of Kita (Scheme 79).\(^{53}\) 5-Iodo-\(m\)-xylene was used as the starting material, which was treated with
PIFA (1 equiv) in the presence of BF$_3$.Et$_2$O (2 equiv) at -78 °C. This compound has been shown to be a superior catalyst for the cyclisation of aryl alkynes and gives better yields compared to PhI (82% compared with 37%) (Scheme 80).

![Scheme 79](image)

With this new biphenyl catalyst in hand, the cyclisation reaction was attempted again. This time a superior 33% yield was obtained, however the dihydrooxazole was not formed in this case. Instead, oxazole 105 was formed. In both of these reactions, the remainder of the mass balance was unreacted starting material (Scheme 81).
The reason for the over-oxidation to the aromatic heterocycle is unclear, however pleased with this proof of concept we decided to prepare a second substrate for investigation. Accordingly, N-(2,2-dimethylpropyne)benzamide (106a) was prepared from the commercially available amine in an analogous fashion to amide 101 (Scheme 82).

![Scheme 82](image)

Upon subjecting amide 106a to the previously employed Sonogashira reaction conditions, it was observed that none of the expected coupled product was formed (Scheme 83).

![Scheme 83](image)
In the $^1$H NMR spectrum were two doublets at 4.25 and 4.74 ppm respectively and these cannot be due to the expected product or the starting material. After further investigations, 4,4-dimethyl-5-methylene-2-phenyl-4,5-dihydro-oxazole (107a) was accepted as the product from this reaction but in low yield (20%). Note that the phenyl group from iodobenzene is not incorporated in to the product.

Surprised and delighted by this unexpected reactivity, we decided to investigate this process in order to develop optimised conditions. The first question to answer was which metal salt was responsible for the cyclisation: Cu or Pd. Running the reaction with Pd(PPh$_3$)$_4$ but no CuI led to no product being formed. Eventually it was found that 10 mol% CuI in DCM at room temperature led to oxazoline formation providing 107a in 73% yield (Scheme 84).

![Scheme 84](image)

In order to ascertain the effect of using different metal salts on this cyclisation, different catalysts were used instead of CuI. In the event, all of the copper and silver catalysts worked very well (Table 2). Stoichiometric quantities of sodium iodide and potassium t-butoxide were also tested and about 20% yield was obtained in both cases. However, it was decided to continue with CuI as it is cheap and easy to handle.
With these optimised conditions in hand, various benzamide derivatives were prepared in order to investigate their cyclisations. Amides 106b, 106c, 106d were prepared in good yields, from the amines and acid chlorides as before (Scheme 85). Also, amides with cyclohexyl substrates were synthesised (106e, 106f, 106g, 106h) from the commercially available propargyl amines (Scheme 86).[^56]

---

[^56]: 106b, 106c, 106d, 106e, 106f, 106g, 106h

---

Table 2 (a) yield determined by $^1$H NMR analysis of the amide reaction mixture, (b) 1 equiv was used.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield/%$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgOAc</td>
<td>99</td>
</tr>
<tr>
<td>Cu(OAc)$_2$</td>
<td>99</td>
</tr>
<tr>
<td>Cu(OTf)$_2$</td>
<td>99</td>
</tr>
<tr>
<td>KOrBu$^b$</td>
<td>18</td>
</tr>
<tr>
<td>Na$I^b$</td>
<td>20</td>
</tr>
<tr>
<td>CuSO$_4$</td>
<td>99</td>
</tr>
<tr>
<td>CuCl</td>
<td>99</td>
</tr>
</tbody>
</table>

---

**Scheme 85**

Ar = p-Cl-C$_6$H$_4$, 106b, 92%.
Ar = p-OMe-C$_6$H$_4$, 106c, 99%.
Ar = p-NO$_2$-C$_6$H$_4$, 106d, 39%.
These amides were subjected to the developed reaction conditions and the five membered rings were formed in low yields (20-45%). It was decided to switch to DCE as the solvent so that reactions could be heated at 80 °C. Under these more forcing conditions, the cyclisations worked well and in higher yields (82-93%) (table 3).

Scheme 86
<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="106b" /></td>
<td><img src="image" alt="107b" /></td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="106c" /></td>
<td><img src="image" alt="107c" /></td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="106d" /></td>
<td><img src="image" alt="107d" /></td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="106e" /></td>
<td><img src="image" alt="107e" /></td>
<td>91</td>
</tr>
</tbody>
</table>
The reaction worked with electron-withdrawing and electron-donating aromatic substituents. However, the former generally took longer to react (up to 48 hours to reach completion for nitro substituents entries 3 and 7).

In order to expand the substrates scope, heteroaromatic amides (106i to 106l) were prepared in an analogous fashion to the phenyl derivatives and in good yields (Scheme 87).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image" alt="106f" /></td>
<td><img src="image" alt="107f" /></td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="106g" /></td>
<td><img src="image" alt="107g" /></td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="106h" /></td>
<td><img src="image" alt="107h" /></td>
<td>76</td>
</tr>
</tbody>
</table>

Table 3
These indole, thiophene and furan derivatives were tested as starting materials using our standard reaction conditions. Thankfully, cyclisation was successful and the oxazoline rings were obtained in good yields (Scheme 88).

Surprisingly, when \(N\)-(2-methylbut-3-yn-2-yl)-2-(thiophen-2-yl)acetamide \textbf{106k} was subjected to the reaction conditions two new compounds were obtained (Scheme 89) in a ratio
of 2:1 (107k, 107k\textsuperscript{`}). However, this reaction had been left for longer than standard (72 h instead of 24 h), and it seemed likely that the expected product 107k had been oxidised under the reaction conditions to generate the new compound 107k\textsuperscript{`}. Therefore, the reaction was repeated and stopped after 24h. In this case, 107k was obtained as the only product in 72% yield.

Intrigued by this methylene oxidation process, we decided to investigate this formation. To see if CuI was responsible for the ketone formation, two reactions were carried out with 107k. The first reaction was with CuI and the second reaction was without CuI. Both reactions were performed in DCE at 80 °C (Scheme 90). Analysis of the reaction mixtures showed that the oxidation only occurred in the reaction which contained CuI.
To test the generality of this process \(N\)-(2-methylbut-3-yn-2-yl)-2-phenylacetamide 106m was prepared from phenylacetic acid and 1,1-dimethylpropargyl amine \textit{via} the acid chloride (Scheme 91).

The cyclisation of 106m was attempted with our standard conditions. In this case, intermediate 107m‘ could not be isolated, and the oxidised product 107m was formed in 71% yield (Scheme 92).
The CuCl-catalysed oxidation of diarylmethanes to benzophenones has been reported however an oxygen atmosphere and a dioxyl radical mediating agent was necessary for efficient conversion (Scheme 93).  

![Chemical Structure]

2,2',3,3',5,5'-Hexaphenyl-(1,1'-biphenyl)-4,4'-diol (HPBP)

Scheme 93

To further explore the substrate scope of the cyclisation, 1-(phenylethynyl)cyclohexan-1-amine 108 was prepared from 1-ethynylcyclohexan-1-amine through Sonogashira coupling using standard conditions. Then, this amine was converted to the amide using standard conditions to give 109 in 89% (Scheme 94).

![Chemical Structures]

Scheme 94

The cyclisation of this substrate was attempted using our conditions (Scheme 95), but there was no product obtained according to $^1$H NMR analysis. This result suggests that starting materials containing an internal alkyne do not undergo cyclisation using these conditions.
One possible mechanism of this reaction is shown in Scheme 96. In this case, cationic Cu(I) coordinates with the C-C triple bond to activate it to nucleophilic attack. Then, cyclisation can occur by attack of the C-C triple bond by the amide oxygen to afford the five membered ring intermediate upon loss of a proton. Finally, protonation can occur to generate the final product.

In order to obtain evidence for the above mechanism, 106a was treated with D$_2$O in the presence of K$_2$CO$_3$ in MeCN to prepare the corresponding deuterium substrate (Scheme 97). The D incorporation was 93% at alkyne and 94% at the amide.
The deuterated compound was treated with HCl in order to dedeuterate the amide and protonate it. The target deuterated compound 106n was synthesised in 66% yield (Scheme 98).

\[
\begin{align*}
\text{D} & \xrightarrow{\text{HCl (0.5 M)}} \text{D} \\
\text{H} & \xrightarrow{\text{Ph}} \text{H} \\
\text{106n, 66\%}
\end{align*}
\]

**Scheme 98**

When $^{13}$C NMR was run there was no signal for the two alkyne carbons but when HMBC NMR experiment was run a coupling could be seen between methyl carbon and the alkyne carbon (around 86 ppm) which is closer to it (as shown in the diagram). These carbon signals are known to be weak due to D splitting.$^{58}$

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{O}} \text{N} \\
\text{D} & \xrightarrow{\text{NOe (HMBC)}} \text{D} \\
\text{NMR}
\end{align*}
\]

**Figure 3**

106n was subjected to the standard reaction conditions with CuI in DCE, which led to formation of the five membered ring (Scheme 99). In the event, three compounds were observed by $^1$H NMR analysis of the crude reaction mixture in a 3 : 1 : 1 ratio. The major product was 107a with the two mono-deuterated compounds 107na and 107nb formed in equal and minor amounts.
The product mixture obtained from the deuterium labelling experiment could not be resolved with pure components. However, $^1$H NMR spectroscopy revealed a pair of mutually coupled doublets ($J = 2.9$ Hz) of $\delta = 4.26$ ppm and $\delta = 4.74$ ppm referred to the non-deuterated product 107a (Figure 3). At slightly high field than each of the forgoing doublets was a less intent singlet which was presumed to arise from each of the mono-deuterated species 107na and 107nb.

These results along with the inability of 109 to cyclise led us to postulate that the mechanism proceeds through formation of a copper acetylide followed by cyclisation, proton transfer and protonation to regenerate the Cu(I) catalyst (Scheme 100).
The Cu-catalysed azide alkyne cycloaddition reaction (click reaction) is believed to proceed through copper acetylde formation and cyclisation. However, we cannot completely rule out the alternative mechanism of the Cu(I) catalyst activating the alkyne for cyclisation with the CuI also causing H/D scrambling before cyclisation. Our attempts to alkylate the Cu intermediates with iodomethane or allyl bromide were unsuccessful.

To further investigate the substrate scope and the structural requirements for cyclisation three more compounds were prepared from propargyl amines and acid chlorides (101, 106o, 106p) (Scheme 101)
These compounds were tested as starting materials using our standard reaction conditions in order to cyclise them but without success (Scheme 102).
In order to develop a general route to prepare more substituted amides for use in this cyclisation, we took inspiration from the method reported by Larsen and co-workers (Scheme 103). In this case terminal alkynes, aldehydes and amines were combined under Cu catalysis to generate propargyl amine products. However, the use of amides as the nitrogen component is unknown, and this is what we required for our reaction.
The mechanism of this reaction is shown in Scheme 104. First, copper coordinates to alkyne 110 to form π-complex 111, this increases the acidity of the acetylenic hydrogen which is removed by the amine (or more probably by the hemiaminal intermediate resulting from the reaction between the amine 112 and the aldehyde 113) to give copper acetylide 114. The proton assisted condensation between the amine 112 and the aldehyde 113 generates a molecule of water and the iminium complex 115, which reacts with the copper acetylide 114 to afford the desired propargylamine 116 and regenerate the Cu(OTf)$_2$ catalyst.
Accordingly, we began by mixing benzamide with benzaldehyde and phenylacetylene along with Cu(OTf)₂ in order to prepare \(N\)-(1,3-diphenylprop-2-yn-1-yl)benzamide (Scheme 105). However, when the \(^1\)H NMR spectrum of the crude reaction mixture was obtained there were no signals matching the expected compound. Instead, a mixture of two compounds was evident which were separated by column chromatography and identified as 117 and 118 in 42% and 45% yields respectively.
Product 117 was suspected to be the result of the reaction between benzaldehyde with phenylacetylene, which is a known process. To confirm this hypothesis, we ran the reaction using just these two starting materials and E-chalcone was indeed formed (Scheme 106).

![Scheme 105](image)

Subsequently, attempts were made to convert 117 to 118 by treatment with benzamide under Cu catalyst conditions, but no reaction was evident. Therefore, it was presumed that an alternative pathway was necessary for formation of 118. In an attempt to optimise reaction conditions to prepare 118 selectively we ran several reactions with various catalysts and solvents (table 4).
We ran 14 reactions using different catalysts and solvents (Table 4). Different Cu and Ag salts were used with the same conditions but none of them led to product formation (entries 1-5).

Then, bismuth and caesium catalysts were tested (entries 6 and 7), but no product was
obtained. Different Brönsted acids were then tested using the same conditions (entries 8-10), and with TFA in different solvents (entries 11 and 12), but unfortunately none of these conditions worked. The reaction was attempted again with Cu(OTf)$_2$ as catalyst but using DMSO (entry 13) and DCE (entry 14) as solvents, but unfortunately only the latter set of conditions worked giving the same compounds but in lower yields compared to the original. At this point, the study of this process was abandoned.

In a further attempt to increase the substrate scope of our CuI-catalysed cyclisation, we decided to prepare the thioamide derivatives of some of the amides we had with the intention of cyclising these. However, when 106a was reacted with Lawesson’s reagent in toluene,$^63$ 4,4-dimethyl-5-methylene-2-phenyl-thiazole (119a) was obtained directly without requirement for any catalyst. The same conditions were applied to some other benzamides and heterocycles 119b and 119c were isolated (Scheme 107).

![Scheme 107](image)

In a further attempt to isolate the thioamide analogue, tetraphosphorus decasulfide in pyridine (P$_4$S$_{10}$ in pyridine) was prepared (Scheme 108),$^64$ and added to 106a but no reaction took place.
The proposed mechanism of the cyclisation with Lawesson’s reagent which is in equilibrium with a more reactive dithiophosphine ylide in solution is shown below (Scheme 109). The reaction with a carbonyl gives rise to a thiaoxaphosphetane intermediate. The driving force is the formation of a stable P=O bond in a cycloreversion step that resembles a portion of the mechanism known for the Wittig reaction. Then the cyclisation occurs to give the final product.
In an attempt to convert the alkene to an alkane hydrogenation of 107e was attempted using Pd/C as catalyst under a hydrogen gas atmosphere (Scheme 110). However, instead of the expected product, ring opened 120 was isolated in 53% yield.

Scheme 110

The proposed mechanism of this reaction is shown in Scheme 111. The first step is hydro-palladation of the alkene to form intermediate 121 followed by β-O elimination to give intermediate 122. Reductive elimination of intermediate 122 and then tautomerisation provides intermediate 124. Then, hydro-palladation can take place again to form intermediate 125 followed by reductive elimination to afford product 120.
The cyclisation of amide 106a using other sources of iodine was also considered.

Consequently, 106a was reacted with NIS (N-iodosuccinimide) and 5-(iodomethylene)-4,4-dimethyl-2-phenyl-4,5-dihydrooxazole 126 was formed in excellent yield (Scheme 112).

However, it was decided not to continue this avenue of research.
Satisfied with the mixed success obtained with the alkyne substrates, the development of catalytic conditions for the cyclisation of related alkene substrates was envisaged using *in-situ* generated iodine(III) species (Scheme 113). In this case, the corresponding alcohol would be formed.

![Scheme 113](image_url)

Catalytic hypervalent iodine reactions with alkene substrates are rare, perhaps due to the ease of oxidation of alkenes. For example, Fujita and co-workers reported that the use of iodosylbenzene (PhIO) and BF$_3$.OEt$_2$ with carboxylate starting materials provided a mixture of tetrahydrofurans (49%) and ketones (14%) (Scheme 114).\(^65\)

![Scheme 114](image_url)

Repeating this reaction with a chiral catalyst, which was prepared by the reaction of 2-iodophenol with methyl lactate, resulted in just the furan ring product being formed. Importantly, an 18:82 e.r. was obtained with this catalyst (Scheme 115).\(^66\)
Another recent example employed N-allylamide as the starting material. This was successfully cyclised to the oxazoline ring using PhI(OAc)₂ (PIDA) in AcOH/Ac₂O (5:1) but required the addition of BF₃·OEt₂ (1.2 equiv) for the best result (Scheme 116). Only terminal alkenes were cyclised in this report and only five membered rings were formed.⁶⁷

Previous work and unpublished in the Moran group has led to the development of reaction conditions to cyclise alkene substrates using PhI as the catalyst and Selectfluor as the oxidant in the presence of TFA in MeCN at room temperature (Scheme 117).
With a desire to develop catalytic conditions for the cyclisation of allylamides, N-allylbenzamide 127a was prepared from commercially available allylamine in an analogous fashion to the previous amide (Scheme 118).

Scheme 118

With 127a in hand, the cyclisation was attempted using PhI (0.2 equiv), TFA (2 equiv) and Selectfluor (2 equiv) in MeCN. Excitingly, the expected product (2-phenyl-4,5-dihydrooxazol-5-yl)methanol 128a was obtained but in just 6% yield (table 5 entry 1). It has been found that the work up for this reaction is crucial to obtain the alcohol product. In the workup, NaOH (1M) is added to the reaction mixture which is then extracted with DCM. In order to try to increase the yield above 6%, different iodoarene catalysts were used instead of iodobenzene. Accordingly, when 3-iodoanisole was used the yield was increased up to 9% (entry 2) and the yield was doubled to 13% when 5-iodo-\textit{m}-xylene was used (entry 3).

However, using 2-iodoanisole the yield was raised to a much more satisfactory 62% (entry 4). Then the effect of changing the oxidant was investigated, so \textit{m}-CPBA was used and Oxone but no product was obtained in either case (entries 5, 6 and 7). We ran a reaction without any
iodoarene catalyst to see if Selectfluor was itself responsible for cyclisation but the starting material was recovered unconverted (entry 8).

![Chemical structure](image)

Table 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArI</th>
<th>Oxidant</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI</td>
<td>Selectfluor</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>3-iodoanisole</td>
<td>Selectfluor</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>5-iodo-(m)-xylene</td>
<td>Selectfluor</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>2-iodoanisole</td>
<td>Selectfluor</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>2-iodoanisole</td>
<td>(m)-CPBA</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2-iodoanisole</td>
<td>Oxone</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>PhI</td>
<td>(m)-CPBA</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Selectfluor</td>
<td>-</td>
</tr>
</tbody>
</table>

Following this success, various allylamine derivatives \(127b-127h\) were produced in similar fashion (Scheme 119).

![Scheme 119](image)

Scheme 119

With these substrates in hand, the cyclisation was attempted and the reaction worked with electron-withdrawing and electron-donating aromatic substituents (table 6 entries 1-3). The furan substrate was cyclised in 79% to provide the interesting biheterocyclic compound \(128e\) (entry 4). As discussed above, the cyclisation of di, tri and tetra-substituted alkenes was an
important goal in this project. Therefore, the reaction was attempted using 1,1-disubstituted alkene 127f to provide product 128f in 81% (entry 5). However, the cyclisation of tri-substituted alkene and a furan did not work (entries 6 and 7).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield/%</th>
<th>product</th>
<th>yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>127b</td>
<td>90</td>
<td>128b</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>127c</td>
<td>66</td>
<td>128c</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>127d</td>
<td>99</td>
<td>128d</td>
<td>64</td>
</tr>
</tbody>
</table>
Table 6

*O*-Toluic acid and phenylacetic acid were converted to amides **129a** and **129b** through this route (Scheme 120). Then, the cyclisation reaction was attempted to cyclise these amides to the corresponding rings. In the event, the reaction worked with **129a** to provide compound **130** in 72% (Scheme 121), however the cyclisation conditions failed with amide **129b**.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield/%</th>
<th>product</th>
<th>yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="127e" /></td>
<td>93</td>
<td><img src="image" alt="128e" /></td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="127f" /></td>
<td>90</td>
<td><img src="image" alt="128f" /></td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="127g" /></td>
<td>83</td>
<td>no desired product</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="127h" /></td>
<td>86</td>
<td>no desired product</td>
<td>-</td>
</tr>
</tbody>
</table>
Compound 131 was prepared through the esterification of cis-2-amino-3-cyclopentene-1-carboxylic acid hydrochloride, followed by amidation using 4-methoxybenzoyl chloride to provide the amide product in 81% yield. Then, the cyclisation reaction was attempted using our standard conditions to give product 132 in 53% (Scheme 122). We were pleased to find that only one diastereomer of product was evident in the NMR spectrum to the crude reaction mixture.
Amide 133 was prepared from α-methylstyrene through four steps. The first step was 2-methylallylbromide synthesis by the reaction of α-methylstyrene with N-bromosuccinimide in CCl₄ under reflux.⁶⁹ (3-bromoprop-1-en-2-yl)benzene was treated with phthalimide and K₂CO₃ in DMF at 60 °C to provide the phthalimide compound, which was cleaved by hydrazine hydrate in petroleum ether (40-60 °C) to obtain the free amine. The amine was converted to the amide by addition of the acid chloride to provide the product in 69% yield. Finally, the cyclisation reaction was attempted using our conditions but no reaction occurred and the starting material was lost (Scheme 123). The presence of the phenyl group, presumably, changes the electronics of the alkene such that cyclisation becomes unfavourable.
Also, amide 134 was readily prepared from the amine, however when the cyclisation reaction was attempted using our conditions there was no product obtained and the starting material was destroyed (Scheme 124). It is unclear as to what happened but the presence of the second alkene moiety must be incompatible with the reaction conditions.
Muñiz and co-workers recently reported a method, where indole derivatives can be synthesised through hypervalent iodine(III) mediated oxidation of 2-vinyl anilines. They tested different aryl iodine reagents [PhI(OAc)$_2$, PIFA, Ph(OH)(OTs), PhIO] to find that, using PhIO (1.1 equiv) and 2,4,6-triisopropylbenzenesulfonic acid as oxidant in chloroform at room temperature gave the best yield (Scheme 125). They demonstrated that the reaction is successful for a range of substituted anilines.
Based on this report, it was proposed to test our cyclisation conditions with this substrate to determine whether either the indole ring or oxazine ring would form (Scheme 126).

Accordingly, we prepared \( N \)-(2-vinylphenyl)benzamide 135 from 2-vinylaniline in 84% yield (Scheme 127).\(^7\)

![Scheme 126]

Then, the cyclisation reaction of 135 was attempted using our standard conditions. Unfortunately, there was no sign of either oxazoline or indole ring by \(^1\)H NMR analysis of the crude mixture, and we recovered the starting material.

The proposed mechanism for our catalytic cyclisation reaction is shown in Scheme 128. Initially, 2-iodoanisole must be oxidised to an iodine(III) species, which activates the double bond to attack from the amide oxygen. This leads to five membered ring formation. Then, the iodine(III) must be displaced by TFA or a trifluoroacetate anion to form an unstable product, which by base work up is converted to the stable final compound.
In order to extend the scope of the reaction to include the formation of larger ring sizes, syntheses of homopropargyl amides, bishomopropargyl amides etc. were required. Another member of the Moran group (Somaia Kamouka) prepared homopropargyl amides in an analogous fashion to the above and these cyclised to oxazin in good yields (Scheme 129). However, bishomopropargyl amines are not commercially available and a new synthetic approach was required.

Scheme 128

In order to extend the scope of the reaction to include the formation of larger ring sizes, syntheses of homopropargyl amides, bishomopropargyl amides etc. were required. Another member of the Moran group (Somaia Kamouka) prepared homopropargyl amides in an analogous fashion to the above and these cyclised to oxazin in good yields (Scheme 129). However, bishomopropargyl amines are not commercially available and a new synthetic approach was required.
According to Trudell and Apsunde’s report, primary alcohols can be reacted with primary amines in the presence of an iridium catalyst using microwave irradiation to form amides (Scheme 130). We wanted to use this method in order to prepare longer chain starting materials.

The proposed mechanism of this reaction is showed in Scheme 131. The first step of the reaction involves catalytic oxidation of the alcohol to the corresponding ketone \( \text{138} \) and iridium hydride \( \text{137} \). Intermediate \( \text{138} \) reacts with the primary amide to afford amide \( \text{139} \). Then the addition of the iridium hydride \( \text{137} \) to the C=N bond of \( \text{139} \) can occur to give an amido iridium species \( \text{140} \). This species \( \text{140} \) can react with an alcohol to give the product \( \text{141} \) and regenerate the alkoxo iridium complex \( \text{136} \).
Accordingly, we mixed 4-methylbenzamide (1 equiv) and 5-hexen-1-ol (3 equiv) under the reaction conditions, but unfortunately there was no sign of the desired product in the crude reaction mixture (Scheme 132). The original report did not include examples of alcohols with alkenes or alkynes in them. Possibly this is the limitation of this method.

Moving forwards, we decided to follow a longer, but more precedented, synthetic sequence to prepare the desired compound (Scheme 133). In this method, they used an alcohol (1 equiv) as the starting material and reacted with phthalimide, triphenylphosphine (PPh₃) and
diisopropyl azodicarboxylate (DIAD) in THF to provide the phthalimide product. This was
cleaved to form the amine by adding hydrazine hydrate.

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{PPh}_3, \text{DIAD} & \quad \text{THF} \\
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{NNH}_2 & \quad \text{n} &= 1, 75\% \\
& \quad \text{n} &= 2, 95\% \\
& \quad \text{n} &= 1, 15\% \\
& \quad \text{n} &= 2, 60\%
\end{align*}
\]

**Scheme 133**

We used the same alcohols which they used in this procedure (4-penten-1-ol and 4-hexen-1-
ol) and the corresponding phthalimides were successfully obtained. However, when these
phthalimides were reacted with hydrazine hydrate, there was no sign of the desired amines in
the crude reaction mixture and the phthalimide compounds were not recovered (Scheme 134).

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{PPh}_3, \text{DIAD} & \quad \text{THF} \\
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{NNH}_2 & \quad \text{n} &= 1, 75\% \\
& \quad \text{n} &= 2, 95\% \\
& \quad \text{n} &= 1, 15\% \\
& \quad \text{n} &= 2, 60\%
\end{align*}
\]

**Scheme 134**

In a further attempt to expand the scope of this process, we tried to prepare the thioamide
analogues by the reaction of allylamides (127b, 127c) with Lawesson’s reagent.

Unfortunately we could not get a clean product to apply our cyclisation conditions.
Conclusion:

The preparation of substituted dihydrooxazole rings through two different methods has been demonstrated. The first one required a catalytic amount of CuI to cyclise propargyl amides to dihydrooxazoles. Mechanistic information has been obtained and concomitant benzylic oxidation has been observed in appropriate compounds. This reaction is efficient, easy to carry out and has good scope. In addition, Lawesson’s reagent has been shown to effect direct cyclisation of propargyl amides to the analogous dihydrothiazoles.

The second method presented is the cyclisation of $N$-alkenylamides using catalytic quantities of iodoarenes. 2-Iodoanisole has proven to be a superior catalyst than the other iodoarenes tested in this process. Mono- and disubstituted alkenes have been cyclised to the corresponding five membered rings in good yields.
Future work:

For future work, the cyclisation of different starting materials to prepare further heterocyclic products using 2-iodoanisole as the catalyst is envisaged. For example, the cyclisation of a propargylamide to the corresponding five membered ring has already been achieved but in low yield. It is expected that the use of 2-iodoanisole instead of iodobenzene will lead to a superior yield for this process. Also, the cyclisation of carbamates is expected to produce oxazolidinones (Scheme 135).

![Scheme 135](image1)

In addition, N-alkenylamidines could be used as starting materials to prepare substituted imadazole rings in an analogous manner (Scheme 136).

![Scheme 136](image2)
Experimental part:

General. $^1$H NMR spectra were recorded at 400 MHz. 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 spectra were recorded 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 characterised as broad (br), strong (s), medium (m) and weak (w). All generally available reagents were purchased from Sigma-Aldrich, Fisher and Acros and were used as supplied without further purification. Two grade sizes of silica gel were used in column chromatography (35-75 μm, 63-200 μm).

$N$-(Prop-2-ynyl)benzamide, 101:

In a round bottom flask propargyl amine (0.58 mL, 9.1 mmol, 1 equiv) was dissolved in DCM (10 mL). Then, benzoylchloride (2 mL, 17.2 mmol, 1.89 equiv) and triethylamine (2.54 mL, 18.2 mmol, 2 equiv) were added. The mixture was stirred and left overnight under a nitrogen atmosphere. A saturated solution of NaCl was added (10 mL) and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide 101 (1.2 g, 83%) as a white solid. Melting point: 109-112 °C.
IR\textsubscript{(neat)}: 3288 (m), 3058 (w), 1648 (m), 1536 (s), 1487 (m) cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 2.53 (1H, s), 4.62 (2H, dd, \(J = 2.6, 5.7\) Hz), 6.79 (1H, s), 7.48-7.55 (2H, m), 7.66-7.71 (1H, m), 7.79-7.83 (2H, m).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 29.8, 71.9, 79.5, 127.0, 128.6, 131.8, 133.7, 167.1.

MS: m/z (M + 23) 182.1

HRMS: m/z calc’d for [M + Na]\textsuperscript{+} C\textsubscript{10}H\textsubscript{9}NNaO 182.0576, found 182.0576.

\textbf{N-(3-Phenylprop-2-yn-1-yl)benzamide, 102:}

\[
\begin{array}{c}
\text{Ph} \\
\equiv \\
| \\
\text{N} \\
\text{Ph}
\end{array}
\]

\(N\)-(prop-2-ynyl)benzamide 101 (0.96 g, 6 mmol, 1 equiv) was dissolved in Et\textsubscript{3}N (25 mL), then PhI (0.67 mL, 6 mmol, 1 equiv), CuI (114 mg, 0.6 mmol, 0.10 equiv) and Pd(PPh\textsubscript{3})\textsubscript{4} (35 mg, 0.03 mmol, 0.005 equiv) were added. The mixture was stirred overnight under nitrogen atmosphere. The mixture was concentrated and purified by flash chromatography (5:1) (petroleum ether 40-60 /EtOAc on silica) to give the product 102 as brown solid (0.097 g, 10%).

Melting point: 99-101 °C.

\textbf{IR\textsubscript{(neat)}:} 2309 (w), 2924 (w), 2361 (w), 1639 (m), 1529 (m) cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 4.50 (2H, d, \(J = 5.1\) Hz), 6.36 (1H, br), 7.31-7.37 (3H, m), 7.43-7.47 (4H, m), 7.50-7.54 (1H, m), 7.82 (2H, d, \(J = 8.1\) Hz).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 31.0, 84.0, 85.0, 122.8, 127.4, 128.5, 128.7, 128.9, 129.0, 132.2, 134.3, 167.4.

MS: m/z (M + 1) 236.1.

HRMS: m/z calc’d for [M + H]\textsuperscript{+} C\textsubscript{16}H\textsubscript{14}NO 236.1070, found 236.1073.
Phenyl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 103:

A flask was charged with N-(3-phenylprop-2-yn-1-yl)benzamide, 102 (40 mg, 0.17 mmol, 1 equiv), iodobenzene (3.8 µL, 0.034 mmol, 0.2 equiv), p-toluenesulfonic acid (97 mg, 0.51 mmol, 3 equiv), m-chloroperbenzoic acid (88 mg, 0.51 mmol, 3 equiv) and acetonitrile (1 mL) and stirred at room temperature under an air atmosphere overnight. The reaction mixture was quenched by addition of sat. aq. sodium thiosulfate solution, extracted with dichloromethane, and washed with sat. aq. sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20:1 petroleum ether 40-60 °C/ethyl acetate) to give 103 as a white solid (0.0048 g, 11%).

Melting point: 115-118 °C.

IR
(neat): 2922 (w), 1712 (s), 1650 (s), 1447 (s), 1257 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 4.28 (1H, dd, J = 3.4, 7.8 Hz), 4.45 (1H, dd, 3.5, 11.3 Hz), 5.86 (1H, dd, J = 5.3, 11.1 Hz), 7.40-7.54 (5H, m), 7.62-7.66 (2H, m), 7.98-8.0 (3H, m).

¹³C NMR (100 MHz, CDCl₃): δ 59.5, 80.6, 128.0, 129.3, 129.4, 129.8, 130.0, 132.7, 134.9, 135.0, 165.1, 195.9.

MS: m/z (M + 1) 252.1

HRMS: m/z calc’d for [M + H]⁺ C_{16}H_{13}NO₂ 252.1019, found 252.1026.
**2,2’-Diiodo-4,4’,6,6’-tetramethylbiphenyl, 104:**

In a round bottom flask 5-iodo-m-xylene (0.29 mL, 2 mmol, 1 equiv) was dissolved in dry DCM (5 mL). This mixture was added dropwise to a solution of PIFA (0.43 g, 1 mmol, 0.5 equiv) and BF$_3$.Et$_2$O (0.25 mL, 2 mmol, 1 equiv) under nitrogen atmosphere at -78 °C. The reaction was stirred at same temperature for 3 h, and then the mixture was quenched with saturated aqueous NaHCO$_3$, and extracted with DCM (10 mL x 2). The combined organic layers were washed with brine and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide 104 as a white solid (0.043 g, 5%).

Melting point: 115-118 °C.

IR$_{(\text{neat})}$: 3018 (w), 2910 (w), 1625 (m), 1566 (s), 1056 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.97 (6H, s), 2.33 (6H, s), 7.10 (2H, s), 7.63 (2H, s).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.1, 21.8, 101.4, 131.4, 137.5, 137.6, 139.6, 144.9.

HRMS: m/z calc’d for [M + NH$_4$]$^+$ C$_{16}$H$_{20}$I$_2$N 479.9680, found 479.9665.

**Phenyl(2-phenyloxazol-5-yl)methanone, 105:**

Synthesised according to the representative procedure for formation of 103 using 2,2'-diiodo-4,4’,6,6’-tetramethyl-1,1'-biphenyl (15.7 mg, 0.034 mmol, 0.2 equiv) instead of iodobenzene, to end up with 105 (0.014 g, 33%) as a brown solid.

Melting point: 130-133 °C.
IR (neat): 3129 (w), 2916 (w), 2848 (w), 1648 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.54 (5H, m), 7.66 (1H, t, J = 7.2 Hz), 7.88 (1H, s), 8.01 (2H, d, J = 7.7 Hz), 8.21 (2H, d, J = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 126.6, 127.9, 129.1, 129.3, 129.4, 132.3, 133.6, 137.3, 138.0, 149.3, 165.2, 181.8.

MS: m/z (M + 1) 250.1.

HRMS: m/z calc’d for [M + H]^⁺ C₁₆H₁₂NO₂ 250.0863, found 250.0790.

**N-(2, 2-Dimethylpropyne) benzamide, 106a:**

![Chemical Structure](image)

In a round bottom flask dimethylpropargyl amine (0.96 mL, 9.1 mmol, 1 equiv) was dissolved in DCM (10 mL). Then, benzoyl chloride (2 mL, 17.2 mmol, 1.89 equiv) and triethyl amine (2.54 mL, 18.2 mmol, 2 equiv) were added. The mixture was stirred and left overnight under a nitrogen atmosphere. A saturated solution of NaCl was added (10 mL) and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give 106a as a light yellow solid (1.65g, 97%).

Melting point: 153-155 °C.

IR (neat): 3284 (w), 3239 (w), 3062 (w), 2979 (w), 2930 (w), 1714 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.75 (6H, s), 2.38 (1H, s), 6.40 (1H, s), 7.38 (2H, t, J = 7.2 Hz), 7.38 (1H, t, J = 7.1 Hz), 7.75 (2H, d, J = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 29.1, 31.0, 48.0, 69.6, 87.3, 126.9, 128.8, 131.6, 166.6.

MS: m/z (M + 23) 210.
HRMS: m/z calc’d for [M + Na]$^+$ C$_{12}$H$_{13}$NNaO 210.0889, found 210.0899.

4-Chloro-N-(1, 1-dimethylprop-2-ynyl) benzamide, 106b:

Synthesised according to the representative procedure for formation of 106a using 4-chlorobenzoylchloride (1.5 mL, 11.4 mmol, 1.89 equiv) instead of benzoylchloride, to end up with 106b (1.22 g, 92%) as a white solid.

Melting point: 146-149 °C.

IR$_{\text{(neat)}}$: 3328 (w), 3284 (m), 2990 (w), 1644 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.76 (6H, s), 2.40 (1H, s), 6.15 (1H, s), 7.40 (2H, d, $J = 8.5$ Hz), 7.70 (2H, d, $J = 8.5$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 29.3, 48.5, 69.9, 87.3, 128.7, 129.1, 133.5, 138.1, 165.7.

MS: m/z (M + 23) 244.0.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{12}$H$_{13}$ClNNaO 244.0500, found 244.0489.

N-(1, 1-Dimethylprop-2-ynyl)-4-methoxy-benzamide, 106c:

Synthesised according to the representative procedure for formation of 106a using 4-methoxybenzoylchloride (1.5 mL, 11.4 mmol, 1.89 equiv) instead of benzoylchloride, to provide 106c (1.30g, 99 %.) as a white solid.

Melting point: 87-91 °C.

IR$_{\text{(neat)}}$: 3280 (w), 3271 (w), 2975 (w), 2934 (w), 1638 (s) cm$^{-1}$.
\[^{1}\text{H NMR (400 MHz, CDCl}_3): \delta 1.78 (6\text{H, s}), 2.41 (1\text{H, s}), 3.87 (3\text{H, s}), 6.14 (1\text{H, s}), 6.93 (2\text{H, d, } J = 8.8), 7.745 (2\text{H, d, } J = 8.8).^{77}\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 36.9, 52.1, 55.6, 71.2, 85.9, 113.8, 127.3, 128.8, 162.1, 166.2.\]

MS: \text{m/z (M + 23) 240.1.}

HRMS: m/z calc’d for [M + Na]\(^+\) \(C_{13}H_{13}NNaO_2\) 240.0995, found 240.0995.

**N-(2-Methylbut-3-yn-2-yl)-4-nitrobenzamide, 106d:**

![Chemical Structure](image)

Synthesised according to the representative procedure for formation of 106a using 4-nitrobenzoyl chloride (2.12 g, 11.4 mmol, 1.89 equiv) instead of benzoyl chloride, to provide 106d as a yellow solid (0.54, 39 %).

Melting point: 123-127 °C.

IR\(_{\text{neat}}\): 3278 (w), 2980 (m), 2184 (w), 1520 (m), 1343 (m) cm\(^{-1}\).

\[^{1}\text{H NMR (400 MHz, CDCl}_3): \delta 1.77 (6\text{H, s}), 2.42 (1\text{H, s}), 6.29 (1\text{H, s}), 7.91 (2\text{H, d, } J = 7.7 \text{ Hz}), 8.26 (2\text{H, d, } J = 7.1 \text{ Hz}).\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 29.2, 48.9, 70.3, 86.9, 124.2, 128.5, 140.7, 150.0, 164.8.\]

MS: \text{m/z (M + 23) 255.1.}

HRMS: m/z calc’d for [M + Na]\(^+\) \(C_{12}H_{12}N_2NaO_3\) 255.0740, found 255.0741.

**N-(1-Ethynylcyclohexyl)benzamide, 106e:**

![Chemical Structure](image)
In a round bottom flask 1-ethylcyclohexylamine (50 mg, 0.405 mmol, 1 equiv) was dissolved in 1 mL of DMF. Then, benzoylchloride (114 mg, 0.81 mmol, 2 equiv) and triethylamine (82 mg, 0.81 mmol, 2 equiv) were added. The mixture was stirred and heated at 50 °C for an hour. Then the mixture was left stirring at room temperature overnight under a nitrogen atmosphere. The mixture was concentrated then purified by flash chromatography (5:1 petroleum ether 40-60/EtOAc with 5% Et$_3$N on silica) to give $N$-(1-ethynylcyclohexyl)benzamide as a light brown solid (0.066 g, 72 %).

Melting point: 114-119 °C.

IR (neat): 3287 (w), 2980 (w), 2934 (w), 1638 (s) cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta$ 1.60-2.27 (10H, m), 2.89 (1H, s), 6.13 (1H, s), 7.43 (2H, t, $J$ =7.84 Hz), 7.51 (1H, t, $J$ = 7.14 Hz), 7.78 (2H, d, $J$ = 7.2 Hz).

13C NMR (100 MHz, CDCl$_3$): $\delta$ 22.7, 25.3, 37.2, 52.1, 71.7, 58.7, 127.1, 128.8, 131.8, 135.2, 166.6.

MS: m/z (M + 23) 250.1.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{15}$H$_{17}$NNaO 250.1202, found 250.1202.

$N$-(1-Ethynylcyclohexyl)-4-choloro-benzamide, 106f:  

![Chemical structure](image)

Synthesised according to the representative procedure for formation of 106e using 4-cholorobenzoylechloride (568.1 mg, 3.25 mmol, 2 equiv) instead of benzoylchloride, to provide 106f (0.294 g, 69 %.) as a white solid.

Melting point: 133-136 °C.
IR (neat): 3296 (m), 2971 (w), 2294 (w), 2851 (w), 1643 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.59-2.28 (10H, m), 2.47 (1H, s), 6.22 (1H, s), 7.37 (2H, d, $J$ = 8.8 Hz), 7.71 (2H, d, $J$ = 8.7 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.7, 25.3, 36.9, 52.3, 71.7, 85.4, 128.3, 128.7, 133.3, 137.6, 166.2.

MS: m/z (M + 23) 284.1.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{15}$H$_{16}$ClNNaO 284.0813, found 284.0813.

N-(1-Ethynylcyclohexyl)-4-methoxy-benzamide, 106g.$^{77}$

Synthesised according to the representative procedure for formation of 106e using 4-methoxybenzoylchloride (276.4 mg, 1.62 mmol, 2 equiv) instead of benzoylchloride, to afford 106g (0.193, 93 %.) as a light yellow solid.

Melting point: 106-109 °C.

IR (neat): 3305 (w), 3286 (w), 2931 (m), 2850 (w), 1642 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.29-2.26 (10H, m), 2.47 (1H, s), 3.89 (3H, s), 6.14 (1H, s), 6.89 (2H, d, $J$ = 8.7 Hz), 7.74 (2H, d, $J$ = 8.8 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.5, 25.3, 36.9, 52.1, 55.6, 71.2, 85.9, 113.8, 127.3, 128.8, 162.1, 166.2.

MS: m/z (M + 23) 280.1

HRMS: m/z calc’d for [M + Na]$^+$ C$_{16}$H$_{19}$NNaO$_2$ 280.1308, found 280.1308.
**N-(1-Ethynylcyclohexyl)-4-nitrobenzamide, 106h:**

![Chemical Structure](image)

Synthesised according to the representative procedure for formation of 106e using 4-nitrobenzoylcholoride (0.3 g, 1.62 mmol, 2 equiv) instead of benzoylchloride, to end up with 106h (0.219 g, 99%) as a light yellow solid.

Melting point: 137-140 °C.

IR\(\text{(neat)}\): 3301 (w), 3244 (w), 2939 (w), 2853 (w), 1648 (s), 1522 (s), 1486 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 1.21-1.33 (1H, m), 1.58-1.74 (5H, m), 1.83-1.89 (2H, m), 2.12-2.24 (2H, m), 2.45 (1H, s), 6.37 (1H, s), 7.88 (2H, d, \(J = 8.6\) Hz), 8.19 (2H, d, \(J = 8.6\) Hz).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 22.9, 25.5, 37.2, 53.0, 72.5, 85.1, 124.1, 128.5, 140.9, 149.9, 164.7.

MS: m/z (M + 23) 295.1.

HRMS: m/z calc’d for [M + Na]\(^+\) \(C_{15}H_{16}N_2NaO_3\) 295.1053, found 295.1053.

**N-(1,1-Dimethylprop-2-ynyl)-IH-indole-2-carboxamide, 106i:**

![Chemical Structure](image)

Dimethylpropargyl amine (0.22 mL, 2.1 mmol, 1 equiv) was dissolved in CHCl\(_3\) (10 mL). Then, 1H-indole-2-carbonyl chloride (0.165 g, 9.3 mmol, 4.4 equiv) and triethylamine (0.59 mL, 4.2 mmol, 2 equiv) were added. The mixture was stirred overnight under a nitrogen atmosphere. NaOH (3 M, 5 mL) was added and the mixture extracted with CH\(_2\)Cl\(_2\) (10 mL x
2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether 40-60 /EtOAc on silica) to give N-(1,1-dimethylprop-2-ynyl)-1H-indole-2-carboxamide as a white solid (0.08g, 17 %).

Melting point: 192-194 °C.

IR (neat): 3273 (w), 2980 (w), 1638 (w), 1538 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.81 (6H, s), 2.42 (1H, s), 6.25 (1H, s), 6.82 (1H, d, J = 1.60 Hz), 7.14 (1H, t, J = 7.7 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.49 (1H, d, J = 8.2 Hz), 7.64 (1H, d, J = 8.1 Hz), 9.58 (1H, s).

¹³C NMR (100 MHz, CDCl₃): δ 29.3, 48.0, 69.7, 86.9, 102.0, 112.1, 120.7, 121.9, 124.5, 127.6, 130.8, 136.4, 160.8.

MS: m/z (M + 23) 249.1.

HRMS: m/z calc’d for [M + Na]⁺ C₁₄H₁₄N₂O 249.0998, found 249.0998.

3-Bromo-N-(1,1-dimethylprop-2-ynyl)thiophene-2-carboxamide, 106j:

Thionyl chloride (0.22 mL, 2.93 mmol, 3.4 equiv) was added to 3-bromothiophene-2-carboxylic acid (0.165 g, 0.80 mmol, 2 equiv) in CHCl₃ (3 mL). The mixture was stirred overnight. Then, the solvent was removed under vacuum to provide 3-bromothiophene-2-carbonyl chloride. Then, dimethylpropargylamine (0.22 mL, 2.1 mmol, 1 equiv) dissolved in CHCl₃ (10 mL) was added to the 3-bromothiophene-2-carbonyl chloride (0.165 g, 0.73 mmol, 0.35 equiv). Triethylamine (0.59 mL, 4.2 mmol, 2 equiv) was added to the mixture and stirred overnight under a nitrogen atmosphere. NaOH (3 M, 5 mL) was added and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous
magnesium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc on silica) to give \(N-(1,1\text{-dimethylprop-2-ynyl})-\text{IH}-\text{indole-2-carboxamide}\) as an orange oil (0.596 g, 23 %).

IR\(_{\text{(neat)}}\): 3399 (w), 3295 (w), 3082 (w), 2979 (w), 1647 (s), 1517 (s) cm\(^{-1}\).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 1.69 (6H, s), 2.34 (1H, s), 6.95 (1H, d, \(J = 5.2\) Hz), 7.17-7.25 (1H, m), 7.37 (1H, d, \(J = 5.2\) Hz).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 29.4, 48.6, 70.0, 86.9, 108.7, 130.6, 132.3, 135.9, 159.6.

MS: \(m/z\) (M + 23) 293.9.

HRMS: \(m/z\) calc’d for \([M + Na]^+\) \(C_{10}H_{10}NNaOS\) 293.9558, found 293.9559.

\(N-(1,1\text{-Dimethylprop-2-ynyl})-2-(2\text{-thienyl})acetamide, 106k:\)

![Structure](attachment:image.png)

Synthesised according to the representative procedure for formation of 106j using thionyl-3-acetic acid (0.165 g, 1.16 mmol, 2 equiv), to give 106k (0.23 g, 53%) as a yellow solid.

Melting point: 143-145 °C.

IR\(_{\text{(neat)}}\): 3304 (m), 3203 (m), 3009 (w), 2984 (w), 2935 (w), 1640 (s), 1548 (s) cm\(^{-1}\).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 1.57 (6H, s), 2.30 (1H, s), 3.55 (2H, s), 5.49 (1H, s), 6.99 (1H, dd, \(J = 5.1, 4.8\) Hz), 7.13 (1H, d, \(J = 2.38\) Hz), 7.32 (1H, dd, \(J = 3.0, 4.9\) Hz).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 29.2, 39.2, 48.0, 69.6, 87.3, 123.7, 127.1, 128.7, 135.2, 169.9.

MS: \(m/z\) (M + 23) 230.1.

HRMS: \(m/z\) calc’d for \([M + Na]^+\) \(C_{11}H_{13}NNaOS\) 230.0611, found 230.0615.
N-(1,1-Dimethylprop-2-ynyl)furan-2-carboxamide, 106l:

Synthesised according to the representative procedure for formation of 106a using 2-furyl chloride (1.24 g, 9.5, 2 equiv), to end up with 106l (0.67 g, 73%) as a light yellow solid.

Melting point: 101-104 °C.

IR \text{(neat)}: 3304 (w), 3278 (w), 3116 (w), 1646 (s), 1591 (s), 1528 (s), 1470 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.74 (6H, s), 2.38 (1H, s), 6.43 (1H, s), 6.48 (1H, dd, \(J = 3.48, 3.47\) Hz), 7.10 (1H, dd, \(J = 3.50, 3.48\) Hz), 7.40 (1H, dd, \(J = 1.76, 1.67\) Hz).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 29.4, 48.0, 69.7, 87.1, 112.5, 114.6, 144.0, 148.4, 157.7.

MS: \(m/z\) (M + 23) 200.1.

HRMS: \(m/z\) calc’d for [M + Na]\(^+\) C\(_{10}\)H\(_{11}\)NNaO\(_2\) 200.0682, found 200.0679.

N-(2-Methylbut-3-yn-2-yl)-2-phenylacetamide, 106m:

Synthesised according to the representative procedure for formation of 106j using phenyl acetic acid (1.7 g, 11.4 mmol, 2 equiv) and dimethylpropargyl amine (0.6 mL, 5.7 mmol, 1 equiv), to give 106m (0.69 g, 61%) as a yellow solid.

Melting point: 144-147 °C.

IR \text{(neat)}: 3311 (m), 3206 (m), 3064 (w), 2995 (w), 2935 (w), 1640 (s), 1541 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.59 (6H, s), 2.32 (1H, s), 3.55 (2H, s), 5.52 (1H, s), 7.27-7-39 (5H, m).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 29.1, 44.7, 47.9, 69.4, 87.2, 127.6, 129.3, 129.6, 135.1, 170.3.
MS: m/z (M + 23) 224.1.

HRMS: m/z calc’d for [M + Na]^+ C_{13}H_{15}NNaO 224.1046, found 224.1045.

N-(2-methylbut-3-yn-2-yl)benzamide-d1, 106n:

\[ \text{N-(2,2-Dimethylpropyne)benzamide 106a (0.2 g, 1.06 mmol, 1 equiv.) was dissolved in MeCN (1 mL) and K}_2\text{CO}_3 (0.22 g, 1.59 mmol, 1.5 equiv.) was added to the mixture. After 30 min of stirring, D}_2\text{O (0.96 mL, 53 mmol, 50 equiv.) was added and the mixture was stirred overnight at rt. The mixture was extracted with DCM (10 mL \times 2) and the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was stirred with HCl (0.5 M, 2 mL) for 7 days, and then extracted with DCM (10 mL \times 2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give the product (0.132 g, 66%) as white solid.}

Melting point: 155-158 °C.

IR (neat): 3485 (w), 3238 (w), 2980 (w), 2583 (w), 1639 (s), 1514 (s) cm^{-1}.

\(^1\)H NMR (400 MHz, CDCl3): \( \delta \) 1.77 (6H, s), 6.13 (1H, s), 7.40–7.70 (3H, m), 7.75 (2H, d, \( J = 7.1 \) Hz).

\(^{13}\)C NMR (100 MHz, CDCl3): \( \delta \) 29.4, 48.4, 61.8, 86, 127.2, 128.9, 131.9, 135.2, 166.8.

MS: m/z (M + 23) 211.1.

HRMS: m/z calc’d for [M + Na]^+ C_{12}H_{12}DNNaO 211.0952, found 211.0959.
**N-(2-Methylbut-3-yn-2-yl)acetamide, 106o:**

![Structural formula](image)

Synthesised according to the representative procedure for formation of 106a using acetyl chloride (0.71 mL, 10.01 mmol, 1 equiv), to provide 106o as a colourless oil (0.40 g, 35%).

IR (neat): 3263 (s), 3076 (w), 2983 (w), 1945 (s), 1548 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.57 (6H, s), 1.98 (3H, s), 2.35 (1H, s), 5.68 (1H, s).

¹³C NMR (100 MHz, CDCl₃): δ 24.1, 28.9, 47.5, 69.1, 87.2, 169.2.

MS: m/z (M + 23) 148.1.

HRMS: m/z calc’d for [M + Na]⁺ C₇H₁₁NNaO 148.0733, found 148.0732.

**N-(2-Methylbut-3-yn-2-yl)benzenesulfonamide, 106p:**

1,1-dimethylpropargyl amine (0.96 mL, 9.1 mmol, 1 equiv) was dissolved in 10 mL of DCM. Then, benzenesulfonyl chloride (1.28 mL, 10.01 mmol, 1.1 equiv) was added followed by Et₃N (2.45 mL, 18.2 mmol, 2 equiv) and DMAP (10 mg). The mixture was stirred over night under nitrogen atmosphere. Saturated salt of NaCl was added then extracted by DCM (2 x 10 mL) the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The mixture was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc on silica) to give the product as a yellow oil (1.3 g, 63 %).

IR (neat): 3248 (m), 2986 (w), 2359 (w), 2344 (w), 1448 (m), 1320 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.58 (6H, s), 2.08 (1H, s), 4.91 (1H, s), 7.51 (2H, t, J = 7.8 Hz), 7.58 (1H, t, J = 7.1 Hz), 7.94 (2H, d, J = 7.3 Hz).
13C NMR (100 MHz, CDCl3): δ 30.7, 49.9, 71.3, 85.2, 127.7, 128.7, 132.5, 141.6.

MS: m/z (M + 23) 246.1.

HRMS: m/z calc’d for [M + Na]+ C11H13NNaO2S 246.0559, found 246.0559.

N-(1-(Phenylethynyl)cyclohexyl)benzamide, 109:

1-Ethynylcyclohexylamine (100 g, 0.81 mmol, 1 equiv) was dissolved in Et3N (5 mL) then CuI (16 mg, 0.081 mmol, 10 mol%), PhI (91 μL, 0.81 mmol, 1 equiv) and Pd(PPh3)4 (5 mg, 0.040 mmol, 0.5 mol%) were added. The mixture was left stirring overnight at room temperature then concentrated under reduced pressure. The residue was purified by flash chromatography (5 : 1 : 0.005 petroleum ether/EtOAc/Et3N on silica gel) to provide the product as a brown oil (0.064 g, 45%). This was dissolved in DMF (5 mL) then benzoylchloride (84 μL, 0.72 mmol, 2 equiv) and Et3N (101 μL, 0.72 mmol, 2 equiv) were added. The mixture was stirred overnight and concentrated under reduced pressure. The residue was purified by flash chromatography (5 : 1 petroleum ether 40-60/EtOAc on silica gel) to provide the product as a white solid (0.096 g, 84%).

Melting point: 174–177 °C.

IR(neat): 3285 (w), 3050 (w), 2913 (w), 2851 (w), 1786 (w), 1639 (s) cm−1.

1H NMR (400 MHz, CDCl3): δ 1.30–1.39 (1H, m), 1.63–1.83 (5H, m), 2.08–2.22 (2H, m), 2.26–2.29 (2H, m), 6.22 (1H, s), 7.27–7.29 (3H, m), 7.40–7.50 (5 H, m), 7.77 (2 H, d, J = 7.3 Hz).

13C NMR (100 MHz, CDCl3): δ 23.3, 25.7, 37.3, 53.6, 84.2, 91.4, 123.5, 127.3, 128.4, 128.5, 128.9, 131.7, 132.2, 135.7, 166.7.
**MS:** m/z (M + 23) 326.1.

**HRMS:** m/z calc’d for [M + Na]^+ C_{21}H_{21}NNaO 326.1515, found 326.1508.

**E-chalcone and N-(3-oxo-1,3-diphenylpropyl)benzamide, 117, 118:**

![Diagram of molecules](image)

In an oven-dried sealed tube benzamide (0.5 g, 4.13 mmol, 1 equiv) and Cu(OTf)$_2$ (0.15 g, 0.413 mmol, 0.1 equiv) were dissolved in toluene (5 mL). Then benzaldehyde (0.46 mL, 5.54 mmol, 1.1 equiv) was added, followed by phenylacetylene (0.68 mL, 6.2 mmol, 1.5 equiv). The tube was flushed with nitrogen then sealed. The mixture was stirred and heated at 100 °C for four days. Then, HCl (3M aq, 5 mL) was added to the mixture and it was extracted with Et$_2$O, and then sat aq NaHCO$_3$ (5 mL) was added to the organic layer and extracted with Et$_2$O (2 x 5 mL). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography (20:1 petroleum ether 40-60 /EtOAc on silica), and E-chalcone 117 was collected before N-(3-oxo-1,3-diphenylpropyl)benzamide 118 in the column tubes.

**E-chalcone, 117:** light brown solid (0.36 g, 42%).

Melting point: 59-62 °C.

IR(neat): 3024 (w), 1662 (m), 1604 (s), 1574 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): 7.38-7.41 (3H, m), 7.47-7.50 (2H, m), 7.54-7.58 (2H, m), 7.60-7.64 (2H, m), 7.84 (1H, d, $J = 16$ Hz), 8.04-8.06 (2H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 122.2, 128.6, 128.7, 128.8, 129.1, 130.7, 132.9, 135.0, 138.3, 144.9, 190.5.
MS: m/z (M + 23) 231.1.
HRMS: m/z calc’d for [M + Na]^+ C_{14}H_{12}NaO 231.0780, found 231.0780.

*N-(3-Oxo-1,3-diphenylpropyl)benzamide, 118*: yellow solid (0.61 g, 45%).
Melting point: 154-158 °C.
IR(neat): 3302 (w), 3059 (w), 1681(m), 1578 (w), 1532 (m) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 3.42 (1H, dd, \(J = 6.0, 17.2\) Hz), 3.80 (1H, dd, \(J = 6.2, 17.1\) Hz), 5.77-5.81 (1H, m), 7.18-7.23 (5H, m), 7.32-7.49 (5H, m), 7.48 (1H, t, \(J = 7.4\) Hz), 7.80 (2H, d, \(J = 8.0\) Hz), 7.84 (2H, d, \(J = 8.0\) Hz), 8.04 (1H, s).

\(^13\)C: δ 43.4, 50.5, 126.7, 127.3, 127.6, 128.4, 128.7, 128.8, 128.9, 131.7, 133.7, 134.5, 136.8, 141.4, 167.0, 199.1.
MS: m/z (M + 23) 352.1.
HRMS: m/z calc’d for [M + Na]^+ C_{22}H_{19}NNaO\(_2\) 352.1308, found 352.1308.

4, 4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole, 107a\(^{77}\)

![4, 4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole](image)

In a round bottom flask \(N\)-(2, 2-dimethylpropyne)benzamide (50 mg, 0.27 mmol, 1 equiv) (106a) was dissolved in DCM (5 mL). Then, copper iodide (15.2 mg, 10 mol\%) was added and the mixture was stirred at room temperature overnight. The product was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc on silica) to give 4,4-dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole a yellow oil (0.37g, 73%).

IR(neat): 2972 (w), 2971 (w), 2294 (w), 2851 (w), 1643 (m) cm\(^{-1}\).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.47 (6H, s), 4.26 (1H, d, $J = 2.9$ Hz), 4.76 (1H, d, $J = 2.9$ Hz), 7.42-7.46 (2H, m), 7.49-7.55 (1H, m), 7.99-8.02 (2H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 29.8, 69.1, 82.4, 127.1, 128.1, 128.5, 131.8, 160.0, 168.1.

MS: m/z (M+1) 188.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{12}$H$_{14}$NO 188.1070, found 188.1069.

2-(4-Chloro-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107b:

![Chemical Structure]

4-Chloro-$N$-(1,1-dimethylprop-2-ynyl)benzamide (50 mg, 0.226 mmol, 1 equiv) (106b) was dissolved in DCE (2 mL), and then CuI was added (5 mg, 0.0226 mmol, 0.1 equiv). The mixture was heated under reflux overnight at 80 °C. The product was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc on silica) to provide 107b as a yellow oil (0.044g, 88%).

IR$_{\text{neat}}$: 2974 (w), 2928 (w), 1674 (m), 1309 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.47 (6H, s), 4.28 (1H, d, $J = 2.8$ Hz), 4.76 (1H, d, $J = 2.8$ Hz), 7.42 (2H, d, $J = 8.6$ Hz), 7.94 (2H, d, $J = 8.6$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 30.1, 69.6, 83.2, 125.6, 129.2, 129.8, 138.4, 159.6, 167.9.

MS: m/z (M+1) 222.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{12}$H$_{13}$ClNO 222.0680, found 222.0680.
2-(4-Methoxy-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107c:

Synthesised according to the representative procedure for formation of 107b using \(N\)-(1,1-dimethylprop-2-ynyl)-4-methoxy-benzamide (100 mg, 0.46 mmol, 1 equiv) 106c, to end up with 107c as a colourless oil (0.093 g, 93 %).

IR
(neat): 2972 (w), 2930 (w), 1643 (m), 1609 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.44 (6H, s), 3.84 (3H, s), 4.22 (1H, d, \(J = 2.7\) Hz), 4.71 (1H, d, \(J = 2.7\) Hz), 6.92 (2H, d, \(J = 9.0\) Hz), 7.93 (2H, d, \(J = 9.0\) Hz).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 30.2, 55.7, 69.3, 82.3, 114.2, 119.7, 130.2, 160.0, 162.7, 168.4.

MS: \(m/z\) (M + 23) 240.1.

HRMS: \(m/z\) calc’d for \([M + Na]^+\) \(C_{13}H_{15}NNaO_2\) 240.0995, found 240.0995.

2-(4-Nitro-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107d:
Synthesised according to the representative procedure for formation of 107b using N-(1, 1-dimethylprop-2-ynyl)-4-methoxy-benzamide (20 mg, 0.086 mmol, 1 equiv) 106d to end up with 107d as a yellow solid (0.0175 g, 88%).

Melting point: 103–107 °C.

IR (neat): 3108 (w), 2974 (w), 1679 (m), 1644 (m), 1524 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.46 (6H, s), 4.31 (1H, d, J = 3.0 Hz), 4.78 (1H, d, J = 3.1 Hz), 8.15 (2H, d, J = 8.9 Hz), 8.28 (2H, d, J = 9.0 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 30.0, 70.0, 83.9, 124.0, 129.5, 133.2, 150.0, 158.6, 167.7.

MS: m/z (M + 1) 233.1.

HRMS: m/z calc’d for [M + H]⁺ C₁₂H₁₃N₂O₂ 233.0921, found 233.0937.

4-Methylene-2-phenyl-3-oxa-1-azaspiro[4.5]dec-1-ene, 107e:⁷⁵

![Structure of 107e](image)

Synthesised according to the representative procedure for formation of 107b using N-(1-ethynylcyclohexyl)benzamide (100 mg, 0.44 mmol, 1 equiv) 106e, to provide 107e as a colourless oil (0.091 g, 91%).

IR (neat): 2929 (m), 2853 (w), 1650 (m), 1309 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.53-1.92 (10H, m), 4.26 (1H, d, J = 2.7), 4.76 (1H, d, J = 2.7 Hz), 7.44 (2H, t, J = 7.2 Hz), 7.5 (1H, t, J = 7.1 Hz), 8.03 (2H, d, J = 7.1 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 22.1, 39.3, 57.7, 72.3, 82.5, 127.4, 128.1, 128.4, 131.5, 159.3, 168.4.
MS: m/z (M + 1) 228.1.

HRMS: m/z calc’d for [M + H]^+ C_{15}H_{18}NO 228.1383, found 228.1382.

2-(4-Chlorophenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene, 107f:

![Chemical Structure](image)

Synthesised according to the representative procedure for formation of 107b using N-(1-ethynylcyclohexyl)-4-chloro-benzamide (50 mg, 0.226 mmol, 1 equiv) 106f, to provide 107f as a colourless oil (0.041 g, 82%).

IR (neat): 2929 (m), 2852 (w), 1654 (s), 1489 (m) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 1.47-1.89 (10H, m), 4.23 (1H, d, J = 2.8 Hz), 4.72 (1H, d, J = 2.8 Hz), 7.38 (2H, d, J \(=\) 8.5 Hz), 7.91 (2H, d, J = 8.6 Hz).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 22.5, 26.0, 39.5, 72.5, 83.2, 126.3, 129.1, 129.9, 138.0, 158.8, 168.5.

MS: m/z (M + 1) 262.1.

HRMS: m/z calc’d for [M + H]^+ C_{15}H_{17}ClNO 262.0993, found 262.0991.
2-(4-Methoxyphenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene 107g:

The synthesis was undertaken according to the representative procedure for formation of 107b but with N-(1-ethynylcyclohexyl)-4-methoxy-benzamide (50 mg, 0.226 mmol, 1 equiv) 106g to end up with 107g as a colourless oil (0.048 g, 99 %).

IR\(_{\text{neat}}\): 2929 (m), 2852 (w), 1646 (s), 1510 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.38-1.5 (10H, m), 3.84 (3H, s), 4.22 (1H, d, \(J = 2.4\) Hz), 4.71 (1H, d, \(J = 2.7\) Hz), 6.92 (2H, t, \(J = 9.1\) Hz), 7.95 (2H, d, \(J = 9.0\) Hz).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 22.5, 25.9, 39.5, 55.7, 72.1, 82.8, 114.1, 120.0, 130.2, 159.6, 162.5, 168.6.

MS: m/z (M + 1) 258.1.

HRMS: m/z calc’d for [M + H]\(^+\) C\(_{16}\)H\(_{20}\)NO\(_2\) 258.1488, found 258.1488.

2-(4-Nitrophenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene, 107h:
Synthesised according to the representative procedure for formation of 107b using N-(1,1-dimethylprop-2-ynyl)-4-methoxy-benzamide (20 mg, 0.07 mmol, 1 equiv) 106h, to end up with 107h as a brown solid (0.017 g, 89 %).

Melting point: 68–71°C.

IR\(_\text{neat}\): 3301 (w), 2932 (s), 2853 (m), 1708 (m) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.68-1.90 (10H, m), 4.29 (1H, d, \(J = 3.0\) Hz), 4.78 (1H, d, \(J = 3.0\) Hz), 8.17 (2H, d, \(J = 8.7\) Hz), 8.28 (2H, d, \(J = 9.7\) Hz).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 22.4, 25.9, 39.6, 73.0, 83.9, 123.9, 129.5, 133.6, 149.9, 157.9, 168.2.

MS: m/z (M+1) 273.1.

HRMS: m/z calc’d for [M + H]\(^+\)C\(_{15}\)H\(_{17}\)N\(_2\)O\(_3\) 273.1234, found 273.1239.

2-(IH-Indol-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107i:

Synthesised according to the representative procedure for formation of 107b but with N-(1,1-dimethylprop-2-ynyl)-IH-indole-2-carboxamide (20 mg, 0.088 mmol, 1 equiv) 106i to end up with 107i as a colourless oil (0.017 g, 85 %).

IR\(_\text{neat}\): 3126 (w), 3066 (w), 2968 (m), 1698 (m), 1650 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.46 (6H, s), 4.29 (1H, d, \(J = 3.0\) Hz), 4.78 (1H, d, \(J = 3.0\) Hz), 7.13 (1H, s), 7.25 (1H, d, \(J = 7.5\) Hz), 7.29 (1H, d, \(J = 7.3\) Hz), 7.38 (1H, d, \(J = 8.2\) Hz), 7.68 (1H, d, \(J = 8.0\) Hz), 9.34 (1H, s).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 30.2, 69.2, 83.3, 107.3, 111.9, 121.0, 122.4, 124.8, 125.1, 128.1, 137.5, 155.4, 167.7.

MS: m/z (M + 23) 227.1.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{14}$H$_{15}$N$_2$O 227.1178, found 227.1186.

2-(3-Bromothiophen-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107j:

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

Synthesised according to the representative procedure for formation of 107b using 3-bromo-$N$-(1,1-dimethylprop-2-ynyl)thiophene-2-carboxamide (100 mg, 0.564 mmol, 1 equiv) (106j), to give 107j (0.259 g, 87%) as a brown oil.

IR (neat): 3082 (w), 2973 (w), 2927 (w), 1696 (w), 1637 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.45 (6H, s), 4.25 (1H, d, $J = 3.0$ Hz), 4.75 (1H, d, $J = 2.9$ Hz), 7.06 (1H, d, $J = 5.3$ Hz), 7.40 (1H, d, $J = 5.3$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 26.1, 30.1, 69.6, 83.3, 114.2, 129.8, 133.1, 154.9, 167.6.

MS: m/z (M + 23) 293.9.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{10}$H$_{10}$BrNNaOS 293.9558, found 293.9524.

4,4-Dimethyl-5-methylene-2-(thiophen-2-ylmethyl)-4,5-dihydrooxazole, 107k:
Synthesised according to the representative procedure for formation of 107b using N-(1,1-dimethylprop-2-ynyl)-2-(2-thienyl)acetamide (100 mg, 0.45 mmol, 1 equiv) (106k), to give 107k (0.072 g, 77%) as a dark green oil.

IR\textsubscript{(neat)}: 3108 (w), 2972 (m), 2927 (w), 1667 (s) cm\textsuperscript{-1}.

$^1$H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.35 (6H, s), 3.71 (2H, s), 4.15 (1H, d, $J = 3.0$ Hz), 4.57 (1H, d, $J = 3.3$ Hz), 7.04 (1H, d, $J = 5.0$ Hz), 7.16 (1H, d, $J = 1.8$ Hz), 7.28 (1H, d, $J = 5.0$ Hz).

$^{13}$C NMR (100 MHz, CDCl\textsubscript{3}): δ 29.8, 29.9, 69.0, 82.5, 123.0, 126.3, 128.5, 134.4, 162.0, 168.4.

MS: m/z (M + 23) 208.1.

HRMS: m/z calc'd for [M + Na]$^+$ C\textsubscript{11}H\textsubscript{14}NOS 208.0790, found 208.0789.

(4,4-Dimethyl-5-methylene-oxazol-2-yl)-(2-thienyl)methanone, 107k':

4,4-Dimethyl-5-methylene-2-(thiophen-2-ylmethyl)-4,5-dihydrooxazole 107k (30 mg, 0.14 mmol, 1 equiv.) was dissolved in 1,2-DCE (2 mL) and CuI was added (3 mg, 10 mol%). The mixture was heated at reflux overnight and then concentrated under vacuum. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product 107k$^+$ as a yellow oil (18 mg, 58%).

IR\textsubscript{(neat)}: 2975 (w), 2930 (w), 2360 (w), 1671 (s), 1634 (m) cm\textsuperscript{-1}.

$^1$H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.48 (6H, s), 4.32 (1H, d, $J = 3.2$ Hz), 4.84 (1H, d, $J = 2.9$ Hz), 7.33 (1H, dd, $J = 5.2, 5.1$ Hz), 7.81 (1H, dd, $J = 5.2, 5.1$ Hz), 8.90 (1H, dd, $J = 2.9, 3.0$ Hz).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 27.7, 57.8, 95.3, 125.9, 127.5, 131.0, 136.1, 150.1, 154.0, 158.1.

MS: m/z (M + 23) 244.0.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{11}$H$_{11}$NNaO$_2$ 244.0402, found 244.0402.

2-(Furan-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole, 107i:

![Structure of 2-(Furan-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole](image)

Synthesised according to the representative procedure for formation of 107b using N-(1,1-dimethylprop-2-ynyl)furan-2-carboxamide (100 mg, 0.564 mmol, 1 equiv) (106i) to end up with 107i (0.076 g, 76%) as a brown oil.

IR$_{\text{(neat)}}$: 3649 (w), 2981 (w), 2170 (w), 2156 (w), 2039 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.26 (6H, s), 4.07 (1H, d, $J = 3.1$ Hz), 4.54 (1H, d, $J = 3.0$ Hz), 6.32 (1H, dd, $J = 3.4$, 4.0 Hz), 6.82 (1H, d, $J = 3.4$ Hz), 7.38 (1H, d, $J = 1.5$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 29.7, 69.0, 83.0, 111.7, 115.0, 142.1, 145.7, 152.4, 167.2.

MS: m/z (M + 23) 200.1.

HRMS: m/z calc’d for [M + Na]$^+$ C$_{10}$H$_{11}$NNaO$_2$ 200.0682, found 200.0689.

(4,4-Dimethyl-5-methylene-4,5-dihydrooxazol-2-yl)(phenyl)methanone, 107m:

![Structure of (4,4-Dimethyl-5-methylene-4,5-dihydrooxazol-2-yl)(phenyl)methanone](image)

N-(2-Methylbut-3-yn-2-yl)-2-phenylacetamide 106m (50 mg, 0.25 mmol, 1 equiv) was dissolved in 1,2-DCE (2 mL) and CuI (5 mg, 10 mmol%) was added. The mixture was heated
at reflux for 48 h and then concentrated under vacuum. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product 107m as a yellow solid (38 mg, 71%).

Melting point: (53-56 °C).

IR (neat): 2975 (w), 2930 (w), 2360 (w), 1671 (s), 1634 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.50 (6H, s), 4.34 (1H, d, J = 3.4 Hz), 4.84 (1H, d, J = 3.1 Hz), 7.47-7.51 (2H, m), 7.61-7.65 (1H, m), 8.28-8.31 (2H, m).

¹³C NMR (100 MHz, CDCl₃): δ 29.8, 70.9, 84.9, 128.9, 131.1, 134.8, 134.8, 155.9, 166.2, 182.8.

MS: m/z (M + 23) 238.1.

HRMS: m/z calc’d for [M + Na]⁺ C₁₃H₁₃NNaO₂ 238.0838, found 238.0838.

(Z)-4,4-dimethyl-5-(methylene-d)-2-phenyl-4,5-dihydrooxazole, 107na:

![Structure](image)

Synthesised according to the representative procedure for formation of 107b using N-(2-methylbut-3-yn-2-yl)benzamide-d¹ (106n).

¹H NMR (400 MHz, CDCl₃): δ 1.47 (6H, s), 4.23 (1H, s), 7.42-7.46 (2H, m), 7.49-7.55 (1H, m), 7.99-8.02 (2H, m).
(E)-4,4-dimethyl-5-(methylene-d)-2-phenyl-4,5-dihydrooxazole, 107nb:

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

107nb

Synthesised according to the representative procedure for formation of 107b using N-(2-methylbut-3-yn-2-yl)benzamide-d\(^1\) (106n).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.47 (6H, s), 4.73 (1H, s), 7.42-7.46 (2H, m), 7.49-7.55 (1H, m), 7.99-8.02 (2H, m).

4,4-Dimethyl-5-methylene-2-phenylthiazole, 119a:

In a round bottom flask N-(2,2-dimethylpropyne)benzamide (200 mg, 1.068 mmol, 1 equiv) (106a) was added, and then Lawesson’s reagent (432 mg, 1.086 mmol, 1 equiv) was added. Then, dry toluene (10 mL) was added while the flask was under nitrogen atmosphere. The mixture was heated at 90 °C under reflux overnight. The product was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc on silica) to give 4,4-dimethyl-5-methylene-2-phenyl-thiazole as a yellow oil (0.115 g, 53 %).

IR\(_{\text{(neat)}}\): 2972 (m), 2927 (w), 1604 (m), 1447 (m) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.53 (6H, s), 5.18 (1H, d, \(J = 1.7\) Hz), 5.27 (1H, d, \(J = 1.9\) Hz), 7.39-7.45 (3H, m), 7.77-7.80 (2H, m).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 29.8, 82.8, 103.2, 128.3, 128.9, 131.5, 133.5, 156.7, 160.1.

MS: m/z (M + 1) 203.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{12}$H$_{14}$NS 203.0841, found 203.0853.

2-(4-Chlorophenyl)-4,4-dimethyl-5-methylene-thiazole, 119b:

Synthesised according to the representative procedure for formation of 119a using 4-chloro-N-(1,1-dimethylprop-2-ynyl)benzamide (100 mg, 0.451 mmol, 1 equiv) 106b to provide 1119b as a yellow oil (0.067 g, 63 %).

IR (neat): 2973 (m), 2928 (w), 1606 (m), 1489 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.50 (6H, s), 5.17 (1H, d, $J = 1.6$ Hz), 5.25 (1H, d, $J = 1.6$ Hz), 7.34-7.38 (2H, m), 7.67-7.70 (2H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 29.7, 82.9, 103.5, 129.1, 129.6, 132.0, 137.6, 156.6, 159.6.

MS: m/z (M + 1) 238.0

HRMS: m/z calc’d for [M + H]$^+$ C$_{12}$H$_{13}$ClS 238.0451, found 238.0459.

2-(4-Methoxyphenyl)-4,4-dimethyl-5-methylene-thiazole, 119c:
Synthesised according to the representative procedure for formation of 119a using N-(1, 1-dimethylprop-2-ynyl)-4-methoxy-benzamide (200 mg, 0.921 mmol, 1 equiv) 106c, to end up with 119c as a yellow oil (0.042 g, 20%).

IR\(_\text{neat}\): 2971 (m), 2929 (w), 2837 (w), 1605 (s), 1509 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.53 (6H, s), 3.86 (3H, s), 5.18 (1H, d, \(J = 1.3\) Hz), 5.27 (1H, d, \(J = 1.7\) Hz), 6.91-6.94 (2H, m), 7.72-7.75 (2H, m).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 29.7, 55.5, 82.4, 102.7, 113.9, 126, 129.7, 156.8, 160.2, 162.1.

MS: m/z (M + 1) 234.1

HRMS: m/z calc’d for [M + H]\(^+\) C\(_{13}\)H\(_{16}\)NOS 234.0947, found 234.0947.

\(N\)-(1-Ethylcyclohexyl)benzamide, 120:

\[
\begin{align*}
\text{O} & \\
\text{HN} & \\
\text{Ph} & \\
\end{align*}
\]

4,4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole 107a (40 mg, 0.22 mmol, 1 equiv) and Pd/C (11.7 mg, 0.011 mmol, 0.05 equiv) were mixed with EtOAc under a nitrogen atmosphere, and then a balloon of H\(_2\) was used to replace the nitrogen with H\(_2\), and the mixture was left stirring overnight. The product was purified by flash chromatography (9:1 petroleum ether 40-60 /EtOAc on silica) to give \(N\)-(1-ethylcyclohexyl)benzamide as a white solid (0.029 g, 57%).

IR\(_\text{neat}\): 2922 (m), 2363 (m), 2163 (m), 2027 (s), 2019 (s), 1636 (s), 1525 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.77 (3H, t, \(J = 7.6\) Hz), 1.17-1.61 (10 H, m), 1.85 (2H, q, \(J = 7.6\) Hz), 5.61 (1H, s), 7.33-7.43 (3H, m), 7.65-7.68 (2H, m).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 7.8, 22.0, 25.9, 30.7, 34.9, 56.6, 127.2, 128.5, 131.4, 136.3, 167.0.

MS: m/z (M + 23) 254.2.

HRMS: m/z calc’d for [M + Na]\(^+\) C\(_{15}\)H\(_{21}\)NNaO 254. 1515, found 254.1515.

5-(Iodomethylene)-4,4-dimethyl-2-phenyl-4,5-dihydrooxazole, 126:

\[
\text{\begin{tikzpicture}
  \node[draw, circle] (a) at (0,0) {\text{O}};
  \node[draw, circle] (b) at (1,0) {\text{N}};
  \node[draw, circle] (c) at (0.5,1) {\text{Ph}};
  \node[draw, circle] (d) at (0.5,0) {\text{I}};
  \draw (a) -- (b);
  \draw (b) -- (c);
  \draw (c) -- (d);
\end{tikzpicture}}
\]

4,4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole 107a (50 mg 0.27 mmol, 1 equiv) was dissolved in acetone (2 mL), then NIS (153 mg, 0.68 mmol, 2.5 equiv) and K\(_2\)CO\(_3\) (37 mg, 0.27 mmol, 1 equiv) were added to the mixture which was left stirring overnight at room temperature. The mixture was quenched by addition of saturated aqueous Na\(_2\)S\(_2\)O\(_3\) and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum, to provide 126 as a yellow oil (0.84 g, 99%).

IR\(_{\text{(neat)}}\): 3065 (w), 2977 (w), 2928 (w), 1710 (w), 1669 (s), 1637 (s) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.61 (6H, s), 5.68 (1H, s), 7.34 (2H, t, \(J = 7.5\) Hz), 7.42 (1H, t, \(J = 7.5\) Hz), 7.86 (2H, d, \(J = 7.5\) Hz).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 46.0, 71.1, 125.7, 127.0, 128.3, 128.6, 132.2, 159.1, 163.0.

MS: m/z (M + 23) 236.1.

HRMS: m/z calc’d for [M + Na]\(^+\) C\(_{12}\)H\(_{12}\)NNaO 235. 9856, found 236.0010.
**N-allylbenzamide, 127a**: 

![Chemical Structure of 127a]

In a round bottom flask allylamine (0.65 mL, 8.8 mmol, 1 equiv) was dissolved in DCM (10 mL). Then, benzoyl chloride (1.12 mL, 9.68 mmol, 1.1 equiv) and triethylamine (3 mL, 19.36 mmol, 2 equiv) were added. The mixture was stirred overnight under a nitrogen atmosphere. Then, NaOH solution (1 M, 10 mL) was added, and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give a colourless oil (1.40 g, 98%).

IR (neat): 3277 (w), 3050 (w), 2981 (w), 2971 (w), 2234 (w), 2181 (m), 2153 (m), 1994 (m), 1633 (m), 1530 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 4.06-4.09 (2H, m), 5.16-5.27 (2H, m), 5.87-5.97 (1H, m), 6.35 (1H, s), 7.39-7.43 (2H, m), 7.47-7.51 (1H, m), 7.77-7.79 (2H, m).

¹³C NMR (100 MHz, CDCl₃): δ 41.8, 112.4, 114.5, 116.9, 134.2, 144.2, 148.2, 158.6.

MS: m/z (M + 1) 162.0.

HRMS: m/z calc’d for [M + H]⁺ C₁₀H₁₂NO 162.0913, found 162.0919.

**N-allyl-4-chlorobenzamide, 127b:**

![Chemical Structure of 127b]

Synthesised according to the representative procedure for formation of 127a using 4-chlorobenzoyl chloride (1.1 mL, 9.68 mmol, 1.1 equiv). The product was purified by flash chromatography (5:1 petroleum ether 40-60 /EtOAc) to end up with 127b (1.55 g, 90%) as a white solid.
Melting point: 77-80 °C.

IR (neat): 3280 (w), 3062 (w), 1631 (m), 1593 (m), 1532 (m) cm\(^{-1}\).

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 4.06-4.09\) (2H, m), \(5.18\)–5.28 (2H, m), \(5.88\)–5.97 (1H, m), 6.15 (1H, s), 7.40 (2H, d, \(J = 8.4\) Hz), 7.70–7.73 (2H, m).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 42.9, 117.3, 128.7, 129.2, 133.2, 134.3, 138.1, 166.6\).

MS: \(m/z\) (M + 1) 196.0.

HRMS: \(m/z\) calc’d for [M + H]\(^{+}\) C\(_{10}\)H\(_{11}\)ClNO 196.0524, found 196.0525.

\(N\)-Allyl-4-methoxybenzamide, 127c:

![Image](image_url)

Synthesised according to the representative procedure for formation of 127a using 4-methoxybenzoyl chloride (1.30 mL, 9.68 mmol, 1.1 equiv). The product was purified by flash chromatography (3:1 petroleum ether 40-60 /EtOAc) to end up with 127c (1.10g, 66%) as a white solid.

Melting point: 56-58 °C.

IR (neat): 3328 (w), 3064 (w), 1627 (m), 1605 (m), 1542 (m), 1504 (s) cm\(^{-1}\).

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.83\) (3H, s), 4.05-4.08 (2H, m), 5.15-5.26 (2H, m), 5.88-5.97 (1H, m), 6.15 (1H, s), 6.89-6.93 (2H, m), 7.72-7.76 (2H, m).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 42.7, 55.8, 114.1, 116.9, 127.0, 129.1, 134.7, 162.5, 167.3\).

MS: \(m/z\) (M + 1) 192.1.

HRMS: \(m/z\) calc’d for [M + H]\(^{+}\) C\(_{11}\)H\(_{14}\)NO\(_2\) 192.1019, found 192.1020.
**N- Allyl-4-nitrobenzamide, 127d:**

![ChemicalStructure](image)

Synthesised according to the representative procedure for formation of 127a using 4-nitrobenzoyl chloride (1.53 g, 9.68 mmol, 1.1 equiv). The product was purified by flash chromatography (3:1 petroleum ether 40-60 /EtOAc) to end up with 127d (1.81g, 99%) as a yellow solid.

Melting point: 120-124 °C.

IR (neat): 3367 (w), 3232 (w), 1645 (m), 1597 (m), 1524 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 4.08-4.12 (2H, m), 5.20-5.30 (2H, m), 5.88-5.98 (1H, m), 6.38 (1H, s), 7.92-7.96 (2H, m), 8.26-8.29 (2H, m). ⁷⁸

¹³C NMR (100 MHz, CDCl₃): δ 43.1, 117.7, 124.2, 128.5, 133.8, 140.4, 149.9, 165.7.

MS: m/z (M + 1) 207.1.

HRMS: m/z calc’d for [M + H]⁺ C₁₀H₁₁N₂O₃ 207.0764, found 207.0770.

**N- Allylfuran-2-carboxamide, 127e;**

![ChemicalStructure](image)

Synthesised according to the representative procedure for formation of 127a using 2-fuorylchloride (0.95 g, 9.68 mmol, 1.1 equiv) to end up with 127e (1.35 g, 93%) as dark green oil.

IR (neat): 3317 (w), 1651 (w), 1592 (m), 1570 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 3.99-4.01 (2H, m), 5.11-5.23 (2H, m), 5.81-5.91 (1H, m), 6.44-6.46 (1H, m), 6.59 (1H, s), 7.07 (1H, d, J = 3.2), 7.39 (1H, s). ⁷⁹
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 41.7, 112.3, 114.5, 116.8, 134.2, 144.2, 148.1, 158.6.

MS: m/z (M + 1) 152.1.

HRMS: m/z calc’d for [M + H]\(^+\) C\(_8\)H\(_{10}\)NO\(_2\) 152.0706, found 152.0707.

4-Methoxy-N-(2-methylallyl)benzamide, 127f:

\[ \text{Synthesised according to the representative procedure for formation of 127a using 2-methyl-2-propen-1-amine (0.25 g, 3.52 mmol, 1 equiv) and 4-methoxybenzoyl chloride (0.59 mL, 3.9 mmol, 1.1 equiv). The product was purified by flash chromatography (5:1 petroleum ether 40-60/EtOAc) to end up with 127f (0.65 g, 90\%) as a white solid.} \]

Melting point: 92-96 °C.

IR \(_{\text{neat}}\): 3337 (w), 3084 (w), 2979 (w), 1629 (m), 1606 (s), 1544 (m) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.79 (3H, s), 3.85 (3H, s), 4.01 (2H, d, \(J = 5.9\) Hz), 4.87-4.90 (2H, m), 6.11 (1H, s), 6.91-6.95 (2H, m), 7.74-7.77 (2H, m).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 20.9, 45.8, 55.8, 111.4, 114.2, 127.2, 129.1, 142.6, 162.6, 167.2.

MS: m/z (M + 1) 206.1.

HRMS: m/z calc’d for [M + H]\(^+\) C\(_{12}\)H\(_{16}\)NO\(_2\) 206.1176, found 206.1175.

\(N\)-(1-(Cyclohex-1-en-1-yl)ethyl)-4-methoxybenzamide, 127g:
Synthesised according to the representative procedure for formation of 127a using (1-cyclohex-1-en-1-ylethyl)amine hydrochloride (0.25 g, 1.55 mmol, 1 equiv) and 4-methoxybenzoyl chloride (0.25 mL, 1.87 mmol, 1.1 equiv) to end up with 127g (0.332 g, 83%) as a light yellow solid.

Melting point: 118-120 °C.

IR (neat): 3343 (w), 2980 (w), 2970 (w), 2925 (m), 1630 (m), 1608 (m), 1498 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.32 (3H, d, J = 6.8 Hz), 1.55-1.66 (4H, m), 1.95-2.08 (4H, m), 3.84 (3H, s), 4.56-4.63 (1H, m), 5.68 (1H, d, J = 1.0 Hz), 5.91 (1H, d, J = 7.8 Hz), 6.90-6.94 (2H, m), 7.71-7.75 (2H, m).

¹³C NMR (100 MHz, CDCl₃): δ 19.9, 22.8, 23.1, 25.4, 26.3, 50.5, 55.8, 114.1, 121.9, 127.6, 129.0, 138.9, 162.4, 166.5.

MS: m/z (M + 1) 260.2.

HRMS: m/z calc’d for [M + H]⁺ C₁₆H₂₂NO₂ 260.1645, found 260.1648.

*N-(Furan-2-ylmethyl)-4-methoxybenzamide, 127h*:

![Image of N-(Furan-2-ylmethyl)-4-methoxybenzamide](image)

Synthesised according to the representative procedure for formation of 127a using furfurylamine (0.5 mL, 5.15 mmol, 1 equiv) and 4-methoxybenzoyl chloride (0.8 mL, 5.7 mmol, 1.1 equiv). The product was purified by flash chromatography (1:1 petroleum ether 40-60 /EtOAc) to end up with 127h (0.78 g, 66%) as a light brown solid.

Melting point: 112-126 °C.

IR (neat): 3307 (w), 3140 (w), 3106 (w), 1621 (s), 1607 (s), 1573 (w), 1542 (m) cm⁻¹.
In a round bottom flask o-toluic acid (0.4 g, 3 mmol, 1 equiv) was dissolved in chloroform (10 mL). Then, thionyl chloride (0.44 mL, 6 mmol, 2 equiv) was added and the mixture was stirred overnight at room temperature. Then, the solvent was removed, and allylamine (0.8 mL, 11 mmol, 1 equiv) in DCM (10 mL) was added to the mixture followed by triethylamine (2 mL, 22 mmol, 2 equiv). The mixture was stirred and left overnight under a nitrogen atmosphere. Then, NaOH solution (1 M, 10 mL) was added, and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give a yellow solid (0.28 g, 15%).

Melting point: 67-70 °C.

IR (neat): 3280 (w), 2980 (w), 2926 (w), 1638 (m), 1534 (m) cm⁻¹.

^1H NMR (400 MHz, CDCl₃): δ 3.94 (2H, s), 5.07-5.20 (2H, m), 5.78-5.87 (1H, m), 5.97 (1H, s), 7.07-7.13 (2H, m), 7.19-7.26 (2H, m).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 20.1, 42.4, 116.8, 125.9, 126.9, 130.1, 131.3, 134.4, 136.3, 136.6, 170.3.

MS: m/z (M + 1) 176.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{11}$H$_{14}$NO 176.1070, found 176.1067.

*N*-Allyl-2-phenylacetamide, 129b:

\[ \text{N-Allyl-2-phenylacetamide, 129b:} \]

\[ \text{Synthesised according to the representative procedure for formation of 129a using phenylacetic acid (0.4 g, 3 mmol, 1 equiv) to end up with 129b (0.19 g, 10%) as a white solid.} \]

Melting point: 66-69 °C.

IR$_{\text{neat}}$: 3239 (w), 3063 (w), 1658 (m), 1625 (m), 1555 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.61 (2H, s), 3.84 (2H, t, $J = 5.7$ Hz), 5.02-5.07 (2H, m), 5.39 (1H, s), 5.71-5.81 (1H, m), 7.28-7.38 (5H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 42.2, 44.1, 116.4, 127.7, 129.4, 129.8, 134.3, 135.2, 171.2.

MS: m/z (M + 1) 176.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{11}$H$_{14}$NO 176.1070, found 176.1070.
Methyl 2-(4-methoxybenzamido)cyclopent-3-enecarboxylate, 131:

Thionylchloride (0.075 mL, 1.023 mmol, 1.1 equiv) was added dropwise to dry methanol (10 mL) at 0 °C. Then, cis-2-amino-3-cyclopentene-1-carboxylic acid hydrochloride (0.150 g, 0.93 mmol, 1 equiv) was added and the mixture was stirred overnight under a nitrogen atmosphere at 66 °C. Then, the solvent was removed, and 4-methoxybenzoyl chloride (0.13 mL, 0.94 mmol, 1.1 equiv) in DCM (10 mL) was added to the mixture followed by triethylamine (0.21 mL, 2.55 mmol, 2 equiv). The mixture was stirred overnight under a nitrogen atmosphere. Then, NaOH solution (1 M, 10 mL) was added, and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography (20:1 petroleum ether 40-60 /EtOAc) to end up with 131 (0.19 g, 81%) as a yellow solid.

Melting point: 66-69 °C.

IR_{(neat)}: 3288 (w), 2981 (w), 1731 (m), 1628 (m), 1605 (m),1574 (w) cm\(^{-1}\).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.61 (1H, dd, $J = 8.9, 17.3$ Hz), 2.84-2.91 (1H, m), 3.49 (1H, dd, $J = 8.7, 15.2$ Hz), 3.59 (3H, s), 3.83 (3H, s), 5.57 (1H, t, $J = 9.2$ Hz), 5.69 (1H, dd, $J = 2.0, 5.1$), 5.97 (1H, d, $J = 3.2$ Hz), 6.35 (1H, d, $J = 8.7$ Hz), 6.90 (2H, d, $J = 8.7$ Hz), 7.70 (2H, d, $J = 8.3$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 35.4, 45.9, 52.3, 55.7, 56.5, 114.1, 126.9, 129.1, 130.2, 133.8, 162.6, 166.5, 174.6.

MS: m/z (M + 1) 276.1.

HRMS: m/z calc’d for [M + H]$^+$ C$_{15}$H$_{18}$NO$_4$ 276.1230, found 276.1235.

4-Methoxy-N-(2-phenylallyl)benzamide, 133

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

In a round bottom flask α-methylstyrene (5 g, 42 mmol, 1 equiv) was dissolved in 15 mL of CCl$_4$. Then, N-bromosuccinimide (4.7 g, 26.25 mmol, 0.625 equiv) was added, and the mixture was stirred overnight under reflux. The mixture was cooled in an ice-water bath and CCl$_4$ was removed, and then, phthalimide (3.4 g, 23.2 mmol, 0.8 equiv) in DMF (20 mL) was added to the mixture followed by K$_2$CO$_3$ (8 g, 58 mmol, 2 equiv) and the mixture was stirred overnight at 60 °C. Brine (10 mL) was added to the mixture which was extracted with EtOAc (10 mL x 2). The organic layers were combined and dried with anhydrous magnesium sulfate,
filtered and concentrated under vacuum. Then, phthalimide product was dissolved in petroleum ether (40-60 °C) and hydrazine hydrate (0.98 mL, 31.4 mmol, 2 equiv) was added. The mixture was stirred for 15 minutes; the solid was collected by vacuum filtration and washed by Et₂O. The solid was placed in a conical flask and a mixture of DCM/HCl (1:1) was added and stirred for 15 minutes. This was filtered to remove any solid materials. The liquid partition was placed in a separatory funnel and extracted with HCl (6 M). The aqueous layers were combined and basified by slow addition of solid KOH at °C, and then extracted with Et₂O (10 mL x 3). The organic layers were combined and dried with anhydrous magnesium sulfate filtered and concentrated under vacuum to give 0.148 g of the amine product. 4-Methoxybenzoyl chloride (0.17 mL, 1.22. 1.1 equiv) and Et₃N (0.19 mL, 2.22 mmol, 2 equiv) were added to the amine product in DCM (10 mL), and stirred overnight under nitrogen. NaOH solution (2 M) was added, and the mixture extracted with DCM (5 mL x 3). The organic layers were combined and dried with anhydrous magnesium sulfate filtered and concentrated under vacuum to give the product as a yellow solid (0.204 g, 69%).

Melting point: 158-161°C.

IR (neat): 3311 (w), 3006 (w), 1639 (m), 1628 (m), 1603 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 3.83 (3H, s), 4.53 (2H, d, J = 5.7 Hz), 5.32 (1H, s), 5.52 (1H, s), 6.10 (1H, s), 6.89 (2H, m), 7.33 (3H, m), 7.48 (2H, m), 7.68 (2H, m).

¹³C NMR (100 MHz, CDCl₃): δ 44.1, 55.8, 114.1, 114.4, 126.5, 127.0, 128.5, 129.0, 129.1, 138.7, 144.7, 162.6, 167.2.

MS: m/z (M + 1) 268.1.

HRMS: m/z calc’d for [M + H]⁺ C₁₇H₁₈NO₂ 268.1336, found 268.1334.
Methyl 2-(cyclohexa-1,4-dien-1-yl)-2-(4-methoxybenzamido)acetate, 134:

![Chemical structure](image)

Synthesised according to the representative procedure for formation of 131 using \((R)-(-)-2-(2,5\text{-dihydrophenyl})\text{glycine (1 g, 6.5 mmol, 1 equiv) to end up with 134 (0.508 g, 34\%) as a white solid.}

Melting point: 132-135 °C.

IR\textsubscript{(neat)}: 3273 (w), 2952 (w), 2822 (m), 1733 (m), 1636 (s), 1609 (m), 1578 (m) cm\textsuperscript{-1}.

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta 2.65\text{-}2.79 (4H, m), 3.79 (3H, s), 3.85 (3H, s), 5.18 (1H, d, \text{J} = 7.4 \text{ Hz), 5.64\text{-}5.71 (2H, m), 5.86 (1H, s), 6.77 (1H, d, \text{J} = 7.4 \text{ Hz), 6.91\text{-}6.94 (2H, m), 7.76\text{-}7.80 (2H, m).}

\(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta 26.7, 27.1, 53.1, 55.8, 58.2, 114.1, 123.8, 124.1, 124.7, 126.4, 129.3, 130.9, 162.8, 166.6, 171.9.

MS: m/z (M+1) 302.1.

HRMS: m/z calc’d for [M + H]\(^+\) C\textsubscript{17}H\textsubscript{20}NO\textsubscript{4} 302.1387, found 302.1393.

\textbf{N-(2-Vinylphenyl)benzamide, 135:}\textsuperscript{70}

![Chemical structure](image)

In a round bottom flask 2-vinylaniline (1 g, 8.4 mmol, 1 equiv) was dissolved in DCM (15 mL). Then, benzoyl chloride (1.17 mL, 10.08 mmol, 1.2 equiv) and 4-dimethylaminopyridine (1.23 g, 10.08 mmol, 1.2 equiv) were added and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. Then, HCl (3 M, 10 mL) and brine were added, and
the mixture extracted with DCM (10 mL x 2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give a light brown solid (1.58 g, 84%).

Melting point: (152-155 °C).

IR (neat): 3225 (w), 2981 (w), 2354 (w), 1647 (s), 1600 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 5.47 (1H, d, J = 11.0 Hz), 5.72 (1H, d, J = 17.5 Hz), 6.68 (1H, dd, J = 11.1, 17.4 Hz), 7.20 (1H, t, J = 7.6 Hz), 7.23-7.37 (1H, m), 7.49-7.52 (3H, m), 7.55-7.59 (1H, m), 7.87-7.90 (3H, m), 8.04 (1H, d, J = 8.0 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 119.9, 123.8, 125.8, 127.4, 127.4, 127.5, 129.0, 129.2, 130.9, 132.3, 132.7, 134.8, 135.1.

MS: m/z (M + 1) 224.1.

HRMS: m/z calc’d for [M + H]+ C₁₅H₁₄NO 224.1070, found 224.1066.

(2-Phenyl-4,5-dihydrooxazol-5-yl)methanol, 128a:

In a round bottom flask 127a (0.2 g, 1.24 mmol, 1 equiv) was dissolved in acetonitrile (10 mL). Then, 2-iodoanisole (0.0034 mL, 0.248 mmol, 0.2 equiv) was added, followed by trifluoroacetic acid (0.19 mL, 2.48 mmol, 2 equiv) and Selectflour (0.44 g, 1.24 mmol, 1.24 equiv). The mixture was stirred overnight at room temperature. Then, NaOH solution (3 M, 10 mL) was added, and the mixture extracted with DCM (10 mL x 2); the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The product was purified by flash chromatography (1:1 petroleum ether 40-60 /EtOAc) to end up with 128a (0.138 g, 63%) as a light brown solid.
Melting point: 88-90 °C.

IR (neat): 3203 (br), 2921 (br), 2859 (w), 1718 (w), 1644 (s), 1601 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 2.76 (1H, br), 3.71 (1H, dd, J = 12, 6.2 Hz), 3.78-3.87 (1H, m), 3.82 (1H, d, J = 15 Hz), 4.07 (1H, dd, J = 15, 10 Hz), 4.76-4.85 (1H, m), 7.39 (2H, d, J = 7.7 Hz), 7.47 (1H, t, J = 7.7 Hz), 7.93 (2H, d, J = 7.7 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 56.7, 64.5, 80.5, 127.8, 128.5, 128.7, 131.8, 164.4.

MS: m/z (M + 1) 178.1.

HRMS: m/z calc’d for [M + H]⁺ C₁₁H₁₂NO₂ 178.0863, found 178.0865.

(2-(4-Chlorophenyl)-4,5-dihydrooxazol-5-yl)methanol, 128b:

![Chemical Structure Image]

Synthesised according to the representative procedure for formation of 128a using 127b (0.2 g, 1.05 mmol, 1 equiv). The product was purified by flash chromatography (1 : 3 petroleum ether 40-60/EtOAc) to end up with 128b (0.153 g, 69%) as a yellow solid.

Melting point: 159-161 °C.

IR (neat): 3181 (br), 2913 (br), 1642 (m), 1621 (s), 1596 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.89 (1H, s), 3.73 (1H, dd, J = 12, 6.0 Hz), 3.79-3.90 (2H, m), 4.10 (1H, dd, J = 15, 10 Hz), 4.79-4.88 (1H, m), 7.39 (2H, d, J = 8.4 Hz), 7.88 (2H, d, J = 8.4 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 56.8, 64.7, 80.7, 126.4, 129.7, 129.9, 138.0, 163.4.

MS: m/z (M + 1) 212.0
HRMS: m/z calc’d for [M + H]$^+$ C$_{10}$H$_{11}$ClNO$_2$ 212.0473, found 212.0475.

(2-(4-Methoxyphenyl)-4,5-dihydrooxazol-5-yl)methanol, 128c:

Synthesised according to the representative procedure for formation of 128a using 127c (0.2 g, 1.05 mmol, 1 equiv). The product was purified by flash chromatography (1:3 petroleum ether 40-60 /EtOAc) to end up with 128c (0.171 g, 79%) as a bright yellow solid.

Melting point: 124-127 °C.

IR$_{\text{(neat)}}$: 3172 (br), 3171 (w), 2980 (s), 2888 (w), 1649 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.85 (1H, br), 3.72 (1H, dd, $J$ = 12, 6.4 Hz), 3.76-3.89 (2H, m), 3.85 (3H, s), 4.08 (1H, dd, $J$ = 15, 10 Hz), 4.76-4.85 (1H, m), 6.91 (2H, d, $J$ = 8.7 Hz), 7.88 (2H, d, $J$ = 8.7 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 55.7, 56.6, 64.6, 80.4, 113.7, 114.1, 120.3, 130.3, 162.5.

MS: m/z (M + 1) 208.1

HRMS: m/z calc’d for [M + H]$^+$ C$_{11}$H$_{14}$ClNO$_3$ 208.0968, found 208.0972.
(2-(4-Nitrophenyl)-4,5-dihydrooxazol-5-yl)methanol, 128d:

Synthesised according to the representative procedure for formation of 128a using 127d (0.1 g, 0.49 mmol, 1 equiv). The product was purified by flash chromatography (1:5 petroleum ether 40-60 /EtOAc) to end up with 128d (0.068 g, 64%) as a yellow solid.

Melting point: 113-117 °C.

IR (neat): 3363 (br), 3071 (w), 2946 (w), 1645 (m), 1521 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.97 (1H, s), 3.76 (1H, dd, J = 5.7, 12.3 Hz), 3.88-3.94 (2H, m), 4.16 (1H, dd, J = 10.0, 15.2 Hz), 4.86-4.93 (1H, m), 8.16 (2H, d, J = 8.8 Hz), 8.26 (2H, d, J = 8.9 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 57.0, 64.4, 81.1, 123.7, 129.6, 133.7, 149.9, 162.5.

MS: m/z (M+1) 223.1

HRMS: m/z calc’d for [M + H]⁺ C₁₀H₁₁N₂O₄ 223.0713, found 223.0716.

(2-(Furan-2-yl)-4,5-dihydrooxazol-5-yl)methanol, 128e:
Synthesised according to the representative procedure for formation of 128a using 127e (0.1 g, 0.66 mmol, 1 equiv). The product was purified by flash chromatography (1:5 petroleum ether 40-60 /EtOAc) to end up with 128e (0.087 g, 79%) as a brown solid.

Melting point: 100-103 °C.

IR (neat): 3220 (br), 3113 (w), 2962 (w), 2916 (w), 1671 (s), 1562 (w) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 2.20 (1H, s), 3.72 (1H, dd, J = 12, 6.0 Hz), 3.82-3.86 (2H, m), 4.09 (1H, dd, J = 15, 10 Hz), 4.77-4.84 (1H, m), 6.48 (1H, s), 6.96 (1H, d, J = 3.3 Hz), 7.53 (1H, s).

¹³C NMR (100 MHz, CDCl₃): δ 56.5, 64.1, 80.8, 111.9, 114.9, 143.1, 145.6, 1568.

MS: m/z (M+1) 168.1

HRMS: m/z calc’d for [M + H]^+ C₈H₁₀NO₃ 168.0655, found 168.0656.

(2-(4-Methoxyphenyl)-5-methyl-4,5-dihydrooxazol-5-yl)methanol, 128f:⁸⁴

![Structure of 128f](image)

Synthesised according to the representative procedure for formation of 128a using 127f (0.2 g, 0.98 mmol, 1 equiv). The product was purified by flash chromatography (1:3 petroleum ether 40-60 /EtOAc) to end up with 128f (0.189 g, 81%) as a brown oil.

IR (neat): 3234 (br), 2980 (w), 2931 (w), 1638 (s), 1607 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, s), 2.84 (1H, s), 3.56-3.71 (3H, m), 3.82 (3H, s), 4.0 (1H, d, J = 14.5 Hz), 6.85-6.88 (2H, m), 7.82-7.85 (2H, m).
13C NMR (100 MHz, CDCl3): δ 22.8, 55.7, 62.6, 67.9, 86.4, 114.0, 120.6, 130.2, 162.5, 163.4.

MS: m/z (M + 1) 222.1

HRMS: m/z calc’d for [M + H]+ C12H16NO3 222.1125, found 222.1128.

(2-(o-Tolyl)-4,5-dihydrooxazol-5-yl)methanol, 130:

Synthesised according to the representative procedure for formation of 128a using 129a (0.22 g, 1.26 mmol, 1 equiv). The product was purified by flash chromatography (1:1 petroleum ether 40-60/EtOAc) to end up with 130 (0.173 g, 72%) as a yellow oil.

IR (neat): 3271 (br), 2928 (w), 2871 (w), 1639 (s) cm⁻¹.

1H NMR (400 MHz, DMSO-d6): δ 2.54 (3H, s), 3.49-3.56 (1H, m), 3.57-3.64 (1H, m), 3.78 (1H, dd, J = 7.5, 15.0 Hz), 3.98 (1H, dd, J = 10, 15 Hz), 4.64-4.72 (1H, m), 5.05 (1H, t, J = 5.5 Hz), 7.25-7.32, (2H, m), 7.40 (1H, td, J = 7.5, 1.4 Hz), 7.76 (1H, dd, J = 1.2, 7.7 Hz).

13C NMR (100 MHz, DMSO-d6): δ 22.8, 55.9, 63.9, 80.3, 126.9, 128.5, 130.7, 131.7, 132.4, 139.4, 164.3.

MS: m/z (M + 1) 192.1

HRMS: m/z calc’d for [M + H]+ C11H14NO2 192.1019, found 192.1019.
Methyl 6-hydroxy-2-(4-methoxyphenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazole-4-carboxylate, 132:

Synthesised according to the representative procedure for formation of 128a using 131 (0.1 g, 0.4 mmol, 1 equiv). The product was purified by flash chromatography (1:1 petroleum ether 40-60 /EtOAc) to end up with 137 (0.062 g, 53%) as a light brown solid.

Melting point: 159-162 °C.

IR (neat): 3215 (br), 2945 (w), 2846 (w), 1730 (m), 1638 (m), 1607 (m) cm\(^{-1}\).

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): 1.31 (1H, s), 1.85-2.0 (2H, m), 3.44-3.50 (1H, m), 3.79 (3H, s), 3.83 (3H, s), 4.39 (1H, d, \(J = 3.5\) Hz), 4.82 (1H, d, \(J = 7.1\) Hz), 5.03 (1H, t, \(J = 7.3\) Hz), 6.90 (2H, d, \(J = 8.5\) Hz), 7.82 (2H, d, \(J = 8.5\) Hz).

\(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 33.1, 47.8, 52.3, 55.7, 72.5, 75.9, 88.4, 113.9, 119.8, 130.7, 162.6, 164.2, 172.5.

MS: \(m/z\) (M + 1) 292.1

HRMS: \(m/z\) calc’d for [M + H]\(^+\) \(C_{15}H_{18}NO_5\) 292.1179, found 292.1179.
References: