Development of Enantioselective and Catalytic Cyclisation Reactions Using Hypervalent Iodine Compounds

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Finally, I am extremely thankful and indebted to my country Libya for their funding and providing me this opportunity to study a PhD degree.

Abbreviations

Ac: Acetyl.

OAc: Acetate.

Ar: Aryl.

Bz: Benzoyl.

Cbz: benzyloxycarbonyl.

CSA: Camphorsulfonic acid.

CTAB: Cetyltrimethylammonium bromide

d.r.: Diastereomeric ratio.

DIAD: diisopropyl azodicarboxylate.

DIC: Diisopropylcarbodiimide.

DIPEA: Diisopropylethylamine.

DMAP: 4-Dimethylaminopyridine.

DMF: *N,N*-dimethylformamide.

DMP: Dess–Martin periodinane.

DMSO: dimethylsulfoxide.

DMEDA: *N,N′*-dimethylethylenediamine.

ee: Enantiomeric excess.

h: hour.

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

HPLC: High pressure liquid chromatography.

HRMS: High resolution mass spectrometry.

LDA: Lithium diisopropylamide.

M: Molarity (mol/l).

m-CPBA: 3-Chloroperoxybenzoic acid.

Min: Minute.

m.p.: Melting point.

MS: mass spectrometry.

NMR: nuclear magnetic resonance.

IR: Infrared.

PIDA: phenyliodine(III) diacetate.

PIFA: [Bis(trifluoroacetoxy)iodo]benzene.

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

rt: room temperature.

TFA: trifluoroacetic anhydride.

TFE: 2,2,2-Trifluoroethanol.

TfOH: Triflic acid.

THF: tetrahydrofuran.

TMSOTf: Trimethylsilyl triflate.

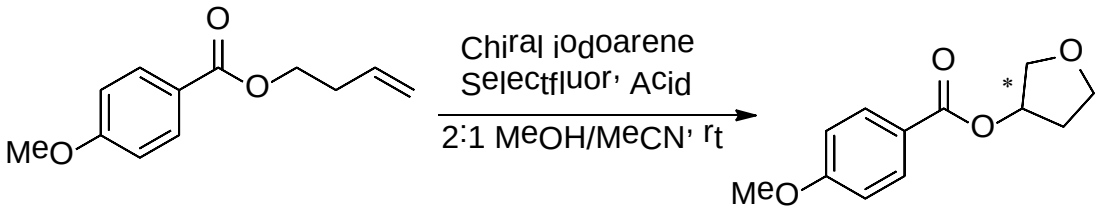
T_3P: 1-Propanephosphonic anhydride.

Ts: Tosyl (4-toluenesulfonyl).

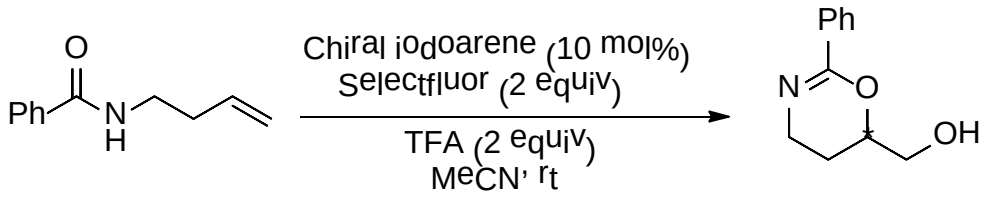
Abstract

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

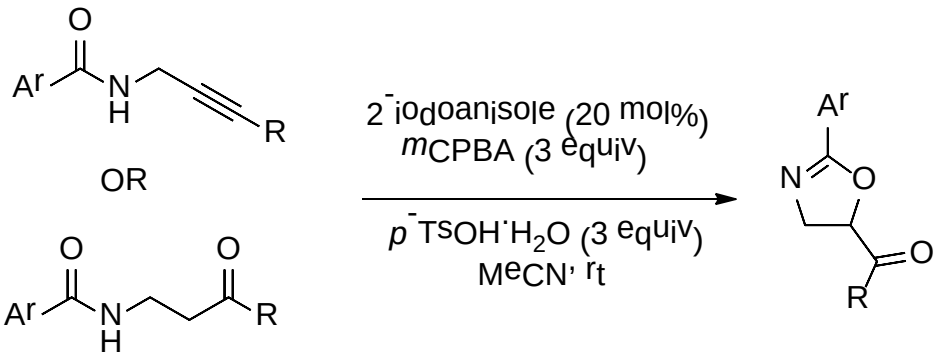
In the first part, the development of the catalytic enantioselective cyclisation of 4-methoxy but-3-enyl benzoate to the 3-hydroxytetrahydrofuran ester using enantiomerically pure chiral hypervalent iodine reagents generated *in situ* is described. A good enantioselectivity of 77% ee was obtained with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



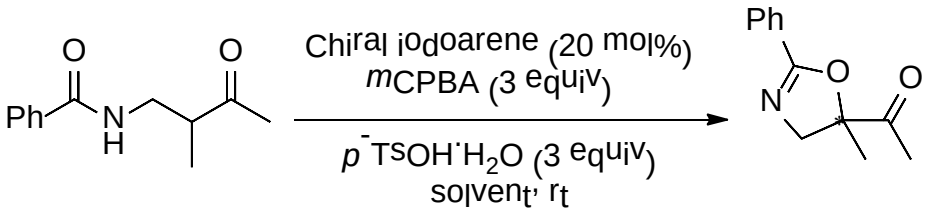
In the second part, the development of catalytic conditions for the cyclisation of *N*-alkenylarylamides induced by iodoarenes leading to the formation of different ring sizes is demonstrated. In addition, the catalytic enantioselective cyclisation of *N*-alkenylarylamides employing chiral iodoarenes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



In the third part, the catalytic cyclisation of both propargyl amides and β-amidoketones using 2-iodoanisole to afford 2-oxazolines in good yields is described.



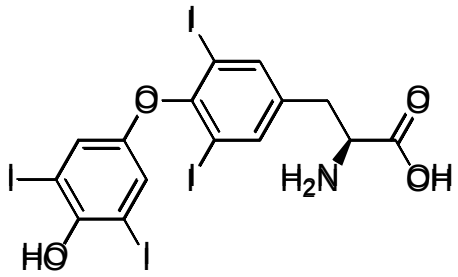
Moreover, the catalytic enantioselective cyclisation of β-amidoketones using several chiral iodoarenes is detailed but, unfortunately almost no enantioselectivities was observed.



1. Introduction to Hypervalent Iodine

1.1. Iodine

Iodine is the chemical element with the symbol I and atomic number 53. Iodine, I_2, is a bluish-black, lustrous solid that is classified as a nonmetal. It has the highest atomic number and atomic weight of the stable Group 17 elements (halogens) where it is the least electronegative and the greatest polarisable element.[1] It forms compounds with most elements, but is less reactive than the other halogens. Iodine is essential in many biological organisms including in the human body, where it is present as a hormone in the thyroid gland Thyroxine **1.** This is important in metabolism regulation.[1]



Thyroxine **1**

1.2. Hypervalent iodine compounds

In 1969 J. I. Musher defined the term hypervalent as molecules of the elements of group 15–18 having more than eight electrons in a valence shell.[2] The first hypervalent iodine compound iodobenzene dichloride ($PhICl_2$) was prepared by German chemist C. Willgerodt in 1886.[3,4]

When iodine is complexed with monovalent ligands, usually electronegative atoms or electron withdrawing groups such as chlorine or acetate, stable polycoordinate, multivalent compounds called hypervalent iodine compounds are formed.[5]

Iodine compounds exist in the +3 oxidation state as iodine(III) or **λ^3-iodanes** or in the +5 oxidation state as iodine(V) or **λ^5-iodanes**. These compounds contain a central iodine atom with an unusual bond called an iodine hypervalent bond (Figure 1) that contains a linear three-center, four-electron (3c–4e) bond (L−I−L) formed by the overlap of the 5p orbital on iodine with the orbitals on the two ligands L. This 3c-4e bond is commonly named as a "hypervalent bond". This bond is highly polarisedand is weaker and longer than a normal covalent bond. The existence of this bond in hypervalent iodine compounds is responsible for their strongly electrophilic reactivity. As two electrons are in a nonbonding orbital, there are not greater than eight electrons on the iodine atom. Therefore, the original definition of hypervalent is not valid. In addition, the bond order of the I-L bonds is formally 0.5 this explains their long length and relative weakness.[5-7]

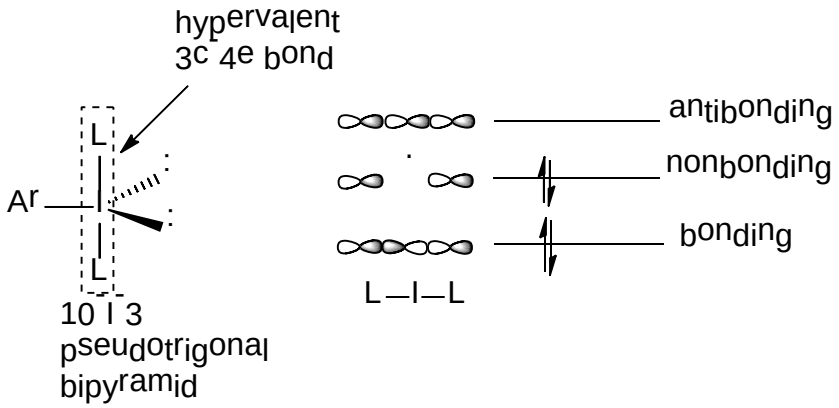


Figure 1

The most common hypervalent iodine compounds are $ArIL_2$ and their geometry are pseudotrigonal bipyramidal. The reason for that is the 3c-4e bond dictates the structure.[5,6] The following common classes of iodine(III) compounds have found extensive applications in organic synthesis (Figure 2).[7]

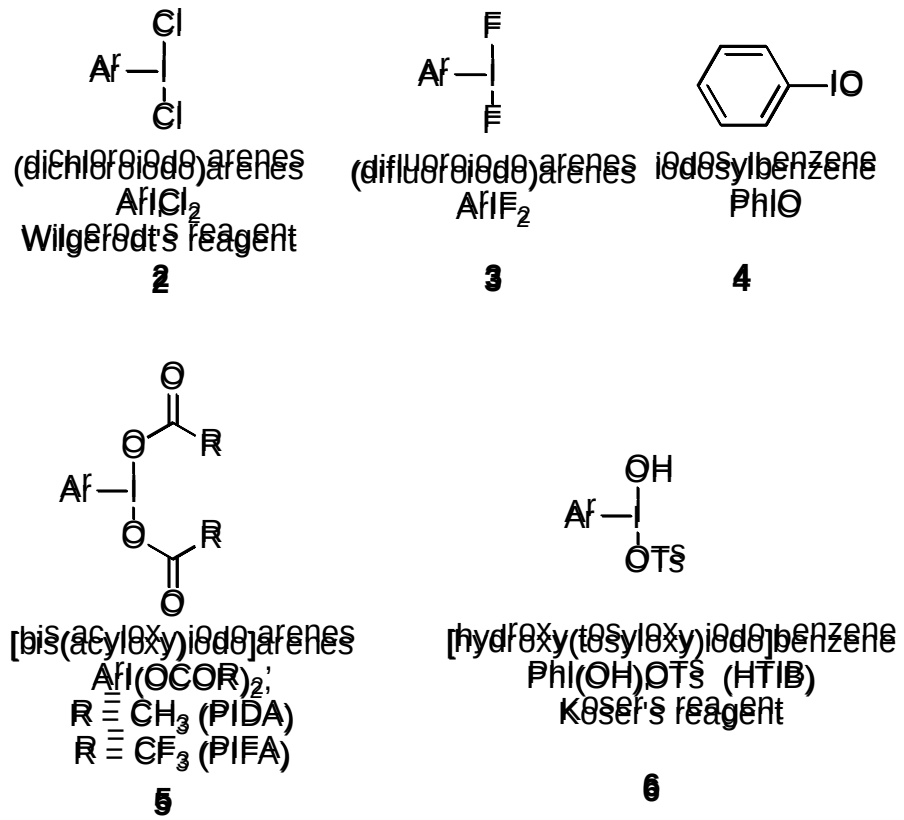


Figure 2

1.3. Reactivity of Trivalent Iodine compounds

Trivalent iodine compounds are widely used as reagents in organic synthesis. Their reactivity is based on the number of carbon and heteroatom ligands on the iodine atom. The most common type consist of one carbon ligand and two heteroatom ligands i.e RIL_2.[7-8] The two heteroatom ligands occupy the apical positions of the pseudotrigonal bipyramid and these iodanes are typically oxidants. Iodine(III) centres are highly electrophilic, making them liable to nucleophilic attack, and the two L ligands act as good leaving groups. The leaving process is termed reductive elimination, in which the λ^3-iodanyl group eliminates with energetically favourable reduction of the hypervalent iodide I(III) to normal valence I(I).[6-8]

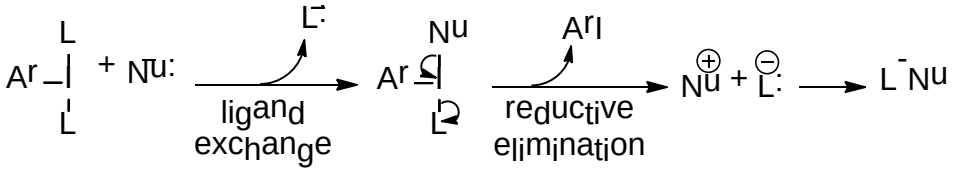


Figure 3

In recent years, the organic chemistry of hypervalent iodine compounds has received considerable attention, due to their oxidising properties and the fact that they are mild and highly selective, possess low toxicity and high stability, and are easy to handle and relatively environmentally friendly. Similar reactivity can be observed with highly toxic heavy-metal oxidisers, such as lead(IV), mercury(II) and thallium(III) reagents as well as expensive and rare transition metals. In addition, metal contamination in drug molecules is an important issue and minimising the use of metals in syntheses is one way to resolve this problem. Moreover, the possibility of forming a covalent chiral backbone on the iodine raises the possibility of enantioselective synthesis.[6-8]

1.4. Chiral Hypervalent Iodine(III) Reagents

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

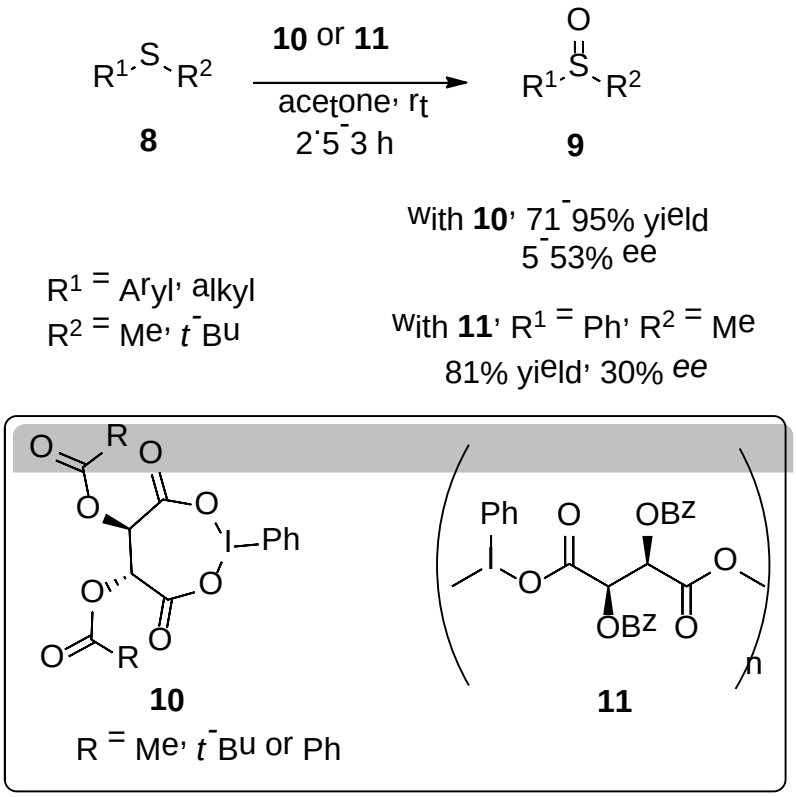
1.5. General Reactivities of Chiral Hypervalent Iodine Reagents

In recent years, great effort has been dedicated to the employment of enantiomerically pure hypervalent iodine reagents in asymmetric synthesis. Examples include the oxidation of sulfids to sulfoxides, α-functionalisation of carbonyl compounds, the dearomatisation of phenols, the functionalisation of alkenes, rearrangement reactions, and heterocyclisations.[5-8]

In addition, enantioselective oxidation reactions have been accomplished under catalytic conditions with chiral hypervalent iodine reagents, in which a catalytic amount of chiral iodoarene is oxidised to the hypervalent iodine species *in situ* using a stoichiometric co-oxidant. In the catalytic variant of the reaction, it is not necessary to prepare the hypervalent iodine compounds, and only a catalytic amount of chiral iodoarene is used as a precursor.[11,12]

1.5.1. Oxidation of Sulfids to Sulfoxides

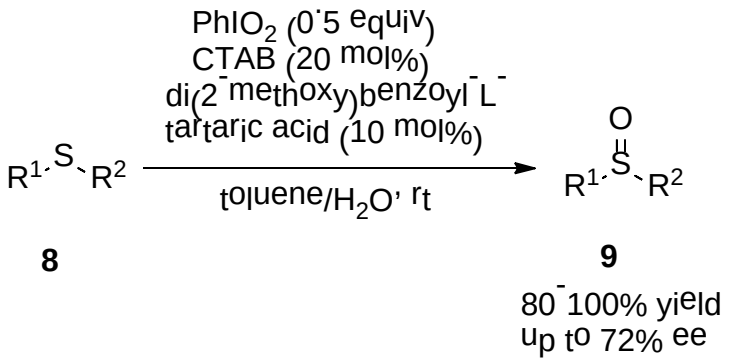
The first synthetically useful application of a chiral iodine(III) was illustrated by Imamoto[13] with **10a-c** and later by Koser[14] with **11** who performed the oxidation of sulfides **8** to sulfoxides **9** in moderate to good yield with selectivities of up to 53% ee with **10** (Scheme 1).



Scheme 1

Kita reported that 10 mol% of a chiral tartaric acid derivative and 20 mol% of cetyltrimethylammonium bromide (CTAB) used with iodoxybenzene ($PhIO_2$) in a cationic reversed micellar system led to the oxidation of sulfides **8** to sulfoxides **9** in high yields and

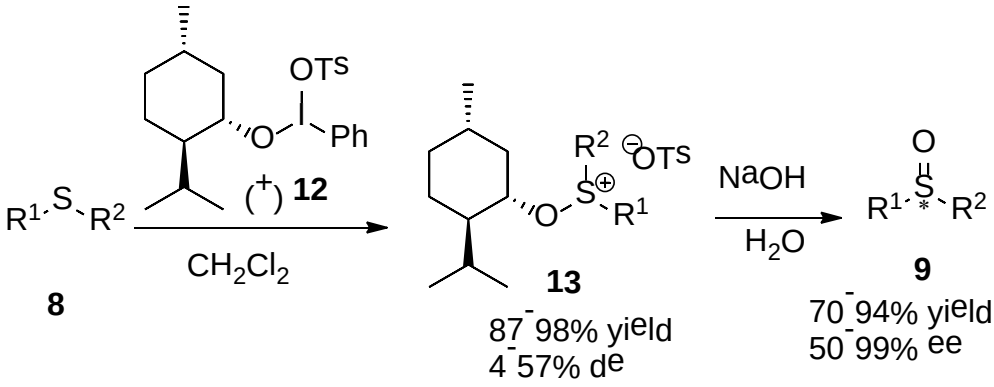
moderate enantioselectivities of up to 72% *ee* (Scheme 2). This is the first example of the asymmetric oxidation of sulfides to sulfoxides by using hypervalent iodine(V) reagents.[15]



Scheme 2

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

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



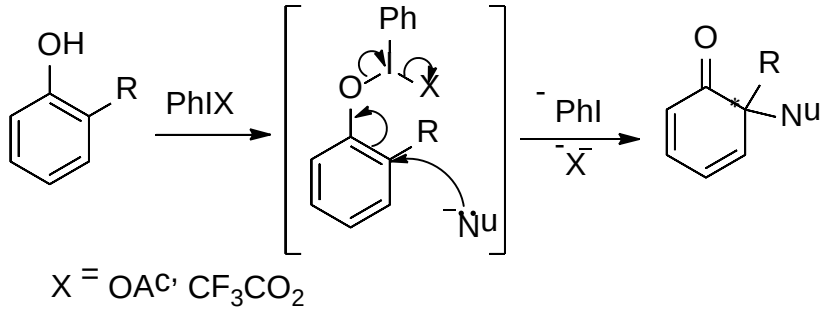
Scheme 3

Other research groups such as those of Chen and Xia,[18] Zhdankin *et al*.[19,20] and Wirth *et al*.[21] have prepared new chiral hypervalent iodine reagents and tested them in the oxidation of

sulfides to sulfoxides. Unfortunately, relatively poor enantioselectivities were observed in all cases.

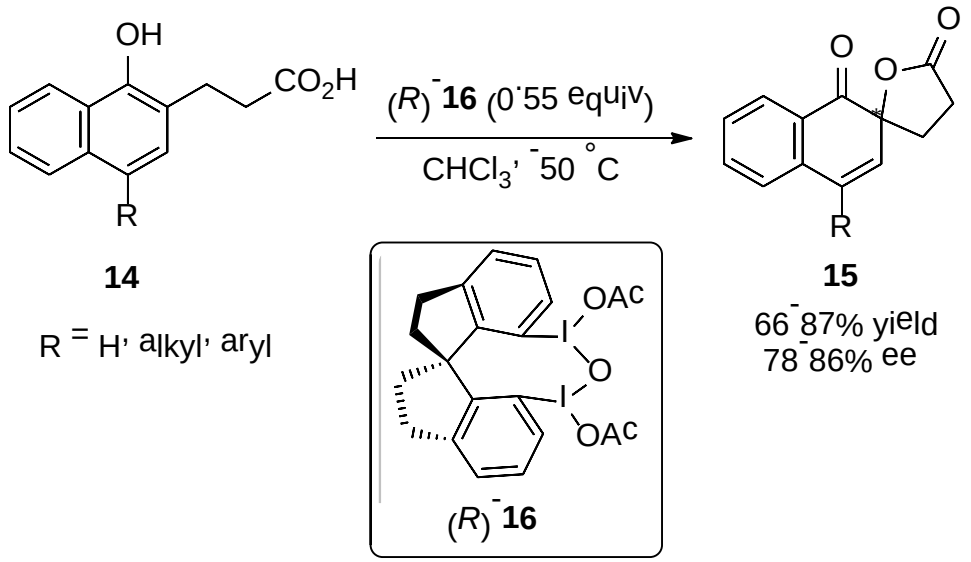
1.5.2. Dearomatisation reaction

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



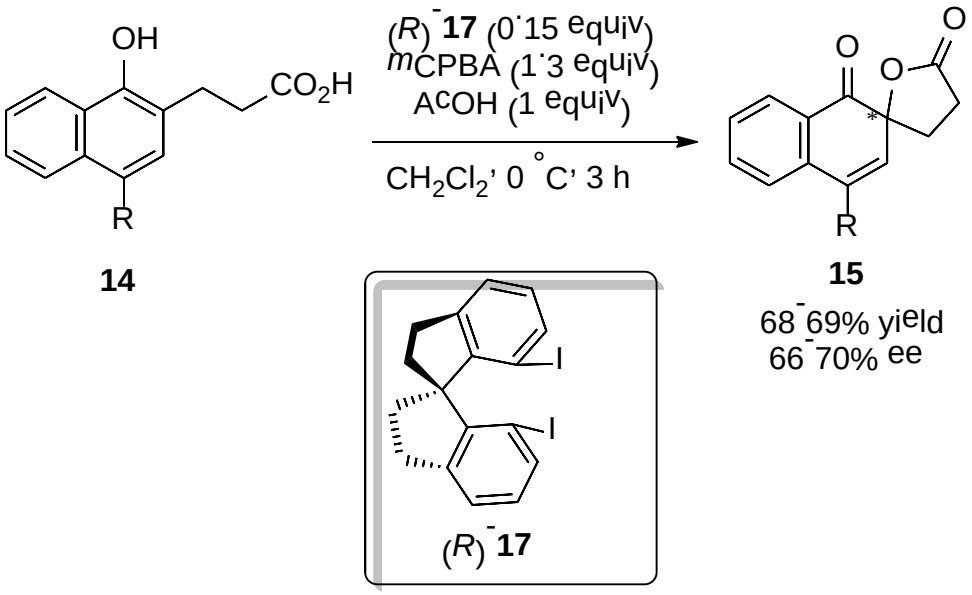
Scheme 4

In 2008 Kita *et al*.[23] reported the first enantioselective dearomatisation reaction using a chiral hypervalent iodine(III) reagent (*R*)-**16**. Iodane (*R*)-**16** has a rigid spirobiindane and it converted 4-substituted α-naphthols **14** into *ortho*-spirolactones **15** with moderate to good enantioselectivities and good yields (Scheme 5).



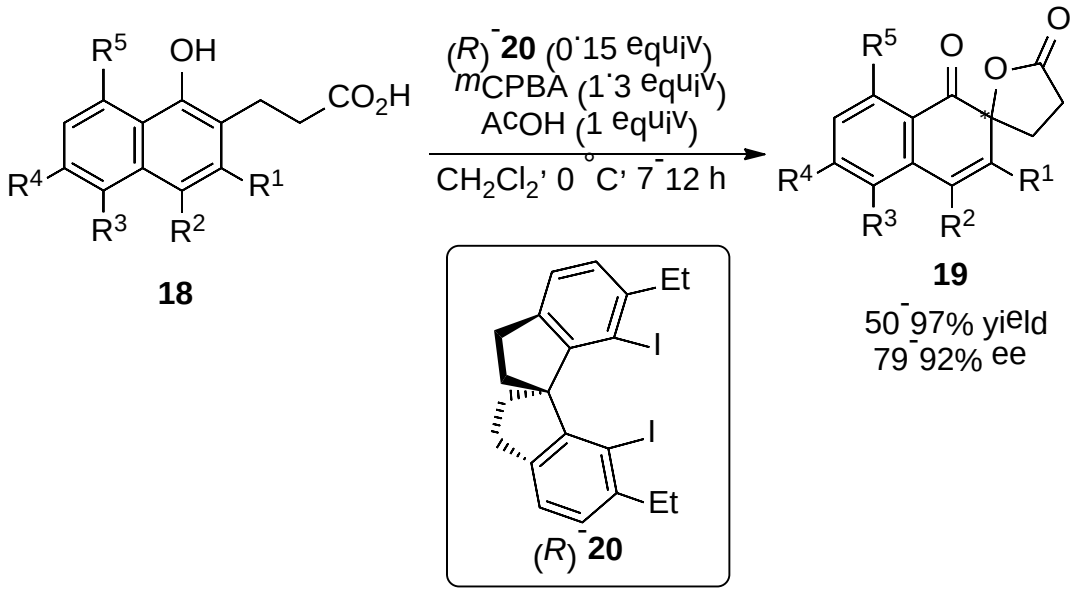
Scheme 5

The same group observed that the reaction could be made catalytic by employing 0.15 equiv of the corresponding iodoarene **17** and using *m*CBPA as a co-oxidant which generates chiral hypervalent iodine *in situ* (Scheme 6).[24] This catalytic reaction has to be performed at a higher temperature to enable oxidation of I(I) to I(III) and the enantioselectivities are diminished as a consequence.



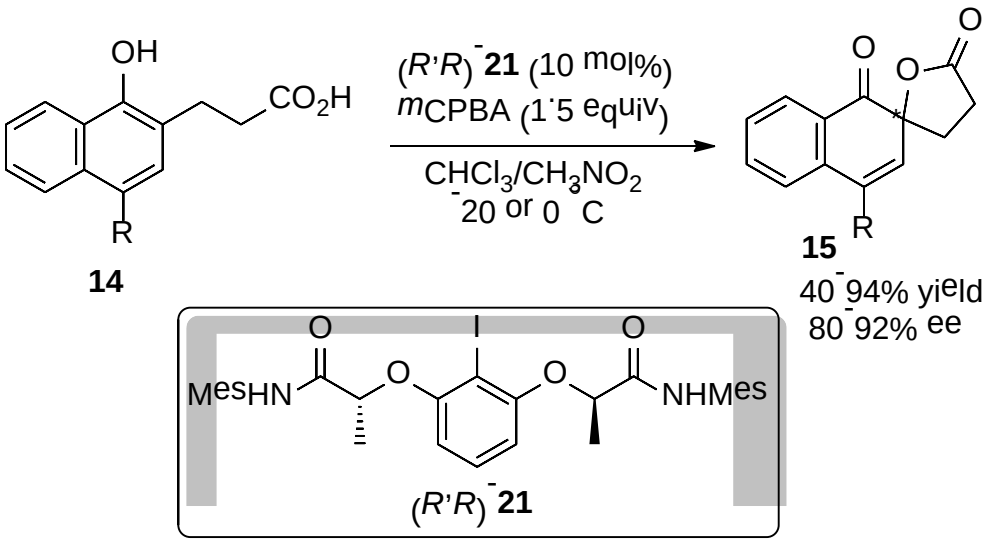
Scheme 6

In 2013, Kita *et al*.[25] reported higher enantioselectivities for this spirolactonisation using a new pre-catalyst (*R*)-**20**. This spirobiindane derivative has an ethyl group in the *o*-position to the iodine and when applied to the spirolactonisation of different naphthol derivatives **18**. The **19** were afforded in excellent yields and enantioselectivities of up to 92% ee (Scheme 7).



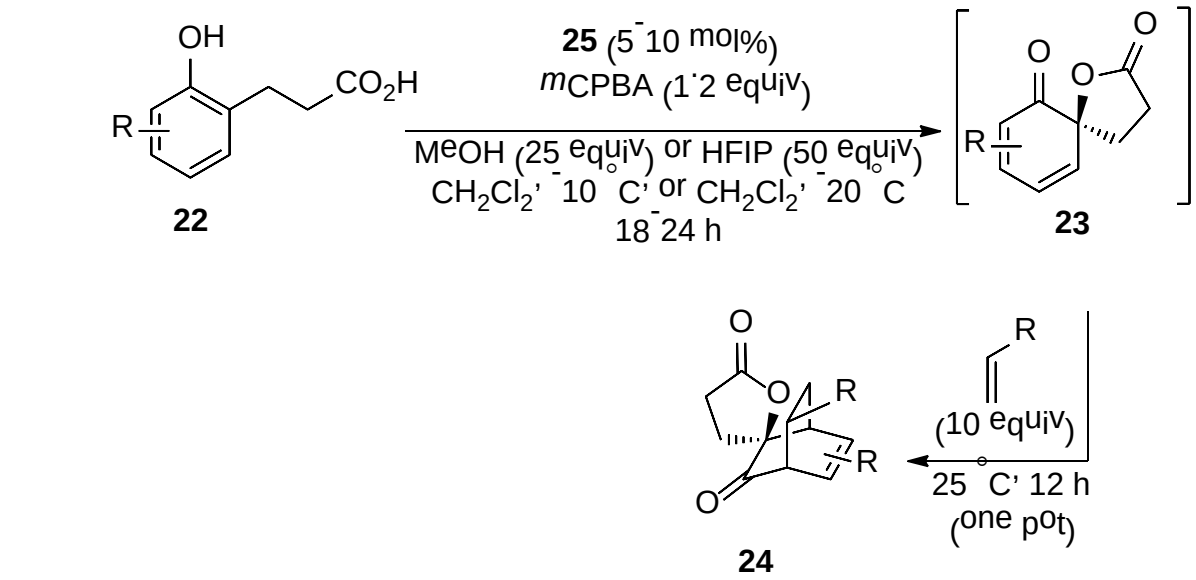
Scheme 7

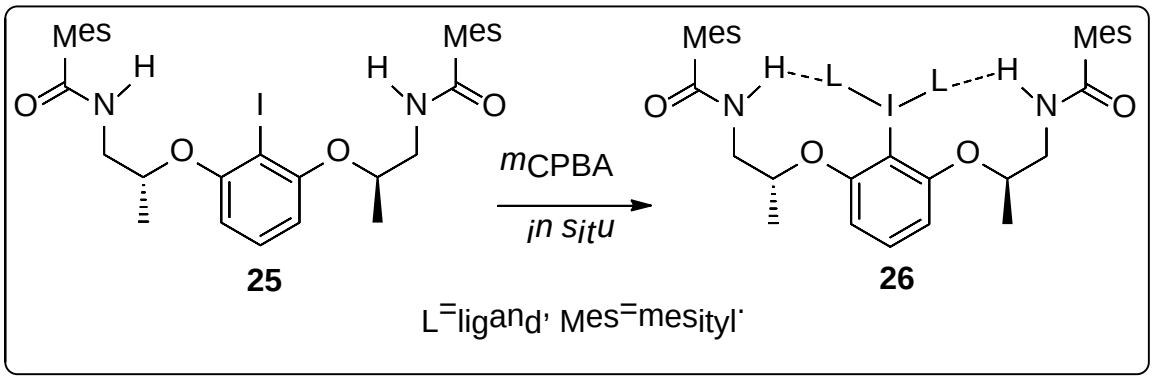
In 2010 Ishihara *et al*.[26] designed and prepared several C_2-symmetric chiral iodoarenes **21** and examined them in catalytic oxidative spirolactonisation reactions. Similar to Kita's catalyst ((*R*)-**20**) higher enantioselectivities of up to 92% ee were observed by using 10 mol% of (*R,R*)-**21** and 1.5 equiv of *m*CPBA as co-oxidant which generated the chiral iodane(III) catalyst *in situ* (Scheme 8). The same authors showed that the selective oxidation of the double bond into an epoxide occurred when using an excess of *m*CPBA in this reaction with good yields and diasteroselectivity.[27]



Scheme 8

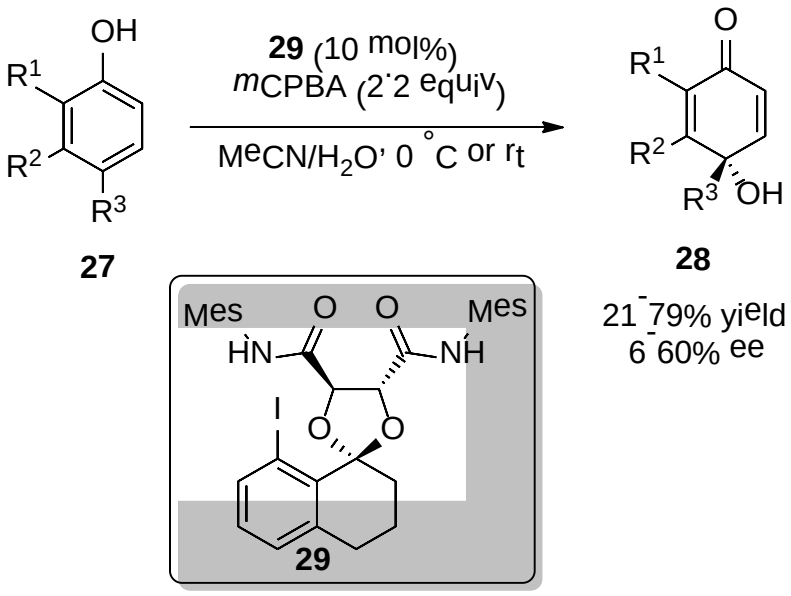
In 2013, Ishihara *et al*.[28] employed their C_2-symmetric chiral iodoarene **25** in the tandem enantioselective catalytic oxidative dearomatisation of phenols **22** and the Diels–Alder reaction. The active hypervalent iodine(III) species **26** was generated *in situ* from the C_2-symmetric chiral iodoarene **25** and *m*CPBA. As a result high to excellent enantioselectivities were observed for the desired cyclohexadienone spirolactones **23** and the subsequent Diels–Alder adducts **24** (Scheme 9).





Scheme 9

In 2013, Harned *et al.*[29] prepared the new chiral aryl iodide pre-catalyst **29** derived from 8-iodotetralone and tartaric acid and used it with 2.2 equivalents of *m*CPBA as co-oxidant in the asymmetric oxidation of phenols **27** to provide the *para*-quinols **28** with moderate to good yields and enantioselectivities (Scheme 10).

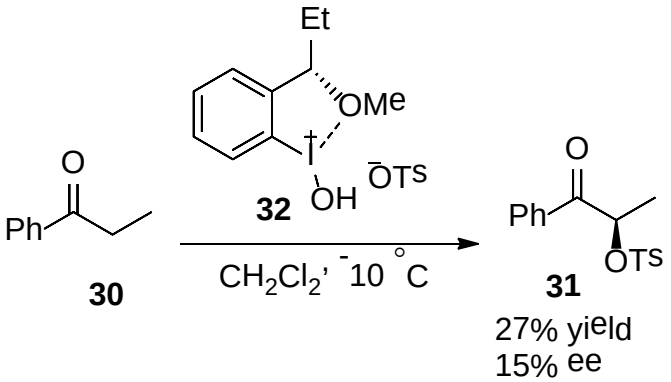


Scheme 10

1.5.3. Functionalisation of Carbonyl Compounds

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

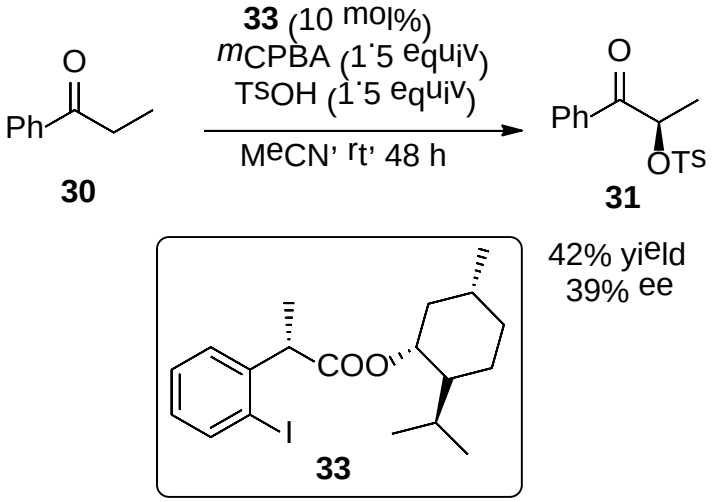
In 1997 Wirth and co-workers[30] reported the first enantioselective α-oxytosylation of propiophenone **30** utilising chiral hypervalent iodine(III) compounds **32** as stoichiometric reagents. They obtained the expected product **31** with 15% ee demonstrating that this was a viable strategy for the preparation of non-racemic chiral compounds (Scheme 11).



Scheme 11

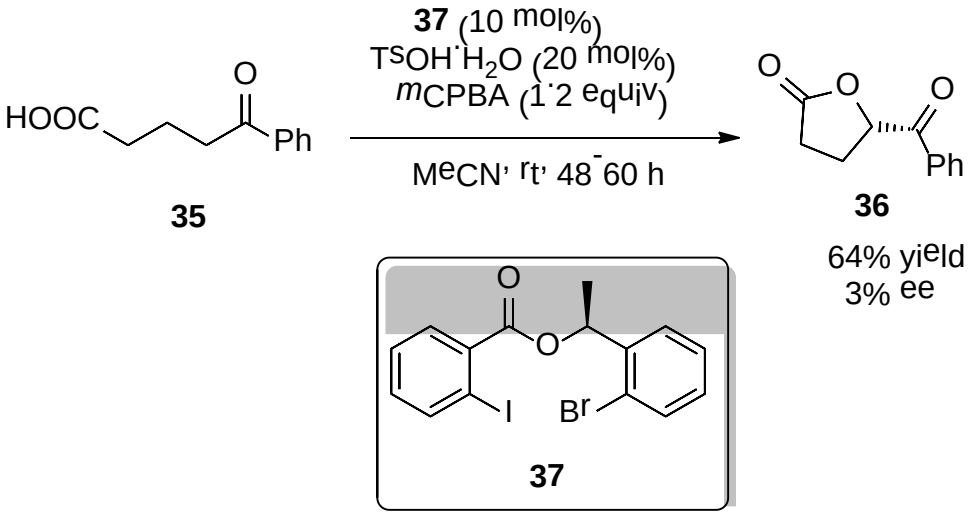
In 1998, the same groups reported derivatives of chiral hypervalent iodine reagent **32** in which they installed an extra *ortho* substituent on the benzene ring and examined these catalysts in the enantioselective α-oxytosylation of propiophenone, which afforded tosylates in up to 28% ee.[31] and with slightly improved enantioselectivities of up to 40% ee in 2001.[32]

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



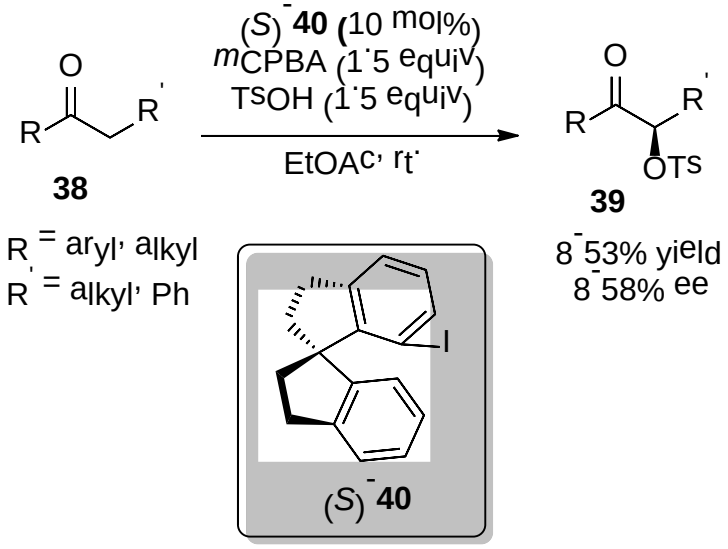
Scheme 12

In 2010, Wirth *et al*.[35] prepared more chiral iodoarene catalysts **37** and employed them in the enantioselective α-oxytosylation of propiophenone but only 26% ee was obtained with 70% yield. Furthermore, they investigated this catalyst in the lactonisation reaction of 5-oxo-5-phenylpentanoic acid **35**, however poor or no enantioselectivity was obtained for the desired product **36** (Scheme 13).



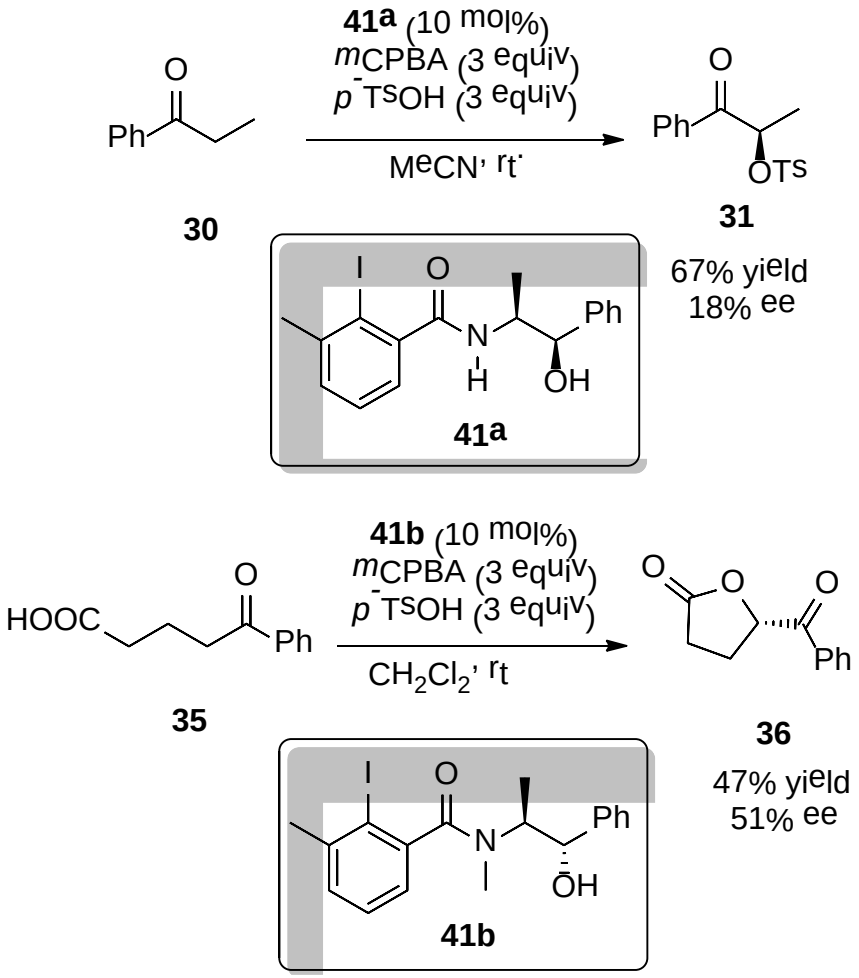
Scheme 13

One year later, in 2011, Zhang *et al*.[36] prepared new chiral iodoarene (*S*)-**40** and derivatives containing a spirobiindane scaffold and tested their chiral inducing ability as a catalyst in the asymmetric α-tosyloxylation of ketones **38** using *m*CPBA as a stoichiometric oxidant. An enantioselectivity of up to 58% ee was achieved for the α-tosyloxylated ketones **39** (Scheme 14).



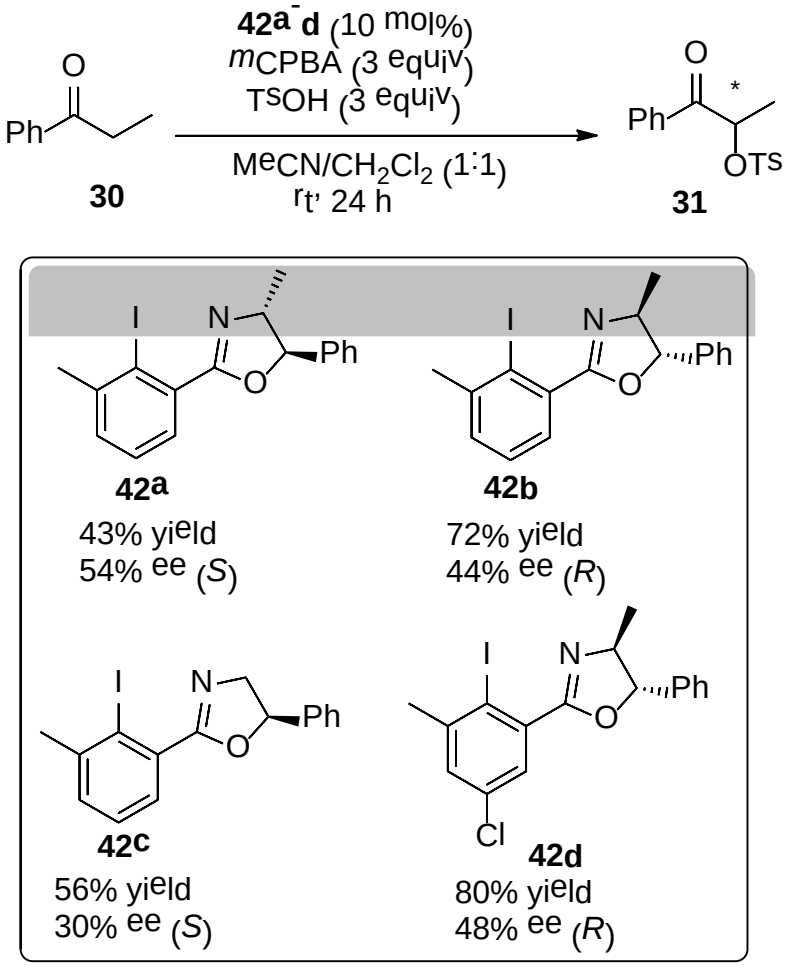
Scheme 14

In 2012, Moran and Rodríguez[37] prepared chiral iodoarenes **41a** and **41b** and they tested **41a** as a pre-catalyst with *m*CPBA as the co-oxidant in the α-oxytosylation of propiophenone **30** observing a good yield (67%) and 18% ee. Also, an improved enantioselectivity of up to 51% ee was obtained for the lactonisation of 5-oxo-5-phenylpentanoic acid **38** by employing pre-catalyst **41b** and *m*CPBA to obtain the corresponding lactone **36** in 47% yield (Scheme 15).



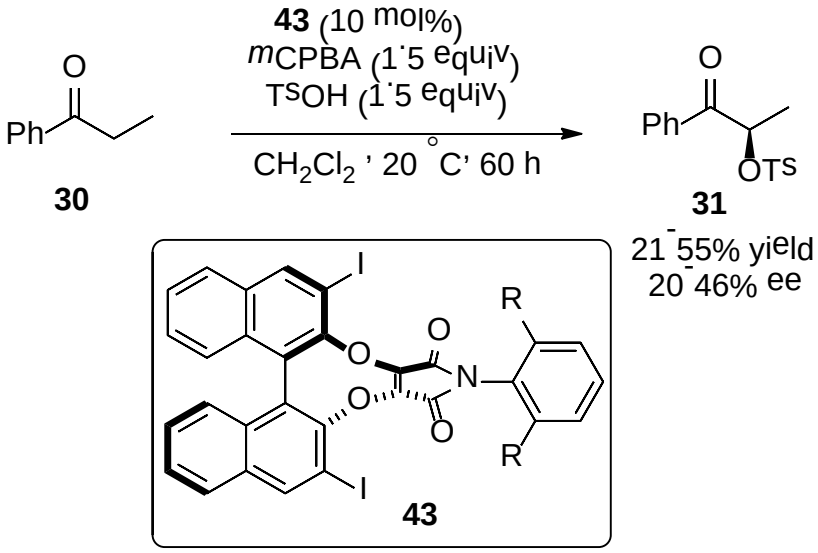
Scheme 15

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



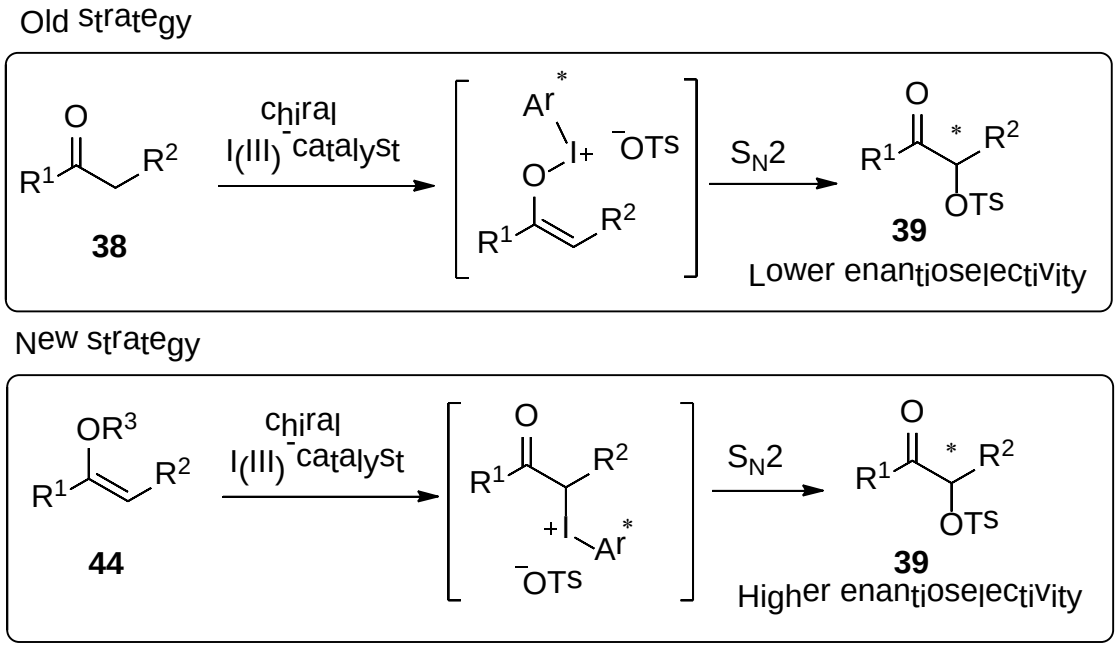
Scheme 16

Berthiol and co-workers designed a new family of hypervalent iodoarene organocatalysts based on 3,3′-diiodo-BINOL-fused maleimides **43**. By applying these new catalysts in the propiophenone oxidation reaction, the enantioselectivity for the expected product was similar to that previously reported using structurally different organocatalysts (Scheme 17).[39]



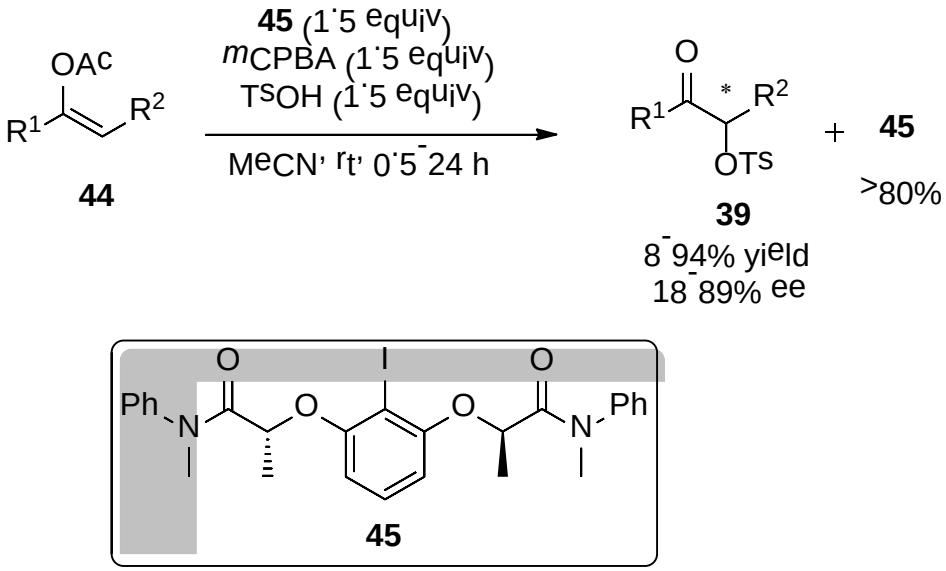
Scheme 17

In 2015, Legault and Basdevant[40] proposed a new strategy for this reaction in which the possibility of higher enantioselectivity could be achieved by using enol derivatives instead of ketone substrates. This would force the reaction to proceed through a C-bonded intermediate pathway instead of through an O-bonded iodane intermediate (Scheme 18).



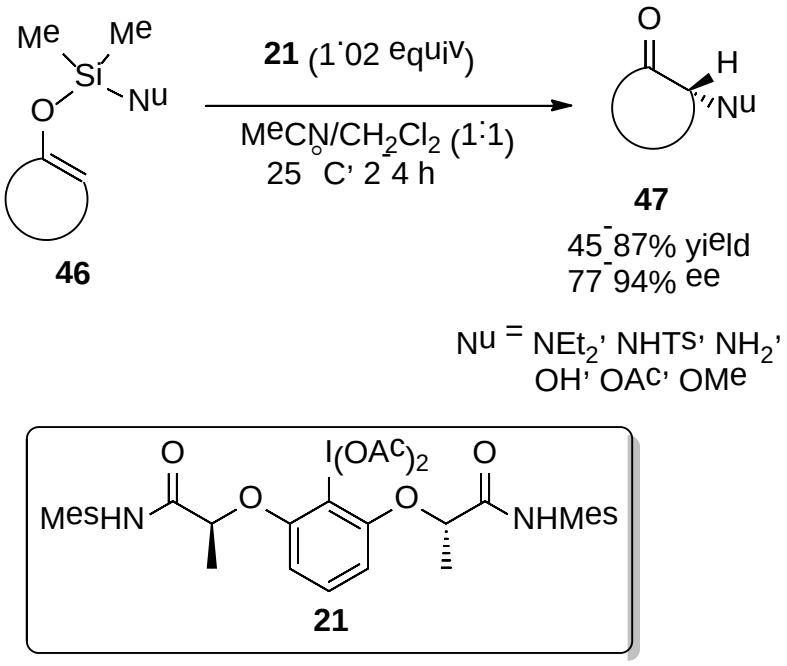
Scheme 18

Using this approach, Legault and Basdevant achieved enantioselectivities of up to 90% ee using chiral iodoarene reagents **45** with enol esters **44** as substrates. Enol **44** can be synthesised readily from the corresponding ketones or alkynes (Scheme 19).[40] Both stoichiometric and catalytic conditions successfully worked in this reaction. The excellent enantioselectivity was obtained when the reaction was carried out in a catalytic system, using 20 mol% of the catalyst **45** with slow addition of a 1:1 mixture of *m*CPBA/TsOH.



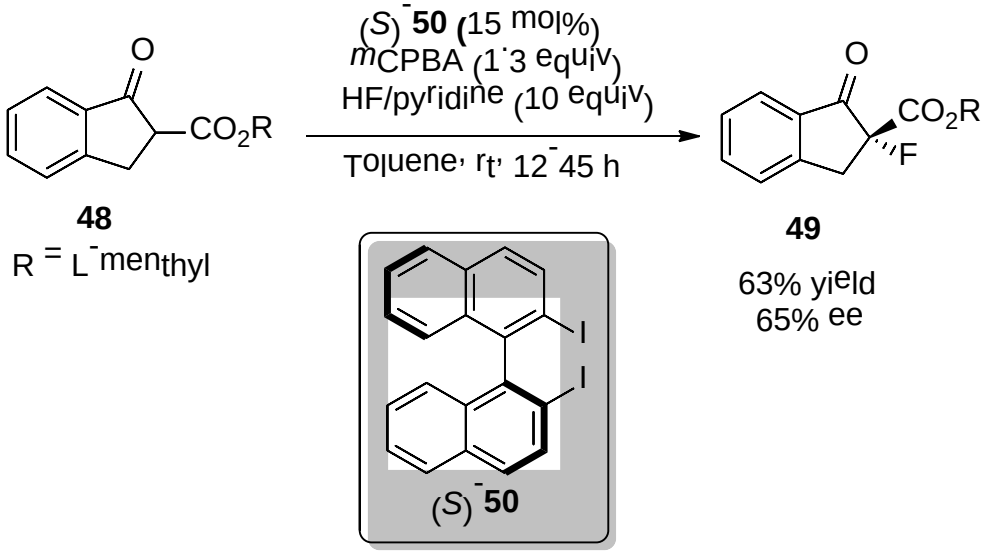
Scheme 19

Wirth and Mizar showed that the lactate-based hypervalent iodine reagent **21** can be successfully employed in stereoselective reactions of cyclic enol ethers **46** by nucleophilic attack on the silyl enol ether. This process provided access to several nitrogen and oxygen substituted cyclic ketones **47** with moderate to high enantioselectivities and yields (Scheme 20).[41]



Scheme 20

In 2014, Kita *et al*.[42] developed an asymmetric fluorination reaction of β-dicarbonyl compounds catalysed by chiral iodoarene **50**. This was the first example of the enantioselective fluorination reaction of β-ketoesters **48** employing a catalytic system consisting of a chiral iodoarene catalyst, HF/pyridine as the fluorine source and *m*CPBA as the co-oxidant which afforded the α-fluorinated β-ketoesters **49** with moderate yields and enantioselectivities (Scheme 21).

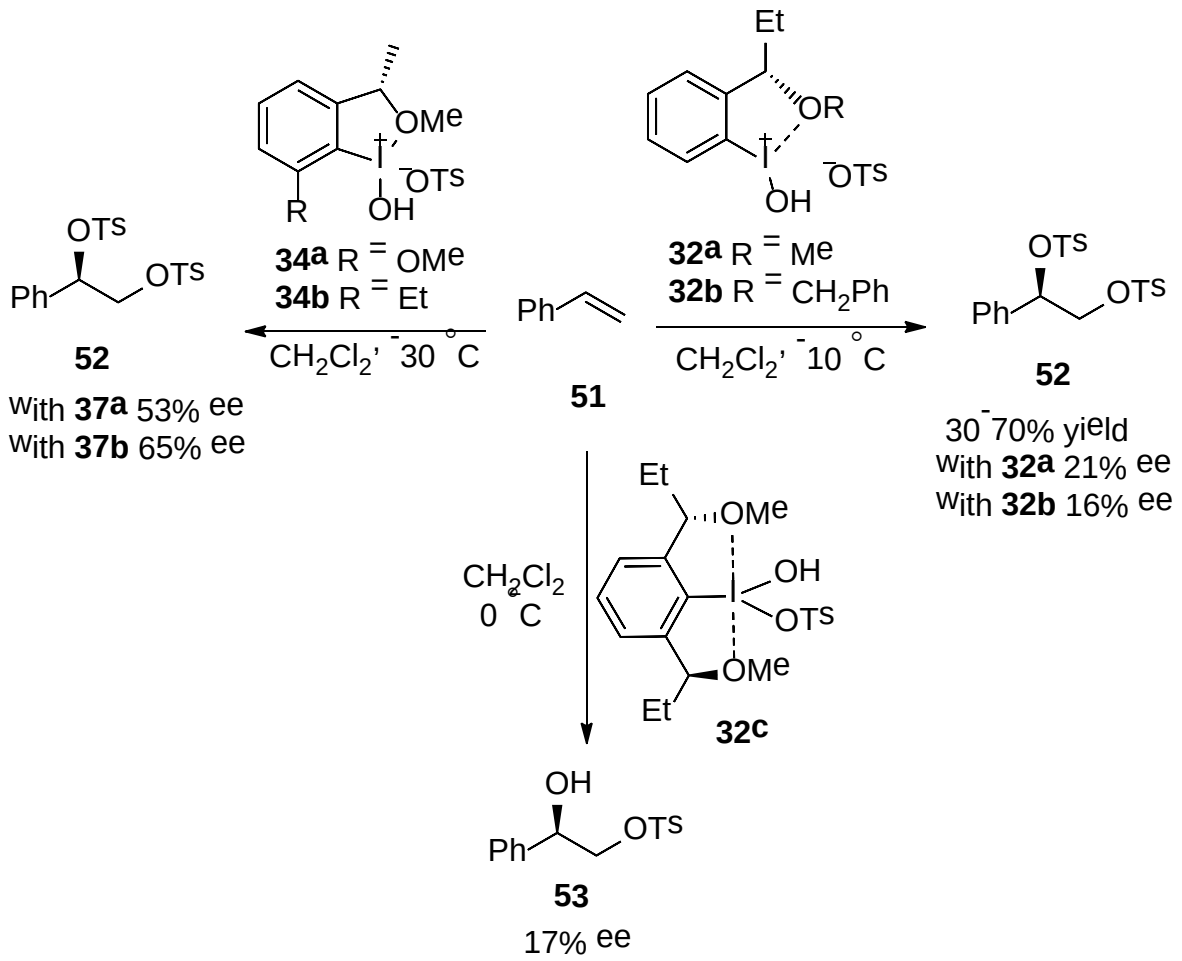


Scheme 21

1.5.4. Functionalisation of alkenes

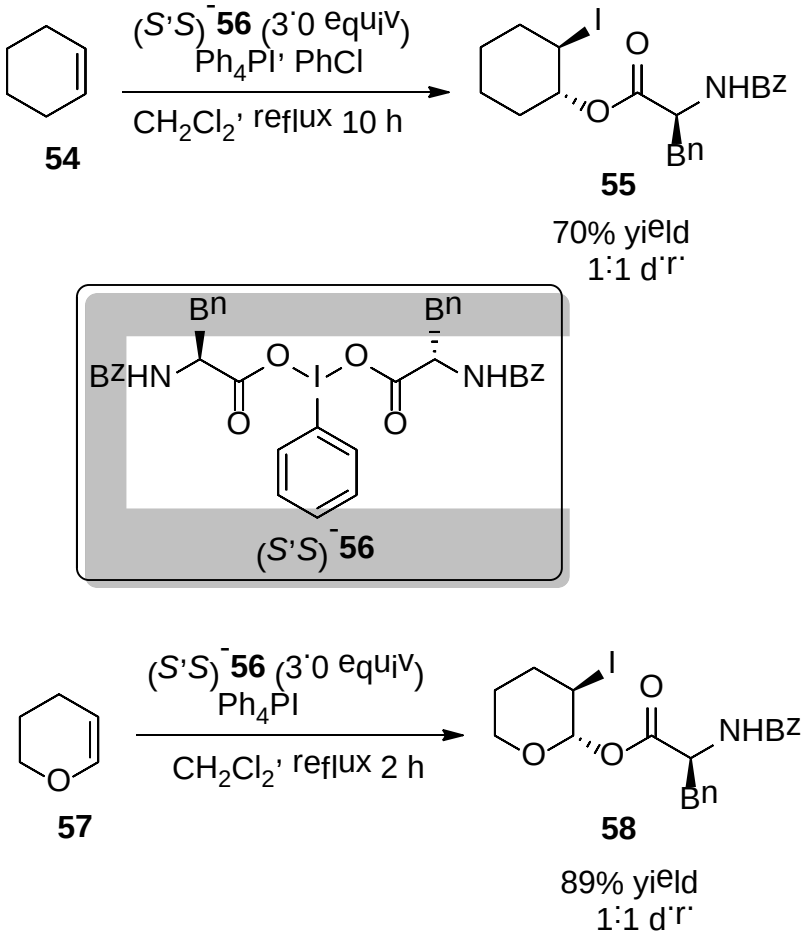
One of the most important reactions in organic synthesis is the asymmetric oxidation of alkenes which allows the fast preparation of polyfunctional chiral compounds.[43] In particular, investigations using chiral hypervalent iodine reagents for this purpose have been reported by numerous research groups.[43-45]

In 1997 Wirth and Hirt[30] prepared three different chiral hypervalent iodine(III) compounds **32 a-c** and tested them in the asymmetric oxidation of styrene under the same conditions that they previously utilised in the α-oxytosylation of ketones (Scheme 11 and 12). Either the dioxytosylated products **52** or the mono(tosyloxy) mono(hydroxy) products **53** were obtained in up to 21% ee. Shortly after, Wirth and Hirt[31] functionalised these reagents further by introducing a methoxy group in the *ortho*-position to the iodine atom and the enantioselectivity was slightly increased up to 53% ee with **34a** for dioxytosylated products **52.** Three years later, the same research group[32] achieved up to 65% ee for dioxytosylated product **52** using chiral iodine(III) **34b** (Scheme 22).



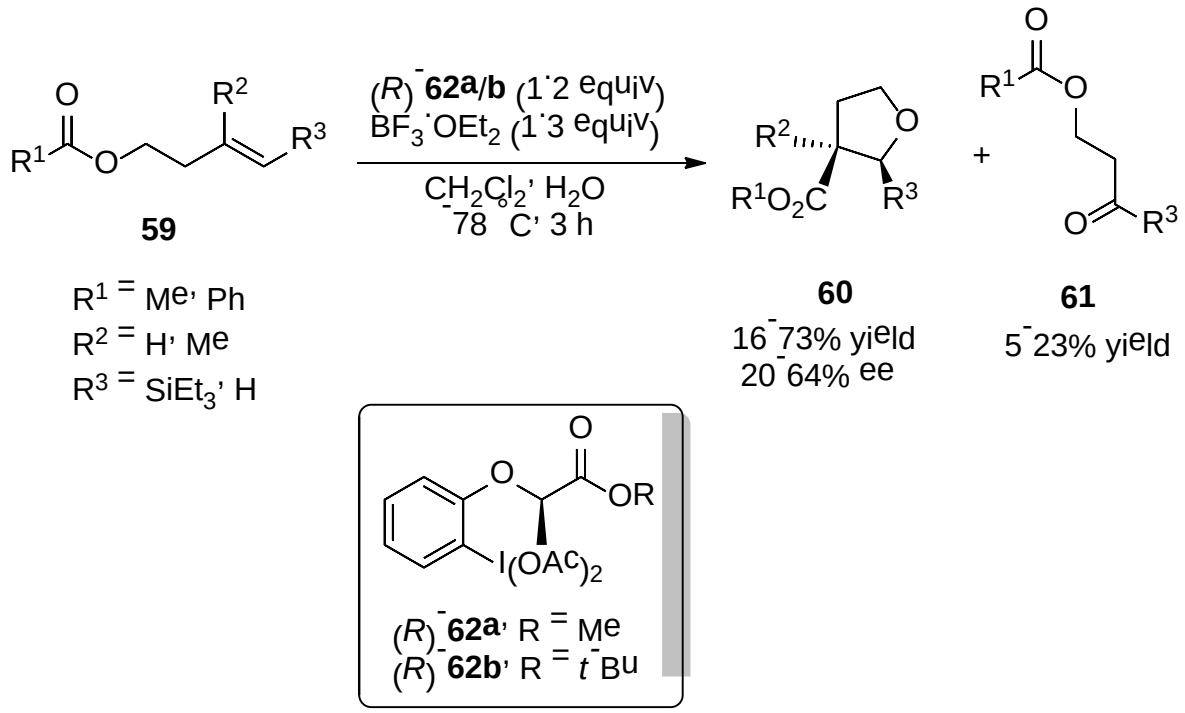
Scheme 22

In 2004, Zhdankin *et al.*[46] prepared new chiral amino acid-derived iodobenzene dicarboxylate (*S*,*S*)-**56.** They employed this reagent with iodide anion in the β-iodocarboxylation reaction of cyclohexene **54** and dihydropyran **55** which afforded a 1:1 mixture of both diastereomers of **57** and **58** in high yield (Scheme 23).



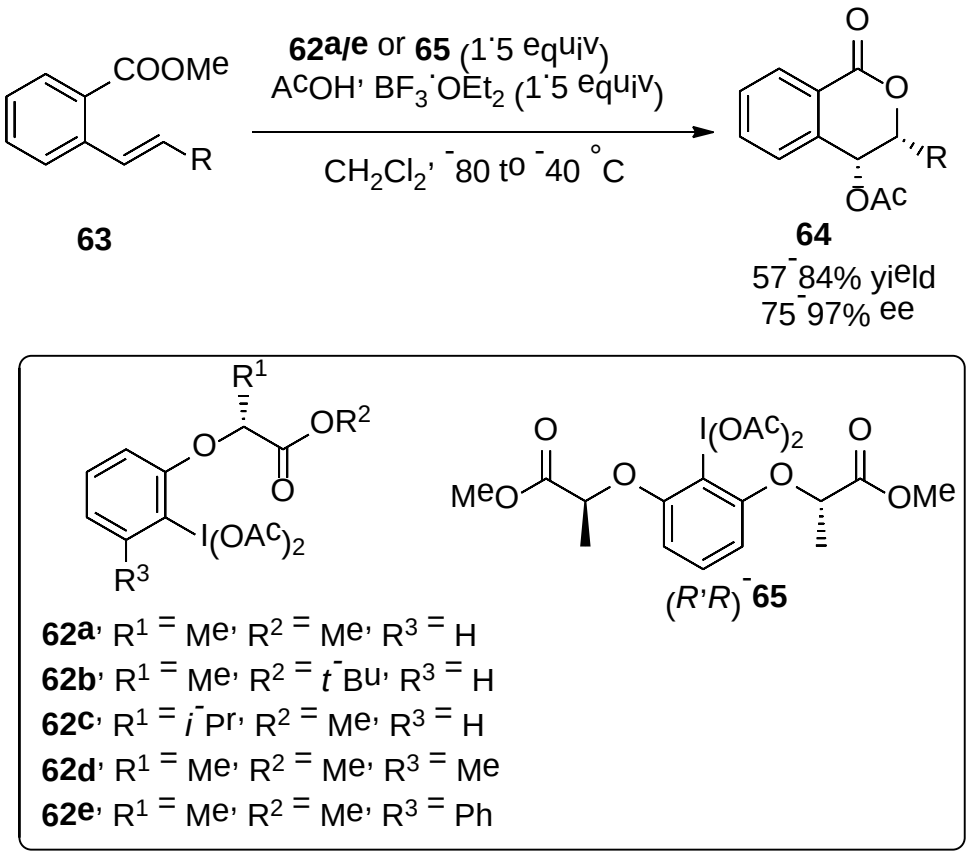
Scheme 23

In 2007, Fujita *et al*.[47] prepared two optically active chiral hypervalent iodine(III) reagents (*R*)-**62** in which chiral ester derivatives were used instead of chiral amides. They employed these reagents in the development of a tetrahydrofuranylation process of acyloxybutenes (*Z*/*E*)-**59.** The tetrahydrofuran products **60** were obtained in up to 64% ee with a small amount of oxo-butyl benzoate **61** being formed (Scheme 24). They also showed that the enantioselectivity was dependent on the electrophilic addition of iodine(III) toward the double bond, the substituents on the acyloxybutene substrates and the nucleophilic addition of the acyloxy group toward the double bond.



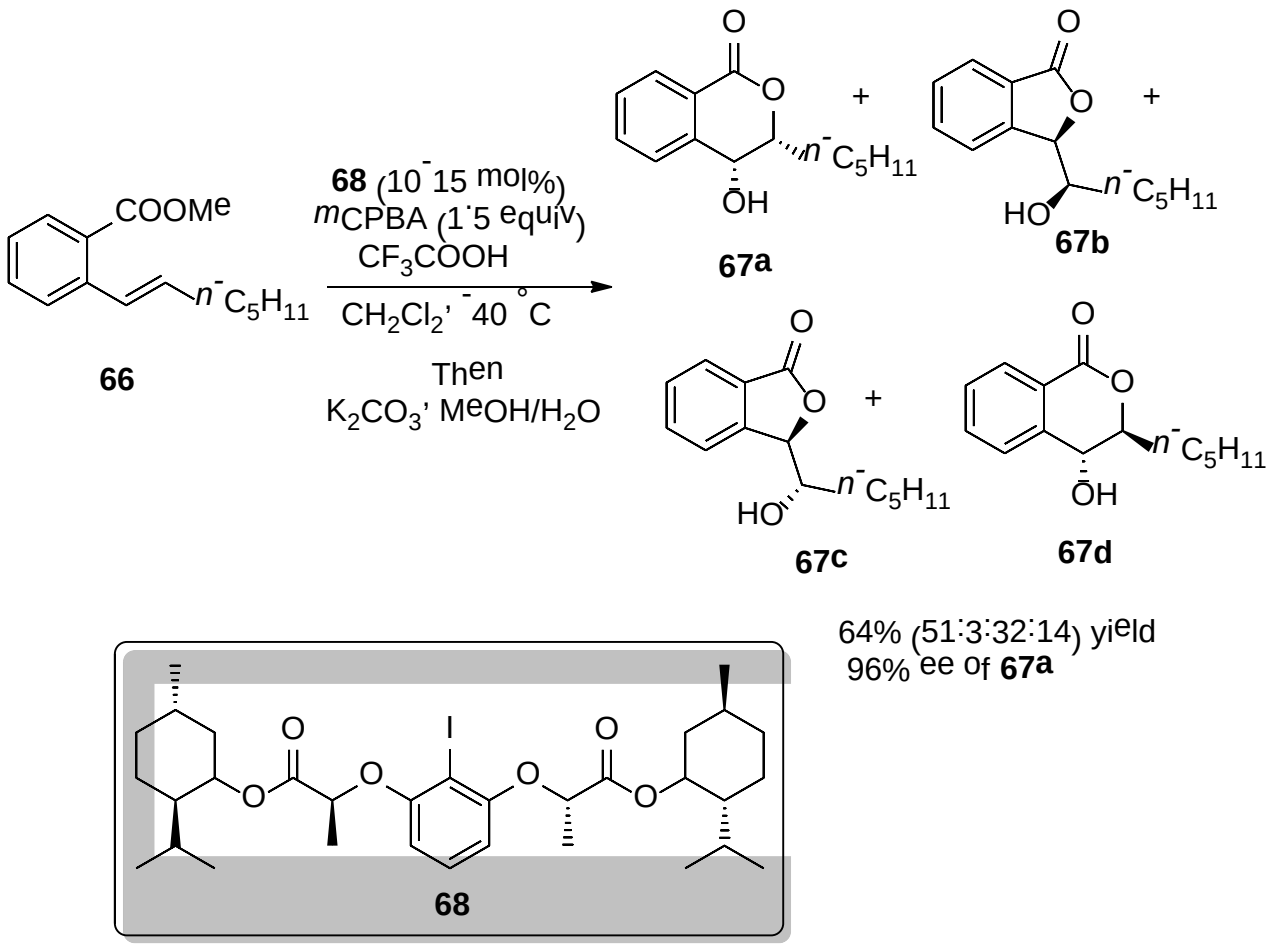
Scheme 24

Three years later, Fujita *et al*.[48] synthesised a new family of lactate-derived optically active hypervalent iodine(III) reagents (*R*)-**64c-e** and (*R*,*R*)-**68**. They utilized these reagents in the enantioselective oxidative lactonization of *ortho*-alkenylbenzoate **67** using stoichiometric amounts of these iodanes in the presence of *para*-toluenesulfonic acid or acetic acid. The corresponding δ-lactones **69** were formed with high regioselectivity and up to 97% ee (Scheme 25).



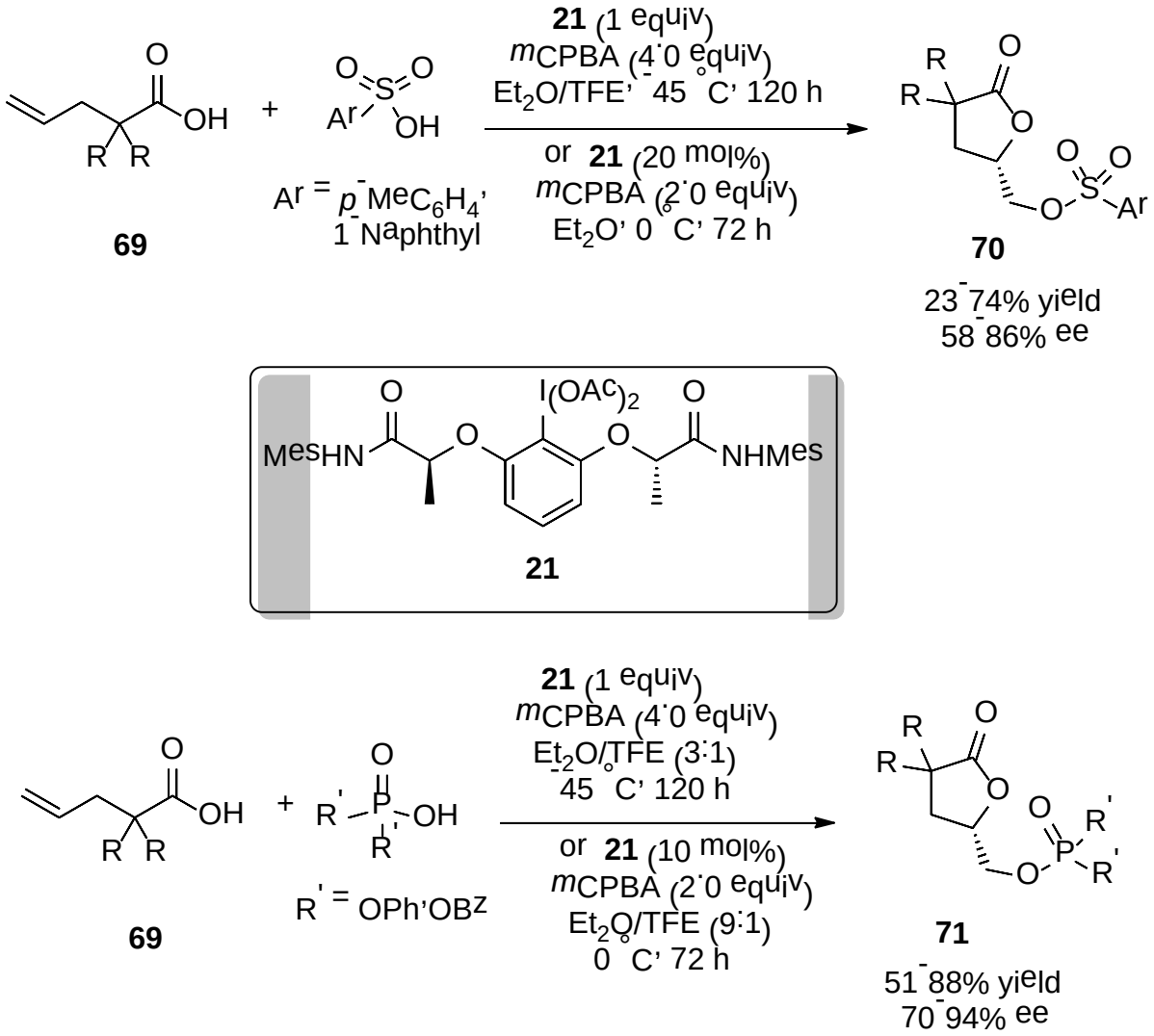
Scheme 25

The same research group prepared several oxyisochromanone natural products following their process using chiral hypervalent iodine reagent generated *in situ* by applying a catalytic amount of chiral lactate-based iodoarene with a stoichiometric amount of *m*CPBA in the enantioselective oxylactonisation of an *ortho*-alkenylbenzoate derivatives **66**. 4-Hydroxyisochroman-1-one derivatives **67** were obtained in excellent enantioslectivities with moderate yields which resulted from the realisation of racemic anti-products by a direct oxidation of **66** by *m*CPBA. They indicated that the lactate moiety on the chiral iodoarene precatalyst could be responsible for the high enantioselectivity of oxylactonisation (Scheme 26).[49]



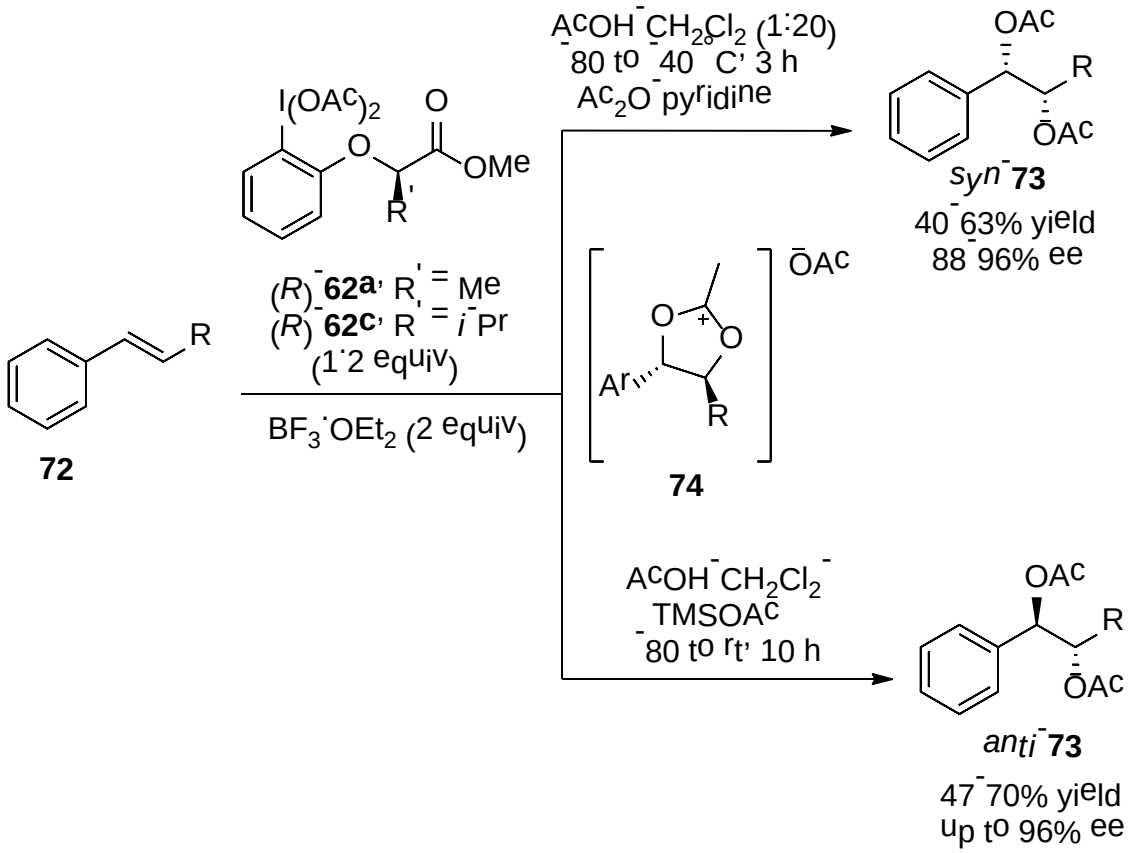
Scheme 26

In 2017, Masson *et al*.[50] reported the first enantioselective sulfonyl- and phosphoryl-oxylactonisation of 4-pentenoic acids derivatives **69** mediated by a chiral aryl-λ^3-iodane. They used a stoichiometric or catalytic amount of chiral iodoarene **21** and achieved moderate to excellent enantioselectivities for sulfonyloxy- and phosphoryloxy-γ-butyrolactones **70** and **71** with acceptable yields (Scheme 27). Notably, high enantioselectivities with lower yields were obtained when a stoichiometric amount of chiral iodoarene was employed. However, using a catalytic amount of chiral iodoarene provided the desired product with lower enantioselectivities and higher yields.



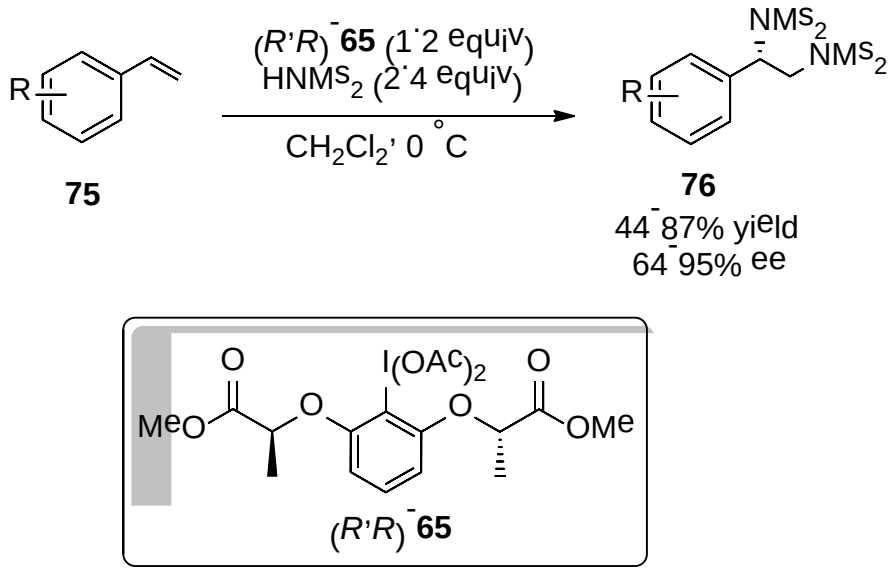
Scheme 27

In 2011 Fujita *et al*.[51] developed the enantioselective Prévost and Woodward reactions by employing hypervalent iodine(III) reagents (*R*)-**62a** and (*R*)-**62c** in the oxylactonisation of alkenes **72**. They selectively observed two products depending on the nature of the nucleophile. When the water was added at the 2-position of 1,3-dioxolan-2-yl cation intermediate **74** the *syn* products (*syn*-**73**) were obtained in moderate yields with up to 96% ee. However, when the acetic acid was added at the 4-position of the cation intermediate **74** the *anti* products (*anti*-**73**) were isolated in good yield and up to 96% ee (Scheme 28).



Scheme 28

Muñiz *et al*.[52] successfully achieved the first example of an enantioselective diamination of an alkene using Fujita's iodane (*R*,*R*)-**65**. They employed this chiral hypervalent iodine(III) reagent in the enantioselective diamination of styrene derivatives **75** which generated enantiopure diamines **76** in moderate to good yields with excellent enantioselectivities of up to 95% (Scheme 29). In 2013, the same research group investigated new dinuclear binaphthyl iodine(III) reagents in the same reaction and obtained the product **76** with up to 32% ee.[53]



Scheme 29

In 2016, Ishihara *et al*.[54] illustrated that the important structural force in chiral hypervalent iodine reagents is a selective hydrogen bonding arrangement (Figure4).

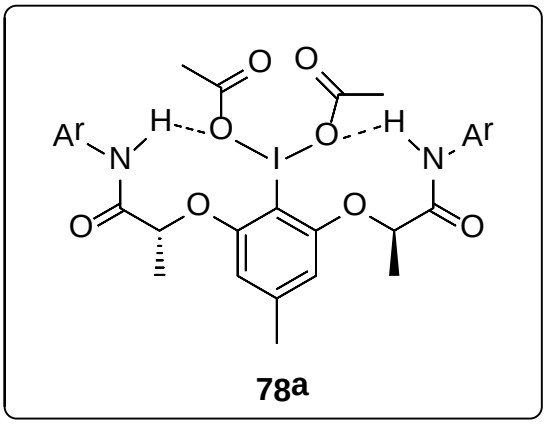
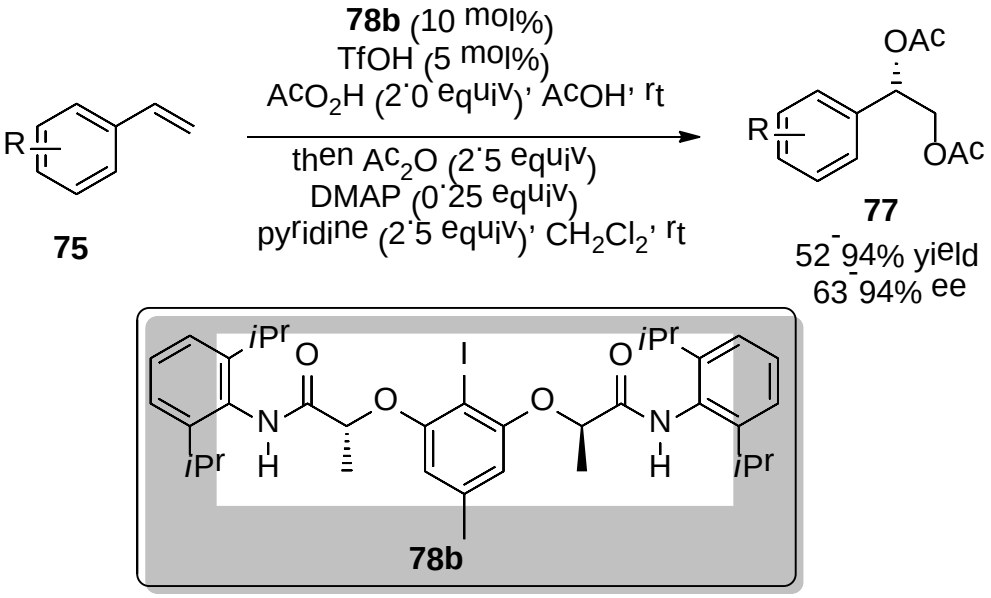


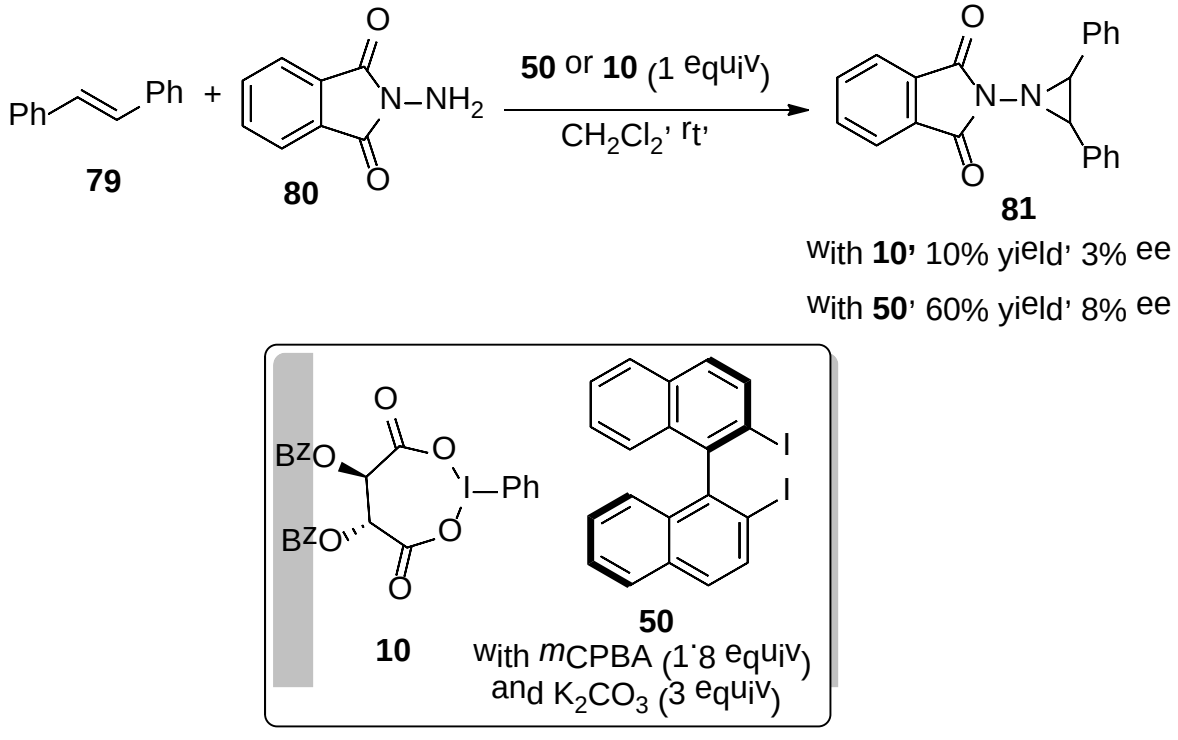
Figure 4

They described the first enantioselective catalytic diacetoxylation of styrenes by employing chiral hypervalent iodine **78b** as a catalyst under mild conditions and the corresponding dioxygenation products **77** were afforded in good to high yields with up to 94% ee (Scheme 30).



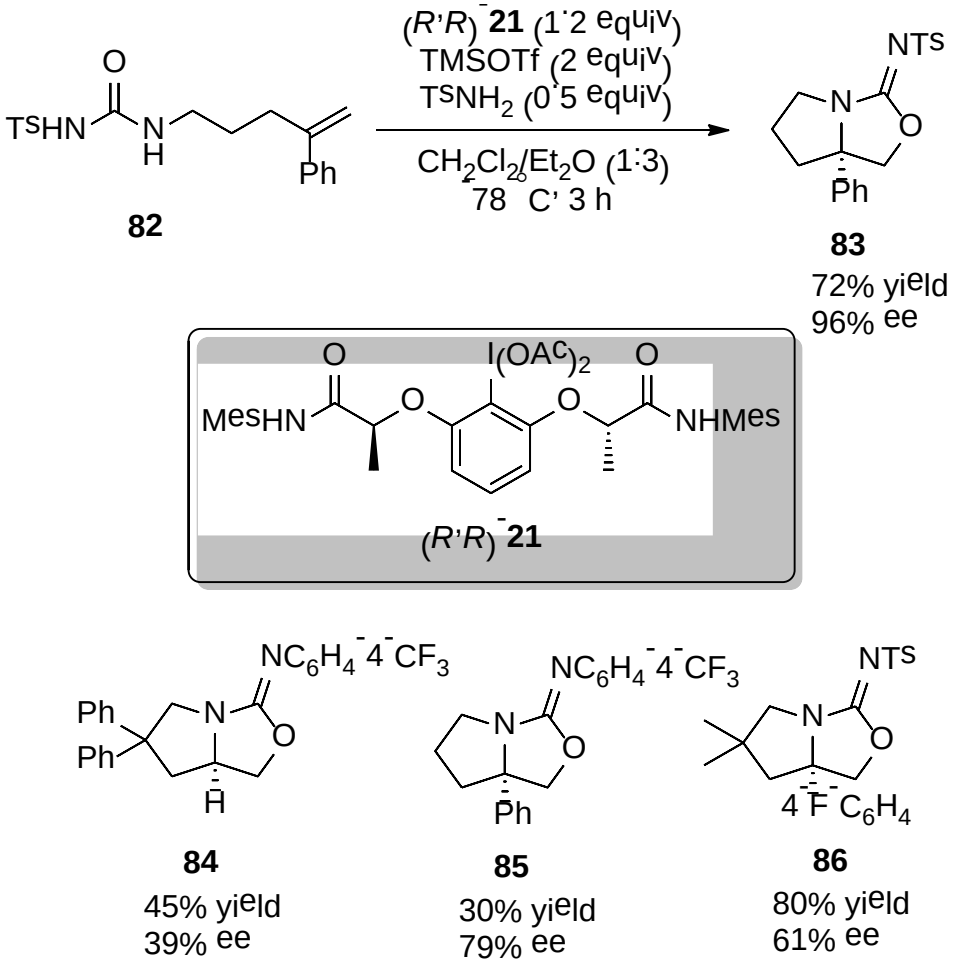
Scheme 30

In 2007, Wirth *et al*.[55] reported the first efforts towards the enantioselective aziridination of alkenes employing two methods. First, employing chiral iodoarene **50** under Che's conditions,[56] and second using stoichiometric Imamoto's reagent[13] **10**. Both reagents provided the expected aziridine **81** in low enantioselectivity (Scheme 31).



Scheme 31

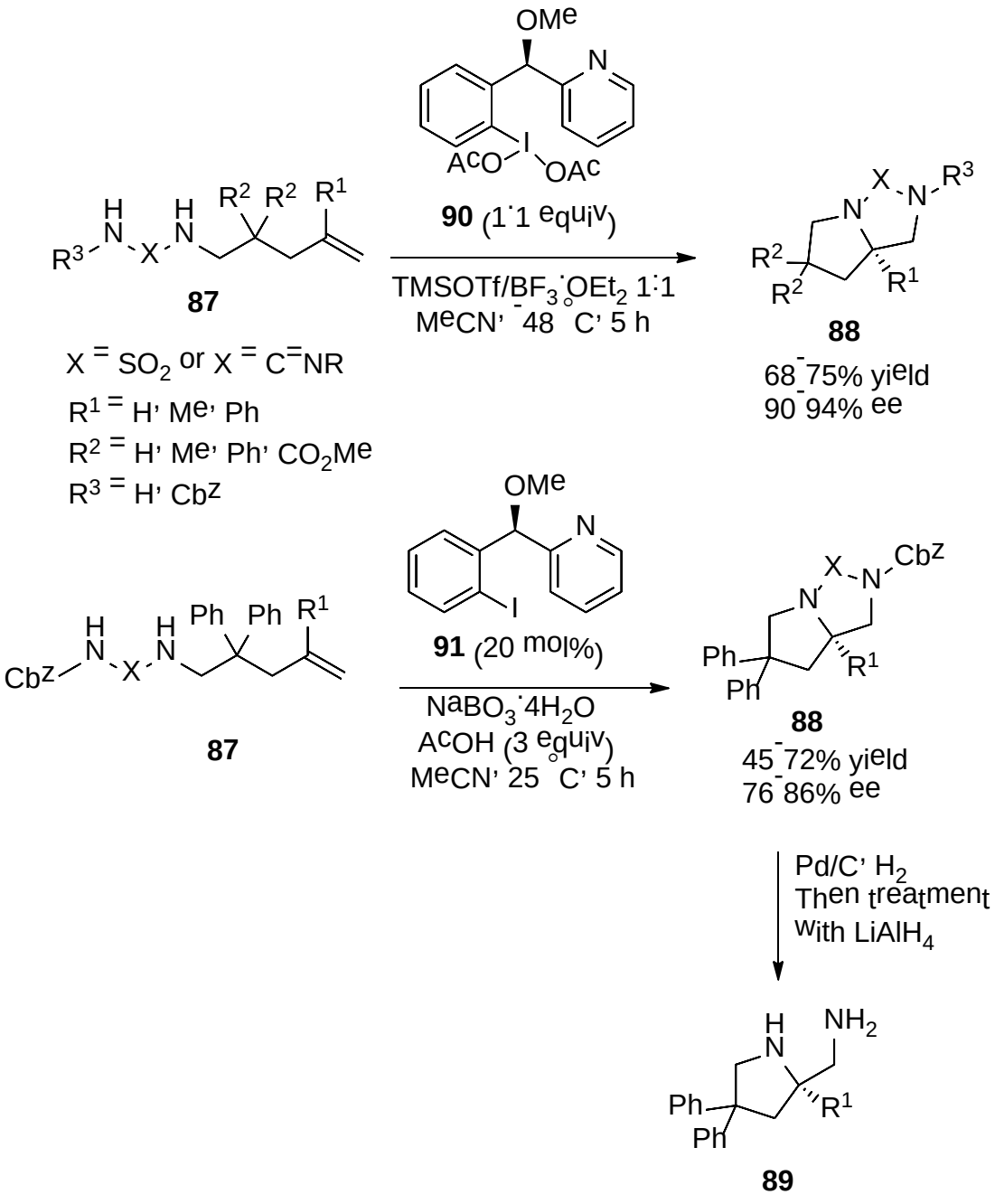
In 2012, Wirth *et al*.[57] investigated the first stereoselective oxyaminations of alkene-urea derivatives **82** promoted by Ishihara's reagent[26] (*R*,*R*)-**21**, to give bicyclic compounds **83** in good yields and up to 96% ee. However, derivatives of **83** were cyclised in only low to moderate enantioselectivities (Scheme 32).



Scheme 32

In 2014, Wirth *et al*.[58] synthesised a new chiral hypervalent iodine(III) reagent **90** and used it as an efficient reagent for the enantioselective intramolecular diamination of alkenes. A stoichiometric amount of **90** afforded the desired bicyclic products **88** in good yields with excellent enantioselectivities of up to 94%. They also achieved moderate enantioselectivities using 20 mol% of precatalyst **91** with sodium perborate as a co-oxidant. This led to formation

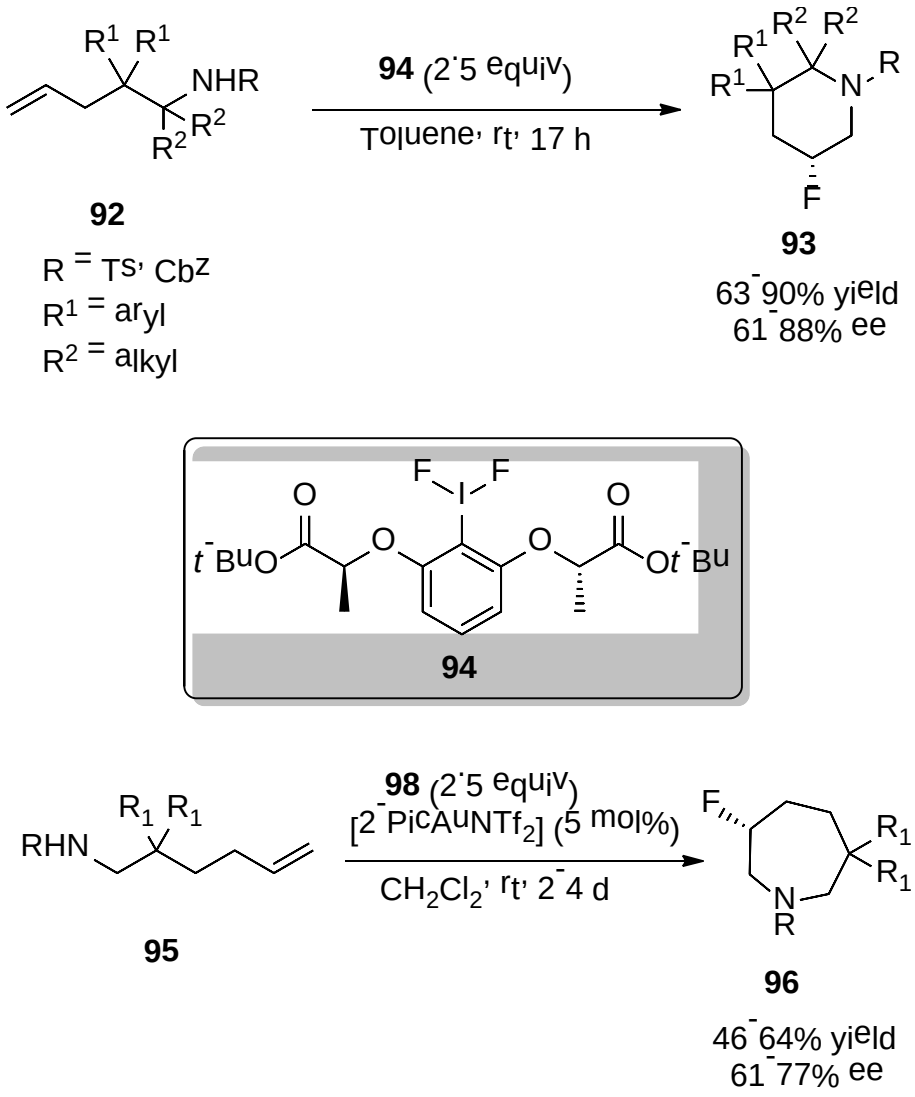
of the bicyclic products in good yields and up to 86% ee. The Cbz and (X) groups were easily removed by reduction using lithium aluminium hydride and resulted in free diamine products **92** (Scheme 33).



Scheme 33

In 2013, Nevado *et al.*[59] reported the first regioselective aminofluorination of alkenes by the synthesis of a new chiral aryliodo difluoride reagent **94.** The aminofluorination of alkenes **92**

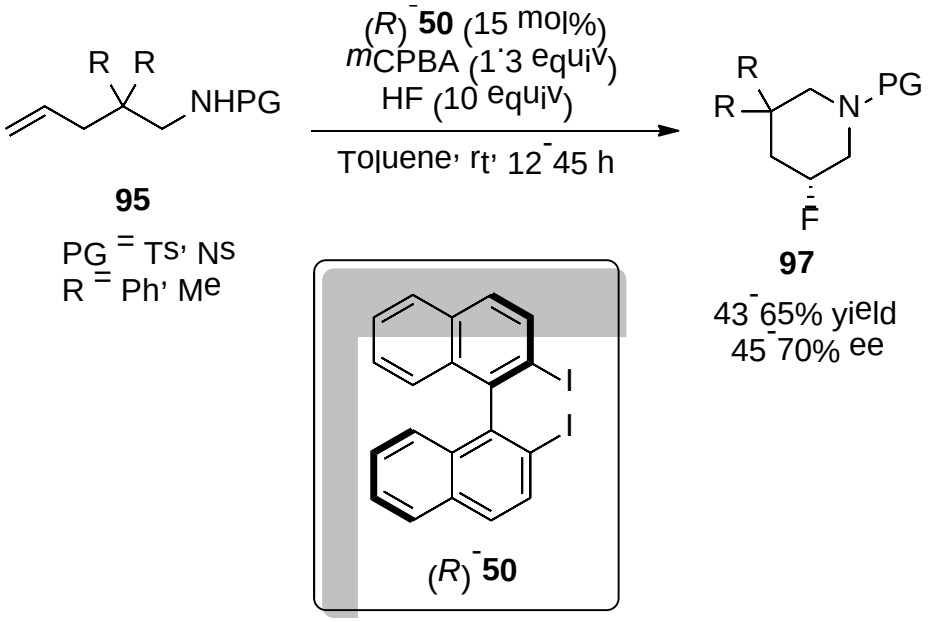
proceeded with high regioselectivity without any additive by employing stoichiometric amounts of **94**. The six-*endo*-cyclised products **93** were isolated in 79% yield with up to 88% ee. The same authors expanded the procedure to give seven-membered β-fluorinated azepanes **96** in good yields and up to 77% ee using **94** although a catalytic amount of a gold complex ([2-PicAuNTf$_2$]) was required (Scheme 34).



Scheme 34

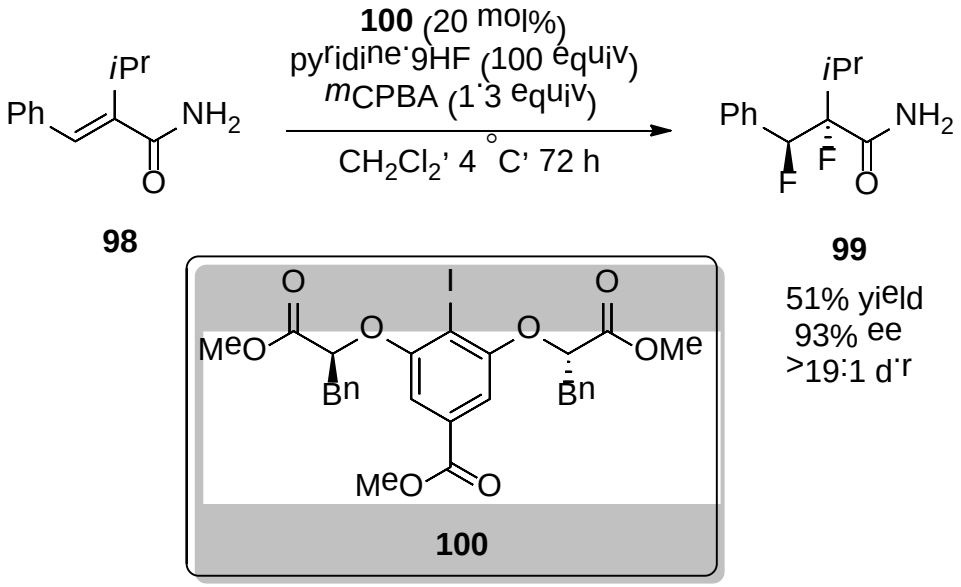
One year later, Kita *at el.*[42] developed a catalytic system for the enantioselective intramolecular aminofluorination of alkenes. They used a catalytic amount of chiral iodoarene **50** in the presence of *m*CBPA as the co-oxidant and the less costly fluorine source

HF. The expected fluorinated products **97** were obtained in good yields and up to 70% ee (Scheme 35).



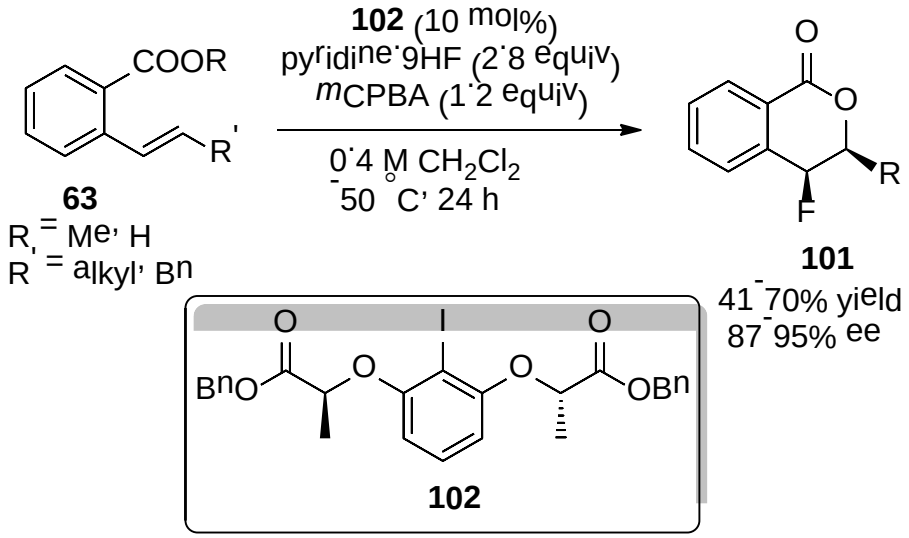
Scheme 35

Very recently, Jacobsen *at el.*[60] described the enantioselective catalytic difluorination of alkenes by a chiral iodoarene with a nucleophilic fluoride source and *m*CPBA as a stoichiometric oxidant. They prepared chiral aryl iodide **100** and utilised it in the enantioselective 1,2-difluorination of cinnamide **98.** The expected product **99** was obtained in moderate yield and excellent enantioselectivity of 93% ee (Scheme 36).



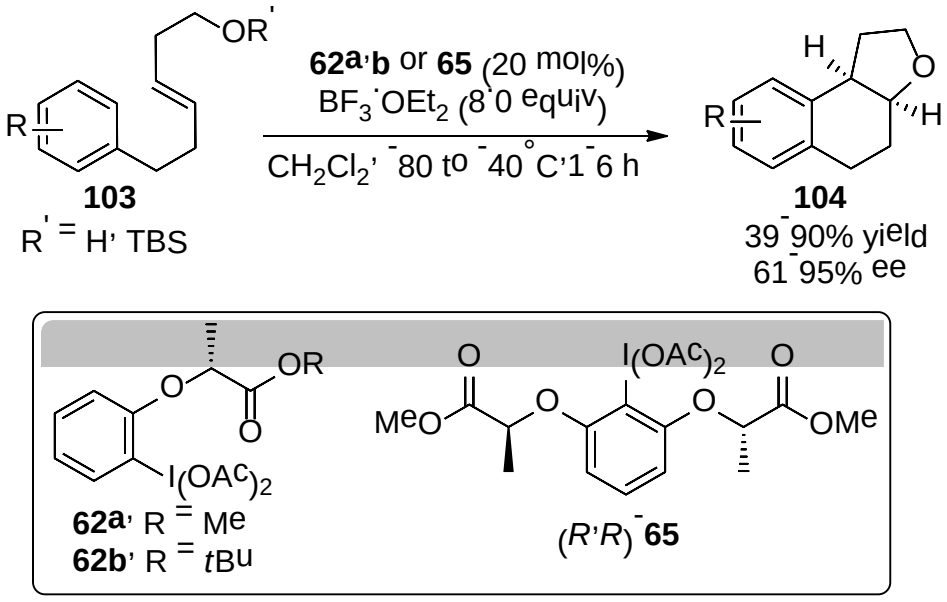
Scheme 36

In the same year, the same authors reported the development of an enantioselective catalytic fluorolactonisation reaction for the synthesis of 4-fluoroisochromanones **101** induced by chiral iodoarene reagents **102** using HF-pyridine as a nucleophilic fluoride source and *m*CPBA as co-oxidant. The expected products containing fluorine-bearing stereogenic centres were formed with excellent enantioselectivity (Scheme 37).[61] They also found that the regioselectivity of the lactonisation reactions obtained using this nucleophilic fluorination systems was the same as when using asymmetric electrophilic fluorination systems previously established.[60]



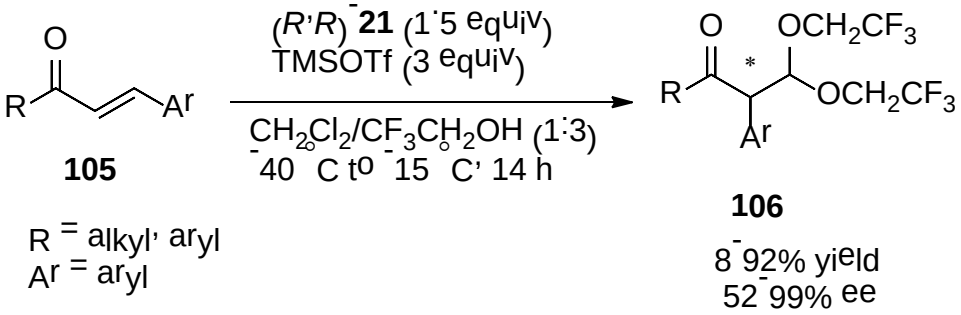
Scheme 37

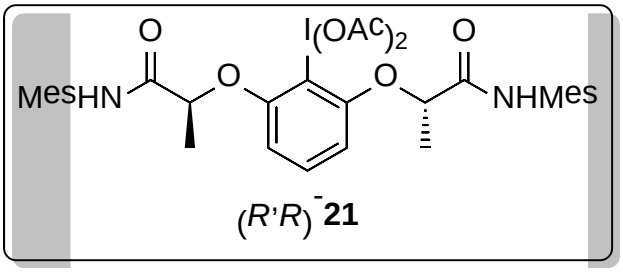
In 2016, Fujita *et al*.[62] achieved enantioselective oxidative C-C bond formation with chiral hypervalent iodine reagents under metal-free conditions. They applied their lactate-based chiral hypervalent iodine reagents **62** and **65** in the enantioselective intramolecular oxyarylation of alkene substrates **103**. This afforded the carbocyclisation products **104** with high enantioselectivities of up to 95% ee. The presence of a silyl protecting group on the alcohol led to higher selectivities (Scheme 38).



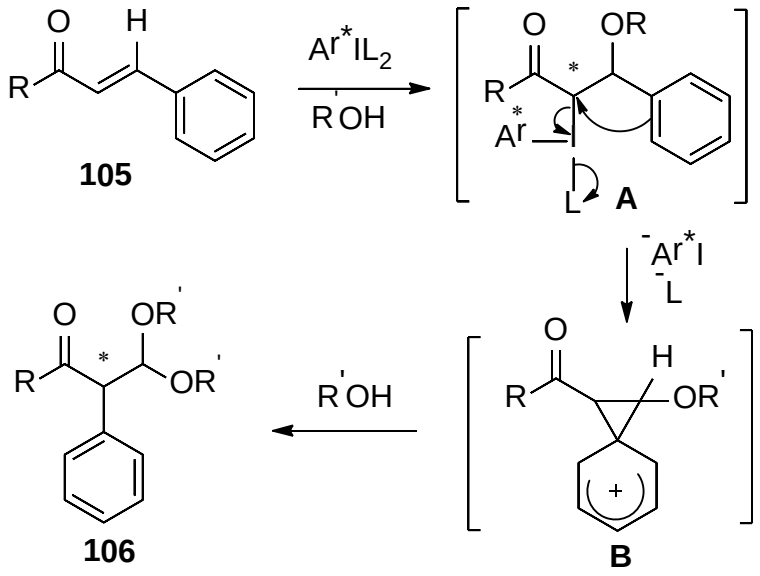
Scheme 38

In 2013, Wirth *et al*.[63] achieved the first stereoselective rearrangement reactions of aryl substituted alkenes **105** mediated by chiral hypervalent iodine(III) reagents **21**. The rearranged product **106** was obtained in high yield with enantioselectivities up to 99% ee (Scheme 39). They proposed a reaction mechanism in which the double bond of the alkene is activated by the hypervalent iodine reagent to generate intermediate **A** which is stabilised by the formation of a phenonium ion **B** followed by a second nucleophile attack to generate the 1,2-migration products **106** (Scheme 40).



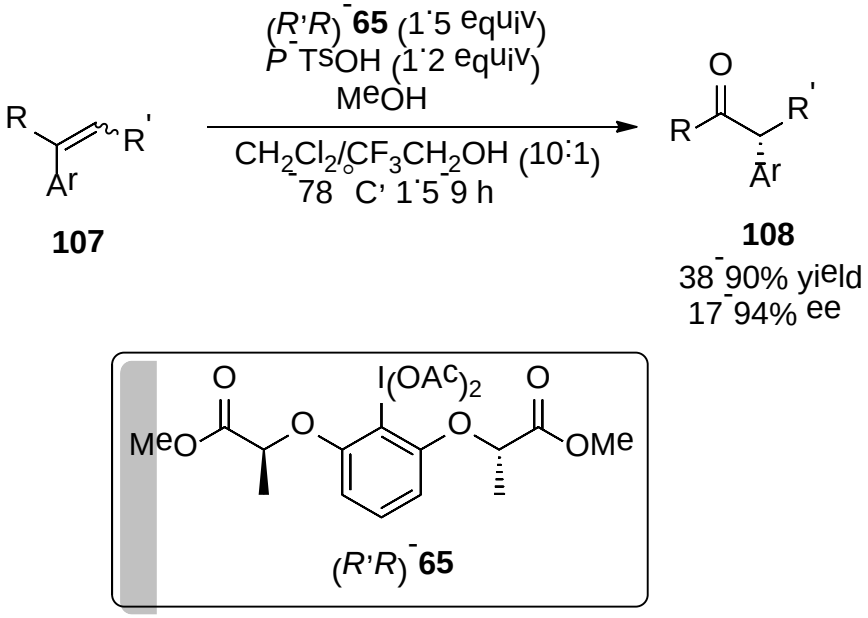


Scheme 39



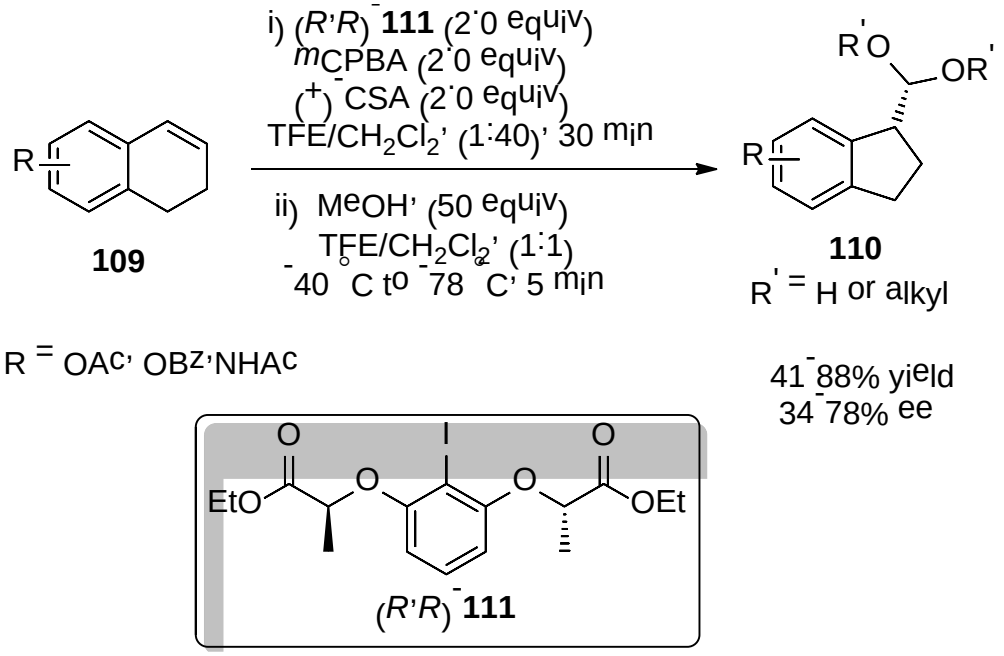
Scheme 40

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



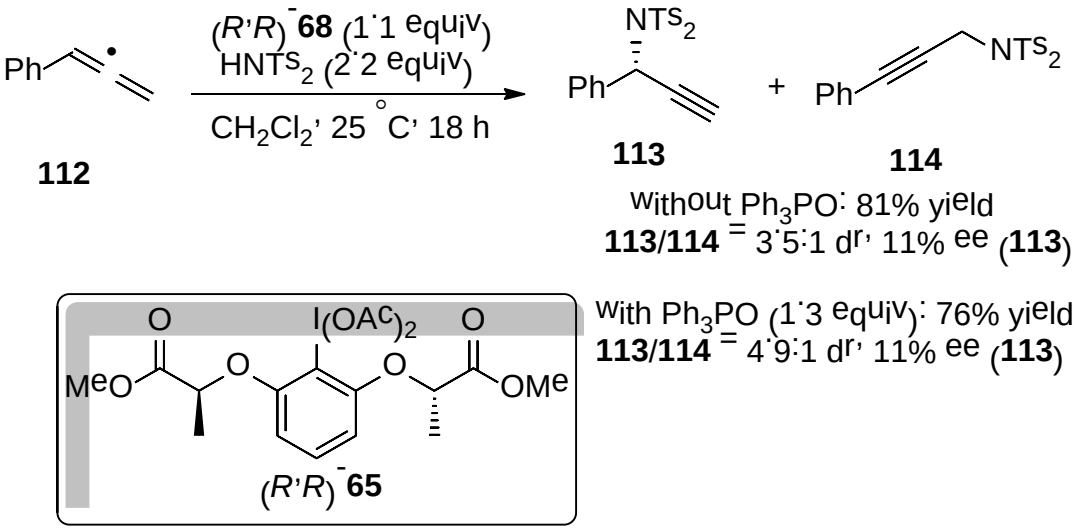
Scheme 41

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



Scheme 42

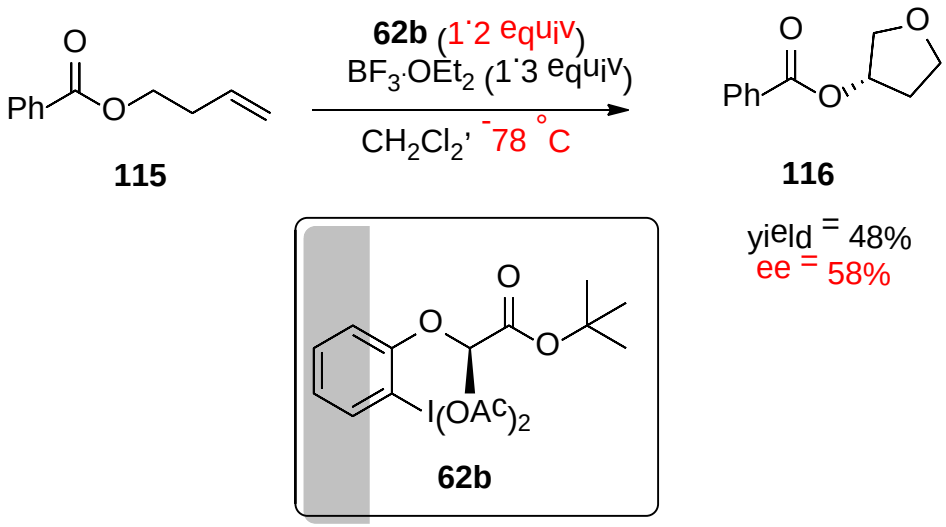
In 2014, Muñiz *et al.*[66] studied the oxidative amination of allenes mediated by a chiral hypervalent iodine reagent **68**. They subjected 1-phenyl allenes **112** to their conditions without any additive and the corresponding internal propargylic amines **113** were obtained with low enatioselectivity and moderate diastereoselectivity. After the combination of the hypervalent iodine reagent with triphenylphosphine oxide the internal regioisomer was observed with a slight improvement in diastereoselectivity and an increase of the enantiomeric excess up to 22% ee (Scheme 43).


Ph
(R,R)-68 (1.1 equiv)
HNTs2 (2.2 equiv)
CH2Cl2, 25 °C, 18 h
NTs2
Ph
+
Ph
NTs2
112
113
114
without Ph3PO: 81% yield
113/114 = 3.5:1 dr, 11% ee (113)
with Ph3PO (1.3 equiv): 76% yield
113/114 = 4.9:1 dr, 11% ee (113)
O
I(OAc)2
O
MeO
O
O
OMe
(R,R)-65

Scheme 43

2. Aims and objectives

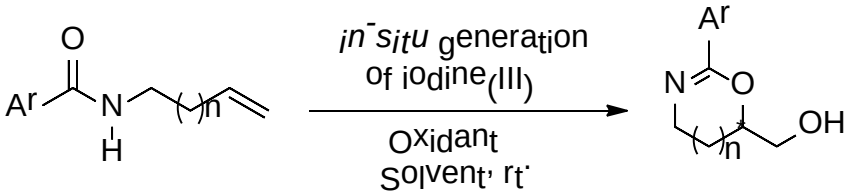
Tetrahydrofuranylation of but-3-enyl benzoate **115** was carried out by Fujita *et al.*[47] using the optically active hypervalent iodine(III) reagents **62b** in the presence of $BF_3.OEt_2$ in dichloromethane at -78 °C. This process gave exclusively 3-benzoyloxytetrahydrofuran **116** in 48% yield and up to 58% ee**.**



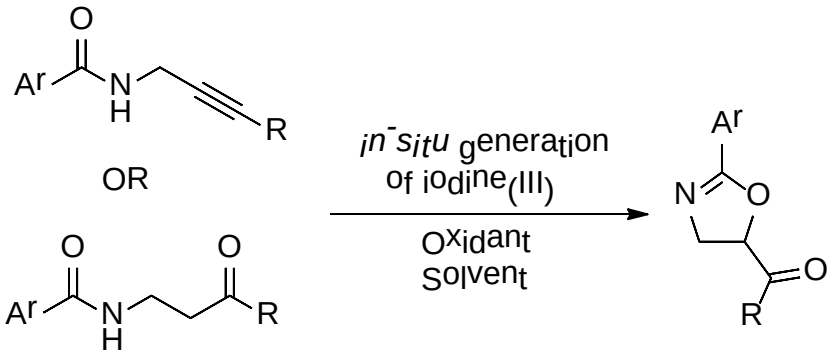
Scheme 44

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

2. The second objective of this work was to develop a catalytic enantioselective cyclisation of amide analogues using chiral aryl iodides at room temperature.



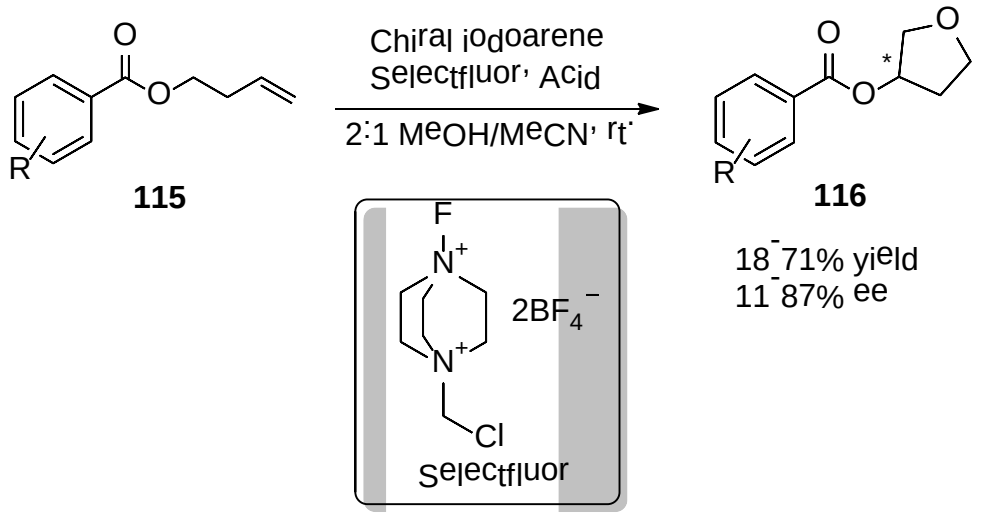
3. The third objective of this work was to develop catalytic conditions for the cyclisation of propargyl amides and the enantioselective cyclisation of β-amidoketones.



3. Results and Discussions

3.1. Cyclisation reactions of esters containing a pendent alkene.

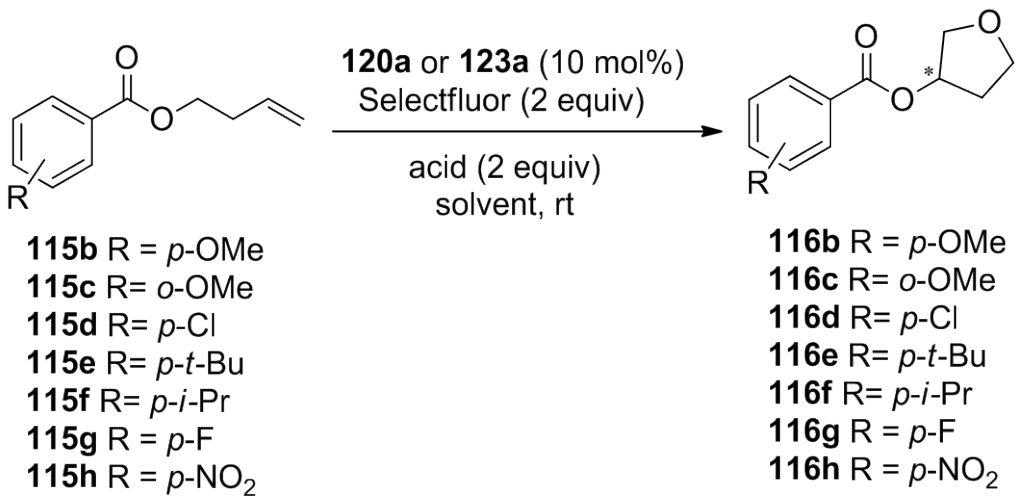
Previously in the Moran group (D.Hammett and E.Bennett unpublished results) optically active iodoarenes were prepared and employed as catalysts in the oxidative cyclisation of substituted but-3-enyl benzoates **115** to form the 3-hydroxytetrahydrofuran esters **116** (Scheme 45).



Scheme 45

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

The cyclisation reactions were performed, first with iodobenzene to generate racemic samples of products **115** in yields reanging from 10-68%. Then the reactions were repeated using catalytic amounts of the chiral aryl iodide **120a** and **123a** to generate the chiral iodine(III) species *in situ* in the presence of Selectfluor as oxidant (Scheme 46).



Scheme 46

The analogues **116b-h** were synthesised to see how the various arene substituents affected the yield and enantioselectivity and the results of these cyclisations are summarised in Table 1.

Entry	Substrate	Catalyst	Yield[a,b] %	ee[c] %
1	**115b**	**120a**	71	20
2	**115c**	**120a**	32	17
3	**115d**	**120a**	42	17
4	**115e**	**120a**	51	14
5	**115f**	**120a**	19	16

6	**115g**	**120a**	18	26
7	**115h**	**120a**	30	11
8	**115b**	**123a**	20	87

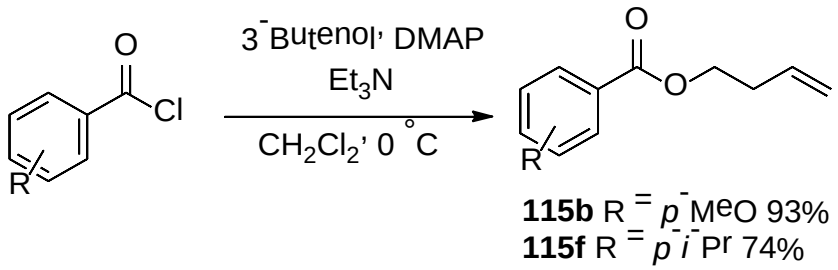
[a] The reaction was typically carried out in acetonitrile (1mL), *p*-TsOH, rt, 18-36 h.
[b] Yield calculated after column chromatography.
[c] Determined by chiral HPLC analysis.

Table 1

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

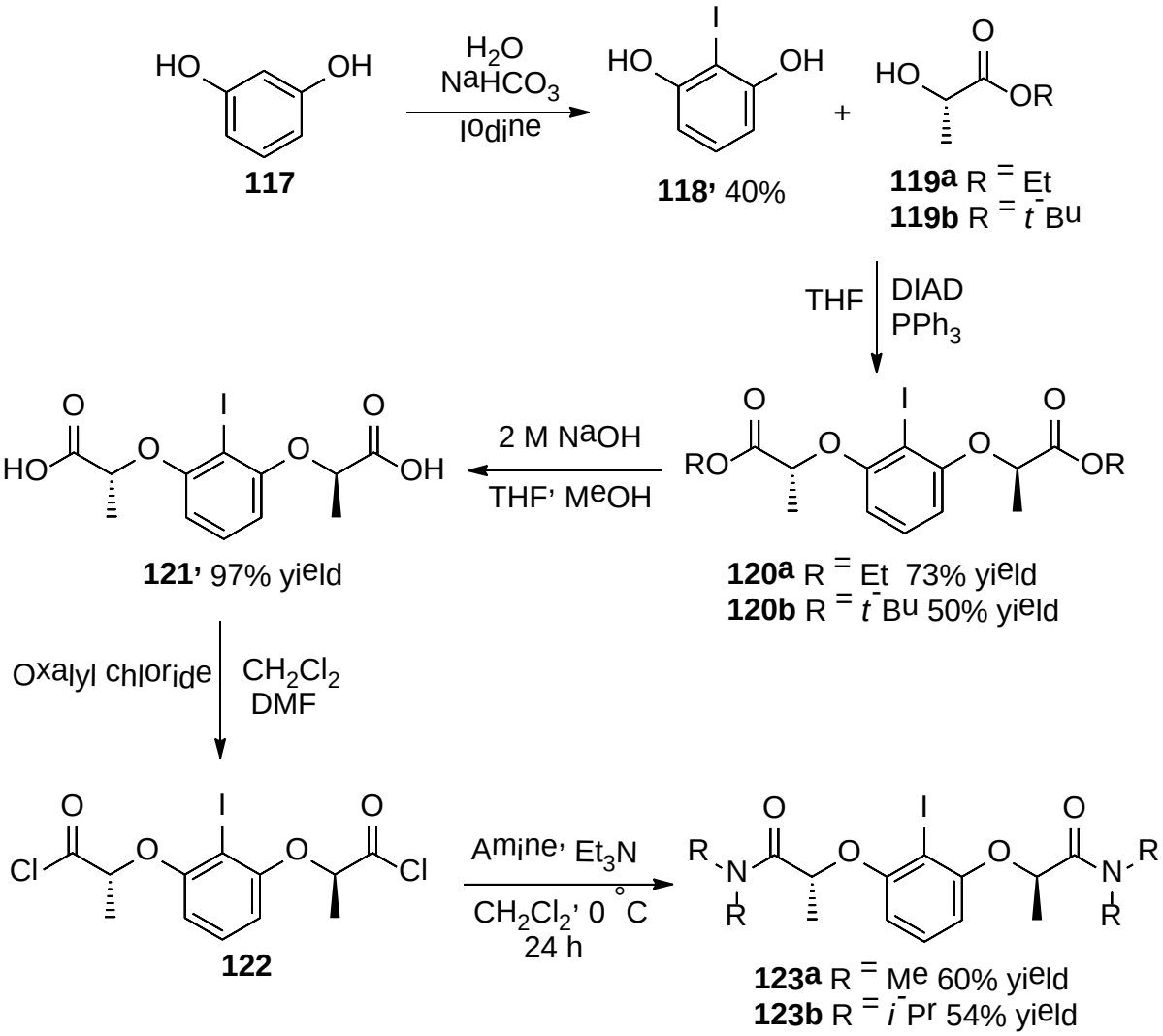
Importantly, the catalytic reaction was only found to occur using Selectfluor as the oxidant: *m*CBPA, Oxone, H_2O_2 and sodium perborate were all found to be ineffective and starting material was recovered.

With these results in hand, the intention to reproduce and improve the previous results of our group was attempted again. First, starting material **115b** used for the cyclisation reaction was prepared in 93% yield in one step from treatment of readily available *p*-methoxybenzoyl chloride with 3-butenol in CH_2Cl_2 in the presence of base (Et_3N) and DMAP at 0 °C.[67] Combound **115c** was also prepared by our group in 74% yield (Scheme 47).



Scheme 47

Next, the synthesis of several chiral iodoarenes using a Mitsunobu reaction was attempted. Following the literature procedure reported by Tsujiyama and coauthors,[68] 2-iodoresorcinol **118** was prepared from resorcinol **117** with iodine using $NaHCO_3$. Then a double Mitsunobu reaction of **118** with optically active ethyl lactate **119a** was effected with diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine (PPh_3) to give the ethyl lactate derived aryl iodide (**120a**) in 73% yield. Diester **120a** was hydrolysed with NaOH to give the chiral *C2*-symmetric acid **121** in quantitative yield. The chiral acid **121** was converted into the acid chloride **122** using oxalyl chloride and treated with dimethyl amine to generate amide **123a** in 60% yield. We also synthesised the novel C_2-symmetric chiral iodoarene **120b** and **123b** via esterification to give **120b** in 50% yield and amidation to give **123b** in 54% yield (Scheme 48).

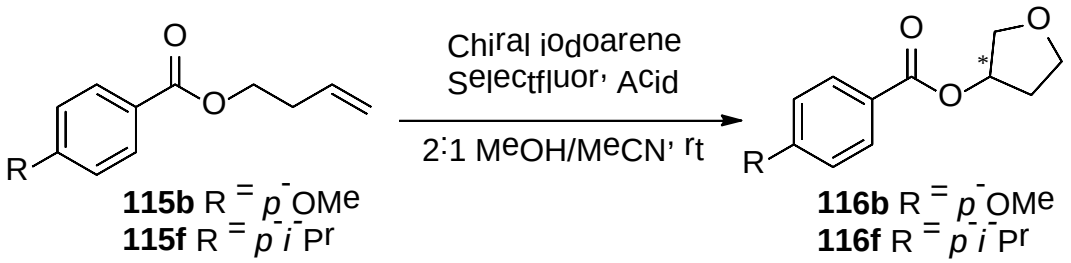


Scheme 48

The utility of using catalytic amounts of these chiral iodoarenes for the enantioselective cyclisation of **115b** to tetrahydrofuran **116b** in the presence of Selectfluor as oxidant using different acids and solvents was examined (Table 2). Firstly, the reaction with **120a** using the conditions shown in scheme 49 was repeated. Unfortunately the yield was very low and as a result, the enantioselectivity was not obtained (entry 1). The use of diester **120b** gave **116b** with 41% ee (entry 2). In contrast, the use of bis(*N*-dialkylamides) **123a** and **123b** further increased the enantioselectivity (entries 3 and 4). Bis(*N*-dimethyl amide) **123a** was the best precatalyst for enantioselectivity giving **116b** with 77% ee but with low yield 20% (entry 3)

and the use of bis(*N*-diisopropyl amide) slightly dropped the enantioselectivity to 65% ee but with better yield 34% (entry 4).

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



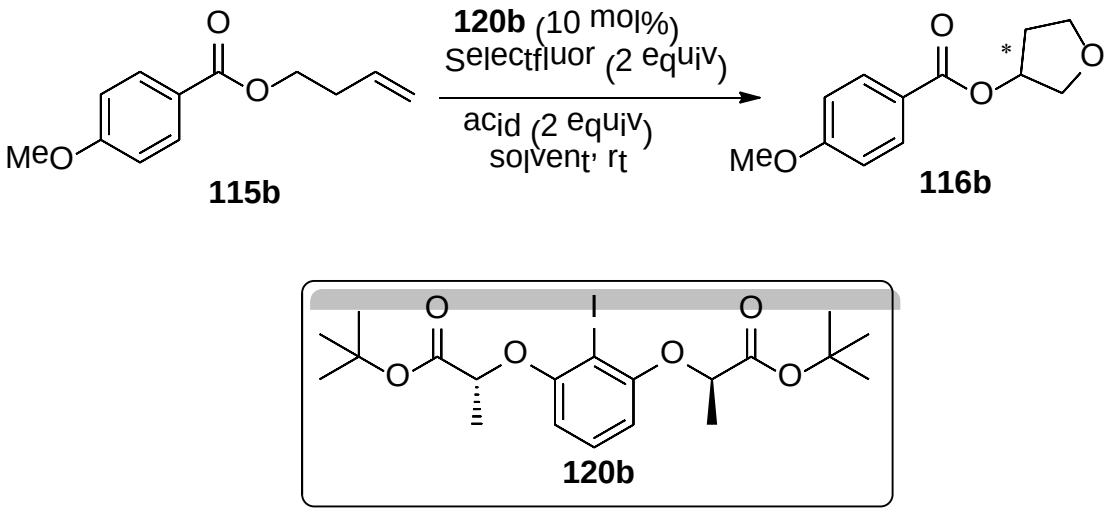
Scheme 49

Entry	Precatalyst	Solvent	Acid	Yield %	ee %
1	**120a**	MeOH:MeCN (2:1)	TFA	>10	N.D.
2	**120b**	MeOH:MeCN (2:1), 10 equiv H_2O	Triflic acid	33	41
3	**123a**	MeOH:MeCN (2:1)	TFA	20	77
4	**123b**	MeOH:MeCN (2:1), 5 equiv H_2O	Bis(trifluoromethane) sulfonimide	35	65

N.D. = Not Determined

Table 2

The use of *t*-butyl ester catalyst **120b** was investigated next (Scheme 50) and the results are showed in Table 3. Previous investigations within our group and others,[57,66] have shown that the solvent composition is important in enantioselective reactions with iodine(III) reagents. First MeCN in the presence of TFA for the cyclisation reaction with 10 mol % of **120b** was screend, which afforded the product in low ee and 22% yield (entry 1). However, it was decided to use the same optimised conditions (2:1 MeOH:MeCN, acid and Selectfluor at rt) that were used by our group for this reaction with **120a**. The use of a 2:1 mixture of methanol and acetonitrile with either TFA or triflic acid did not improve the yield of **116b** (entry 2, 3). However, when 10 equivalents of H_2O and triflic acid were used, the enantioselectivity of **116b** increased to 41% ee and the yield increased to 33% (entry 5). In contrast using the stronger acid bis(trifluoromethane)sulfonamide afforded **116b** in low yield (entry 6). Unfortunately other solvent ratios of methanol and acetonitrile gave the product in very low conversion therefore the enantioselectivity was not obtained.



Scheme 50

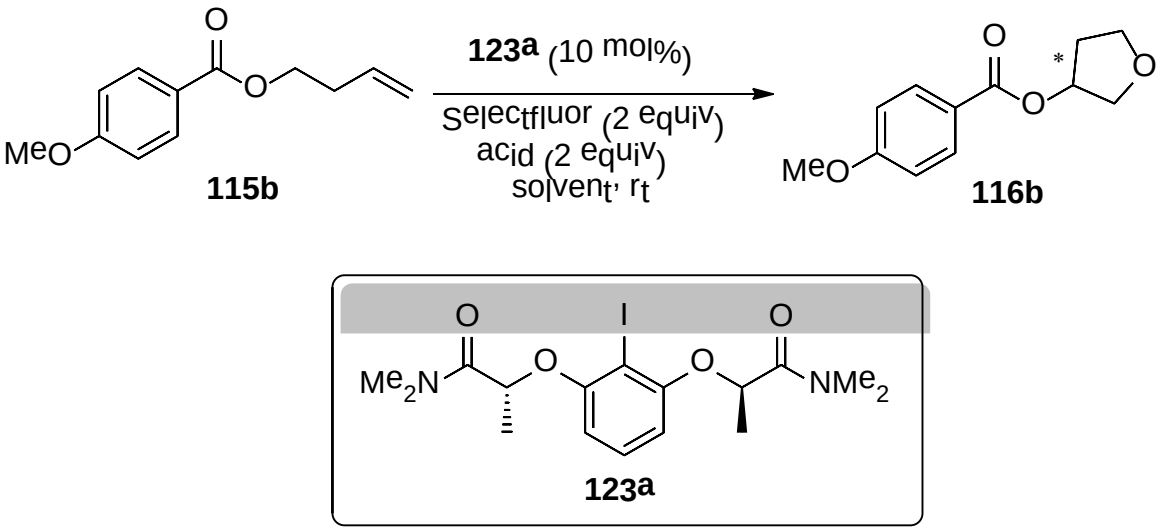
Entry	Solvent	Acid	Yield %	ee %
1	MeCN	TFA	22	1
2	MeOH:MeCN (2:1)	TFA	<5	N.D.
3	MeOH:MeCN (2:1)	Triflic acid	<5	N.D.
4	MeOH:MeCN (2:1), 5 equiv H_2O	Triflic acid	<5	N.D.
5	MeOH:MeCN (2:1), 10 equiv H_2O	Triflic acid	33	41
6	MeOH:MeCN (2:1), 10 equiv H_2O	Bis(trifluoromethane) sulfonimide	<5	N.D.

N.D. = Not Determined

Table 3

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

As mentioned above the enantiomeric excess was not determined when the product **116b** was obtained with very low conversion using other solvent ratios of methanol and acetonitrile (entries 2 and 4). Notably, solvents such as dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene were also screened but no cyclisation product was formed.



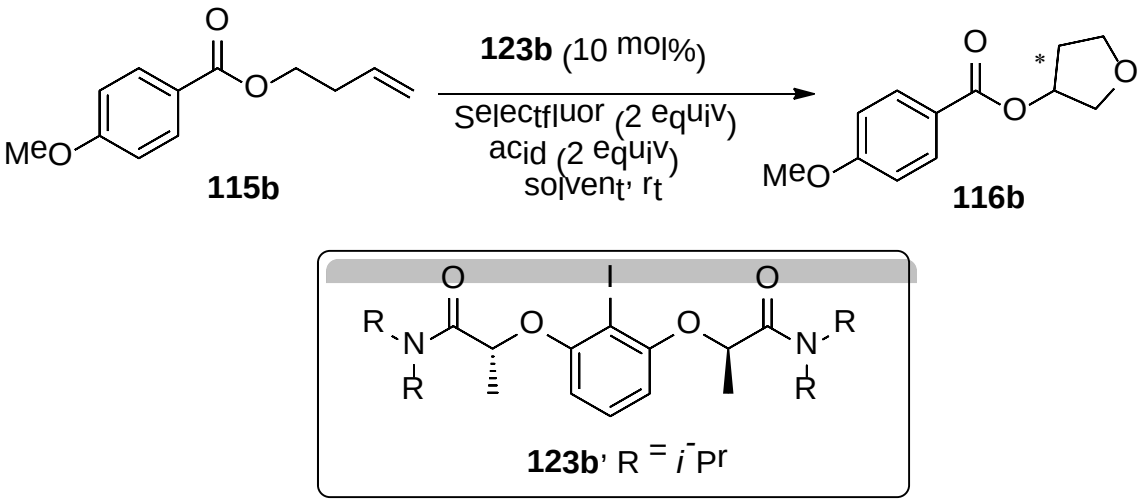
Scheme 51

Entry	Solvent	Acid	Yield %	ee %
1	MeCN	TFA	21	34
2	MeOH:MeCN (1:1)	TFA	<5	N.D.
3	MeOH:MeCN (2:1)	TFA	20	77
4	MeOH:MeCN (5:1)	TFA	<5	N.D.
5	MeOH:MeCN (1:5)	TFA	14	35
6	TFE:MeCN (2:1)	TFA	83	35
7	MeOH:MeCN (2:1), 5 equiv H_2O	Bis(trifluoromethane) sulfonimide	35	33

N.D. = Not Determined

Table 4

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



Scheme 52

Entry	Solvent	Acid	Yield %	ee %
1	MeOH:MeCN (2:1)	TFA	<5	N.D.

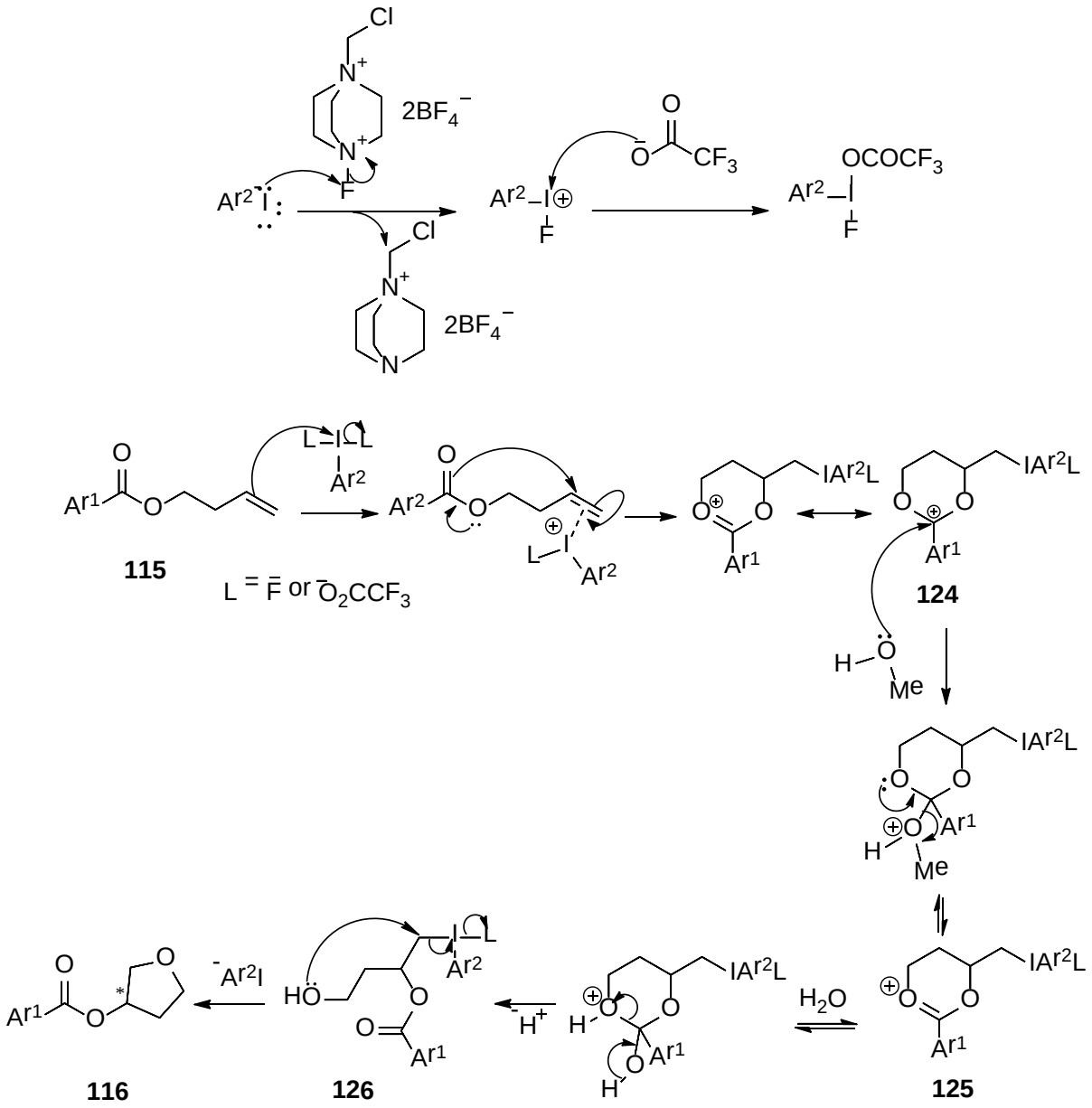
2	MeOH:MeCN (2:1)	Triflic acid	13	N.D.
3	MeOH:MeCN (2:1)	Bis(trifluoromethane) sulfonamide	32	57
4	MeOH:MeCN (2:1), 5 equiv H_2O	Bis(trifluoromethane) sulfonimide	35	65
5	MeOH:MeCN (2:1), 10 equiv H_2O	Bis(trifluoromethane) sulfonimide	<5	N.D.
6	TFE:MeCN (2:1)	Bis(trifluoromethane) sulfonimide	N.R.	-

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

Table 5

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

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



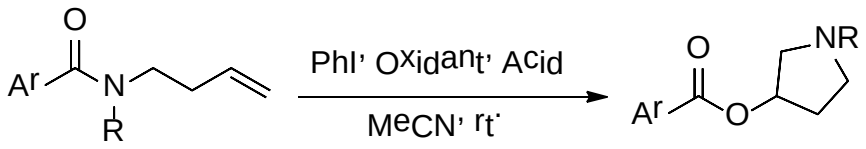
Scheme 53

3.1.1. Conclusion and future work

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

3.2. Cyclisation Reactions of Amides Containing a Pendent Alkene

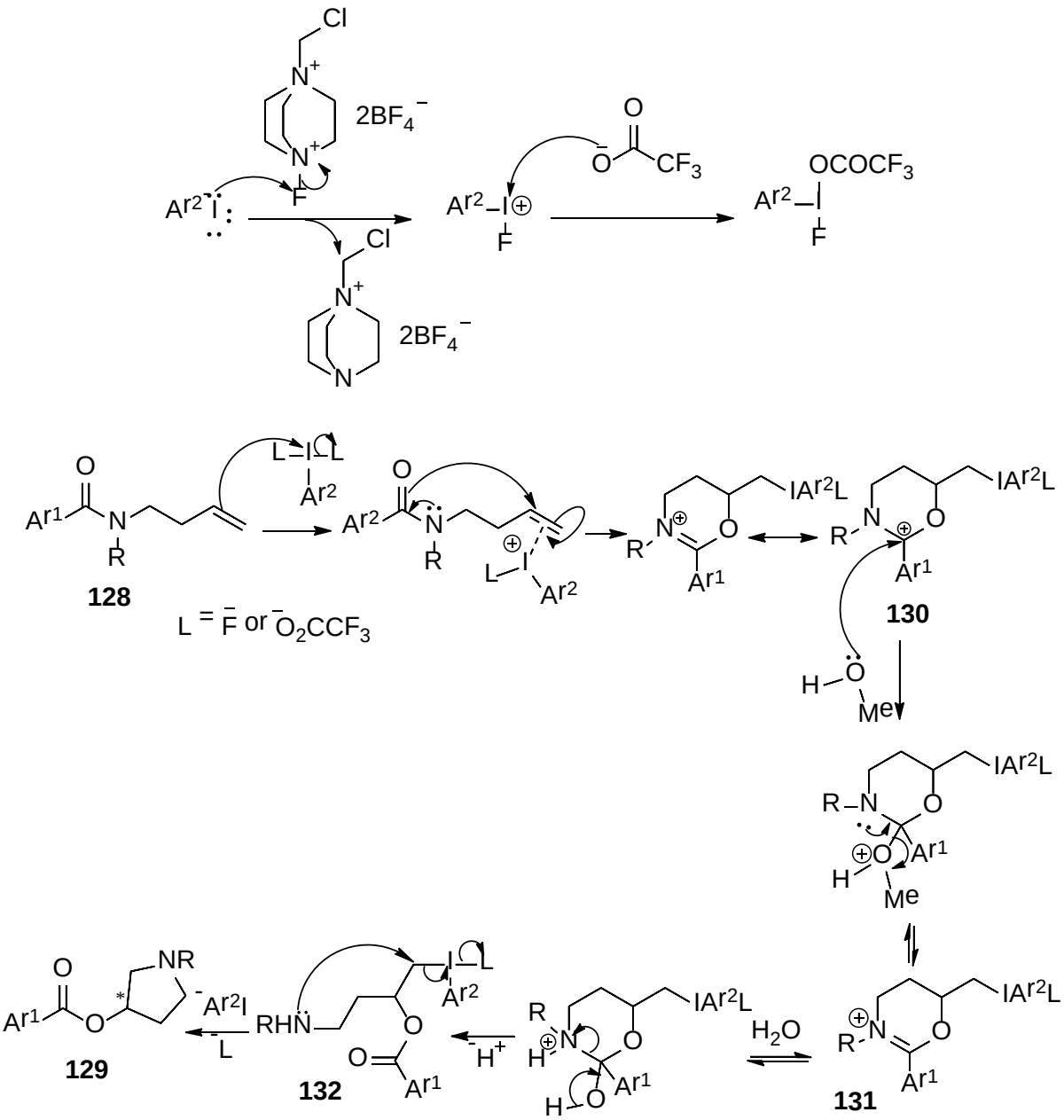
Based on the cyclisation reactions of the ester mentioned in the previous chapter, it was wished to extend this concept towards the cyclisation of amides. The work was started using catalytic amounts of PhI applying similar conditions to those used for the ester to cyclise the amide analogues **128**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



128 **129**

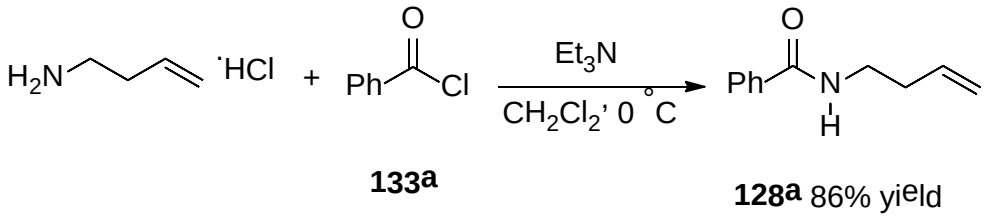
Scheme 54

Analogous to the ester mechanism, the active hypervalent iodine(III) species would be produced through the oxidation of the chiral aryl iodide using Selectfluor. This could coordinate to the alkene substrate **128** and the lone pair on the nitrogen atom could attack the activated alkene resulting in six-membered ring formation i.e. **130**. Methanol could be act as nucleophile and attack the ring **130** to give the carbocation **131** which could be hydrolysed then followed by proton transfer and ring opening to form amine **132** which could re-cyclise to give the pyrrolidine product **129** with elimination of the iodoarene (Scheme 55).



Scheme 55

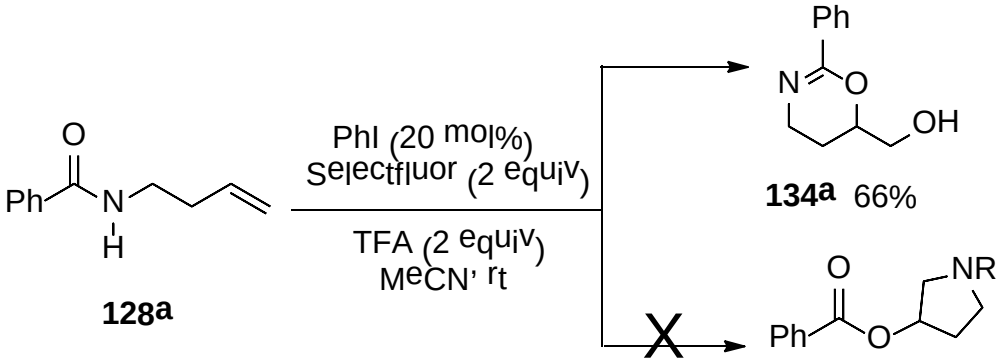
This study conmmenced with the synthesis of substrate **130a** in high yield (86%) using a literature procedure.[69] The reaction of 1-amino-3-butene hydrochloride **132** with benzoyl chloride **133a** in dry dichloromethane in the presence of base (Et_3N) formed **130a** (Scheme 56).



133a **128a** 86% yield

Scheme 56

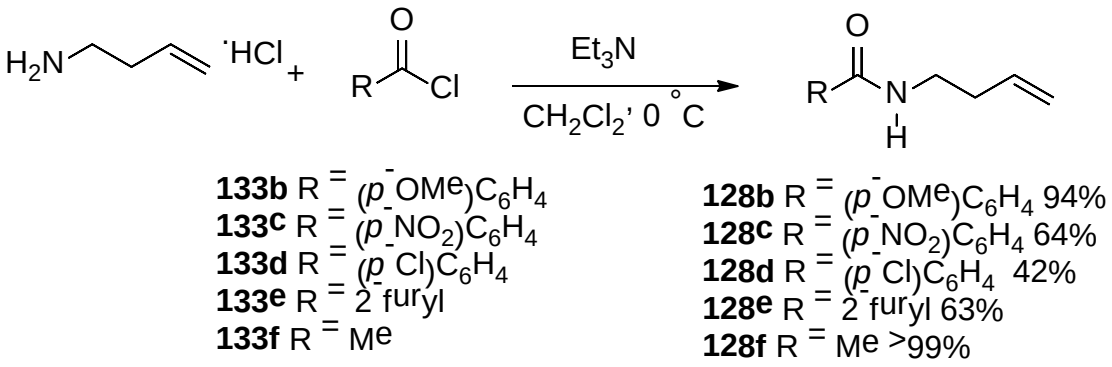
The next plan was to perform the cyclisation reaction using these conditions: 0.2 equiv. of PhI, 2 equiv of Selectfluor, 2 equiv of TFA in MeCN at room temperature. After the reaction was performed we were surprised to find that the ^{1}H spectrum was different to that expected for **129**. After further investigations, it was determined that six-membered ring **134a** was formed in moderate yield (Scheme 57). Obviously, the initial ring closure was successful but the subsequent ring opening and re-cyclisation did not occur.



128a **134a** 66% **129**

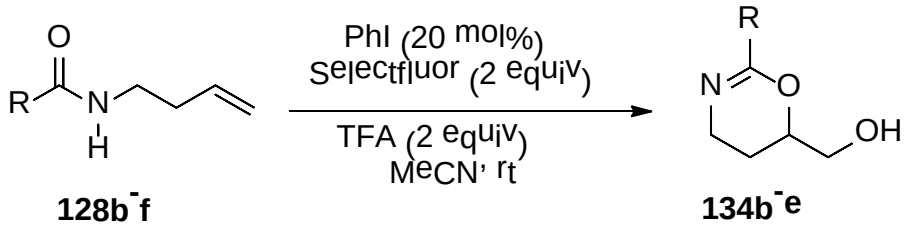
Scheme 57

Pleased with this result, we decided to investigate to see the effects on the yields of the cyclisation with different amides. These substrates were synthesised applying the same method as for **128a** by treating the amines hydrochloride with different acid chlorides **133b-f** to give products **128b-f** in good yields (Scheme 58).



Scheme 58

The addition of a catalytic amount of PhI and Selectfluor to an acetonitrile solution of different alkenyl amides **128b-e** led to the direct cyclisation to afford 5,6-dihydro-4-H-1,3-oxazine derivatives (**134a-e**) in low to moderate yield as shown in Table 6. It is noteworthy that, complete conversation was observed from the NMR but in general the yield was low. The highest yield (40%) was obtained when the Ar was *p*-nitro substituted phenyl (entry 2). However, the lowest yield (14%) was observed when the aryl group was a furan ring (entry 5). Whereas, when the Ar incorporated electronically donating groups at the *p*-position of the phenyl ring (*p*-MeO) the yield was 28% (entry 1). When Ar was a *p*-chloro substituted phenol the yield obtained for the product **134d** was only 23 % (entry 4). It is worth mentioning that the acetamide analogue **128f** was prepared in excellent yield, but it failed to cyclise (entry 5).



128b-f **134b-e**

Scheme 59

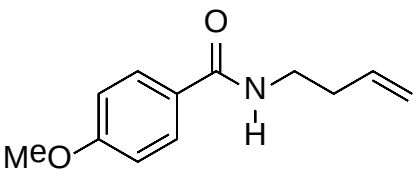
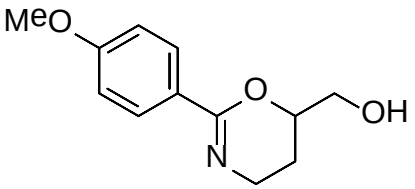
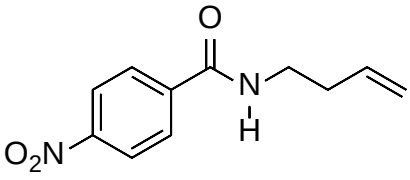
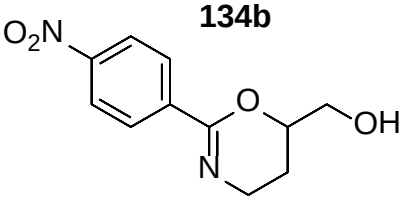
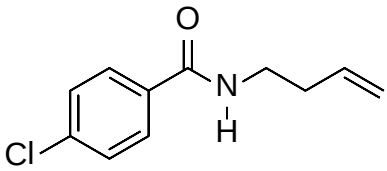
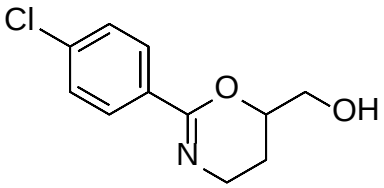
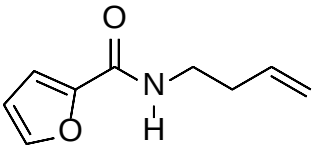
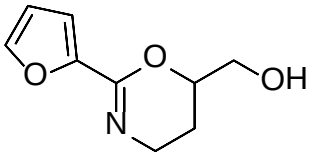
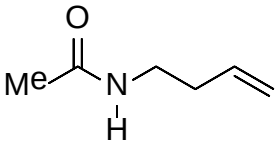
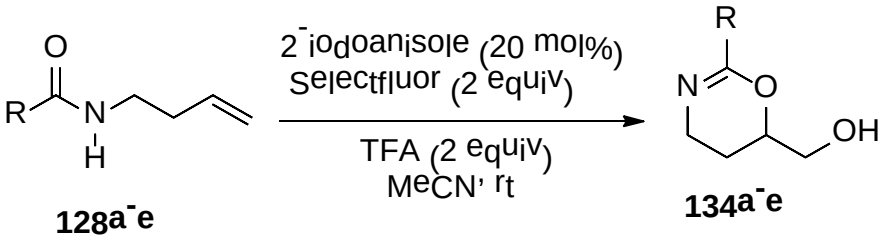
entry	substrate	product	yield %
1	 **128b**	 **134b**	35
2	 **128c**	 **134c**	40
3	 **128d**	 **134d**	23
4	 **128e**	 **134e**	14
5	 **128f**	no reaction	-

Table 6

Concurrent work in the Moran group had shown that 2-iodoanisole can act as a superior catalyst than iodobenzene in similar reactions. Considering our results above, we decided to use 2-iodoanisole instead of iodobenzene with the same conditions and the cyclisation reaction worked well for a variety of arylamides affording the corresponding products in high in good to high yields (Table 7). The highest yield 83% was obtained when the arylamides

bearing phenyl ring. Arylamide derivatives bearing electron-donating substituents such as methoxyl at the *para*-positions of benzene ring provided the desired oxazine in 58% yield (entry 2). While arylamides derivatives bearing electron-withdrawing substituents such as nitro and chloro group at the *para*-positions of benzene ring afforded the desired oxazine in slightly higher yields, 65% and 68% respectively (entry 3 and 4). Additionally, heterocycle substrate, 2-furyl, also successful reacted to provide the desired oxazine in 62% yield (entry 5).



128a-e **134a-e**

Scheme 60

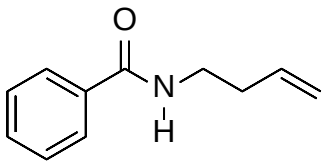
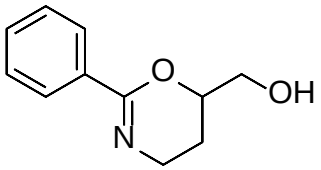
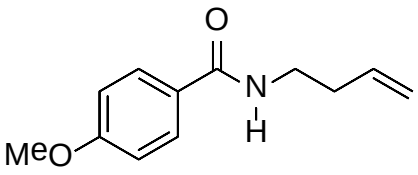
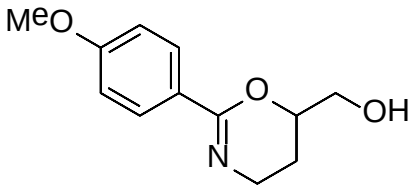
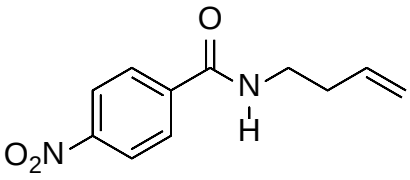
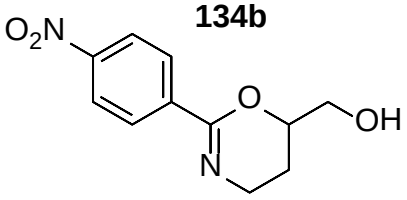
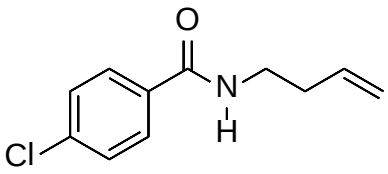
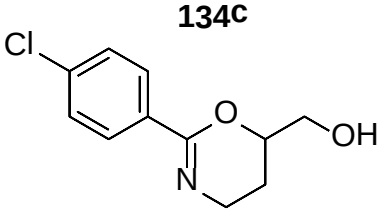
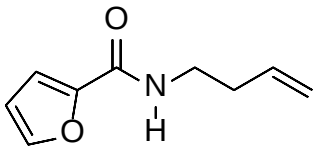
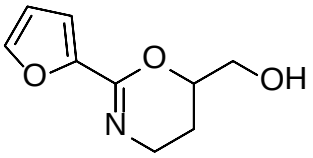
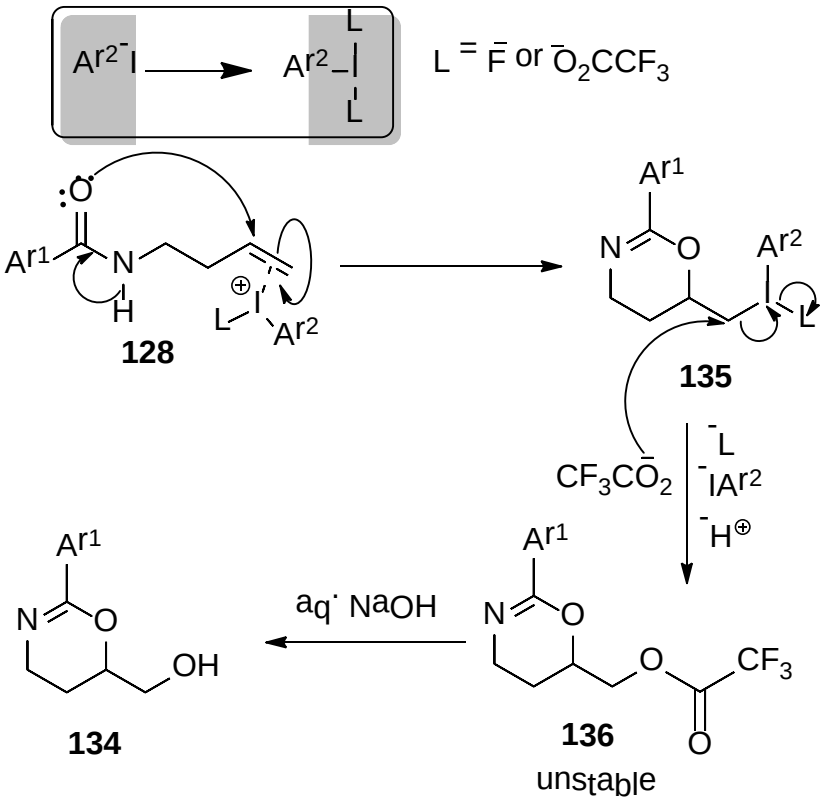
entry	substrate	product	yield %
1	 **128a**	 **134a**	83
2	 **128b**	 **134b**	58
3	 **128c**	 **134c**	68
4	 **128d**	 **134d**	65
5	 **128e**	 **134e**	62

Table 7

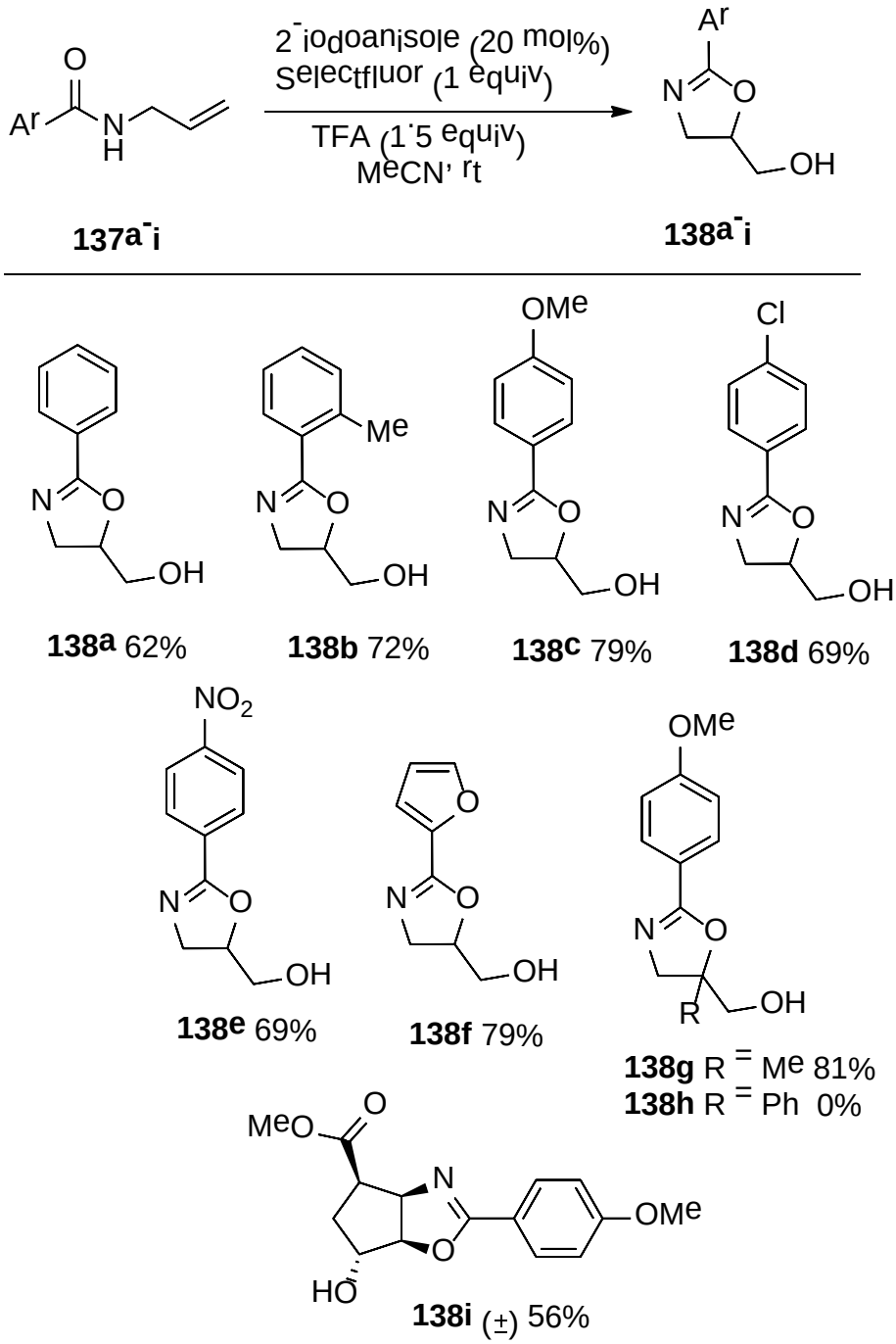
Below is the proposed mechanism for the cyclisation reaction. The iodoarene is oxidised to the iodine(III) species by the Selectfluor, which then coordinates to the alkene of the substrate. The lone pair on the carbonyl oxygen attacks the activated alkene, thus forming the six membered rings. Displacement of the iodoarene by TFA generates an unstable species which can be hydrolysed by aqueous sodium hydroxide solution to form the stable alcohols **134** (Scheme 61).



Scheme 61

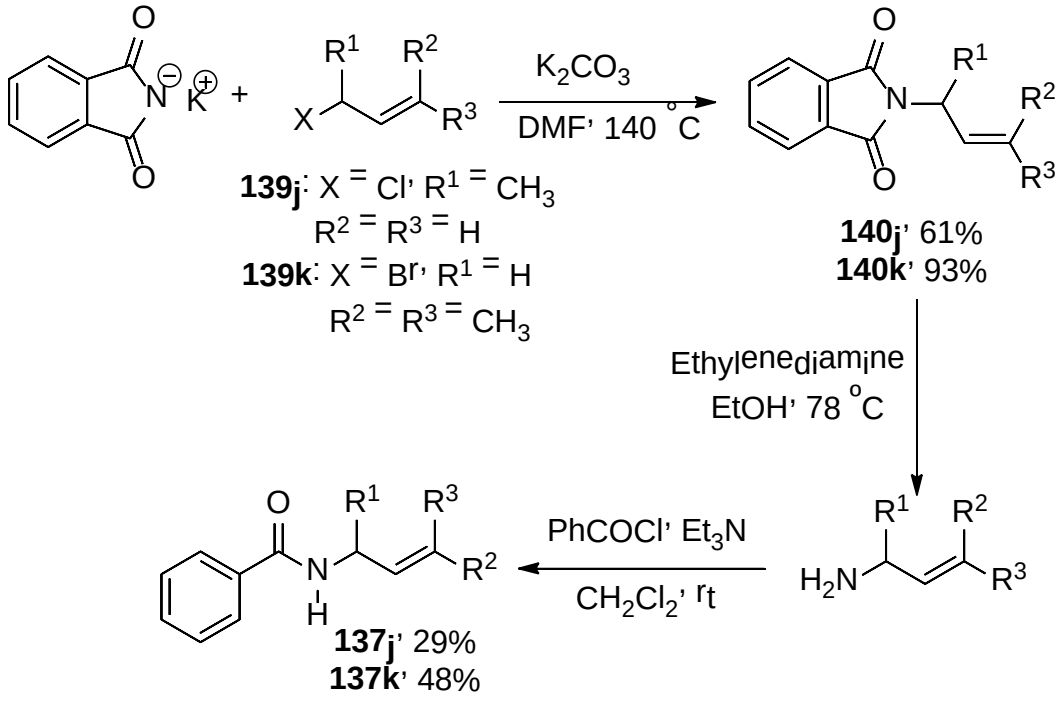
Under similar reaction conditions, the formation of five membered rings has been investigated by another member of the Moran group (Ali Alhalib) in which various *N*-allylamides **137** were prepared in a similar fashion to the above and these amides cyclised to oxazoline **138** in good yields. Annulations of aromatic substituents bearing electron-withdrawing groups such as *o*-Me and *p*-OMe worked well and provided the desired products **138b** and **138c** in slightly high yields compared to electron-donating groups such as *p*-NO_2 and *p*-Cl that afforded the products **138d** and **138e** in 69% yield in both cases. Similarly, the heteroaromatic 2-furyl substrate was tolerated well under these cyclisation conditions and afforded the interesting biheterocyclic product **138f** in 79% yield. The success of the cyclisation reaction of di- and tri-substituted alkenes was found to be dependent on the alkene substituent. When 1,1-disubstituted alkenes were subjected to the cyclisation conditions the cyclisation reaction worked with the methyl derivative and afforded the product **138g** in a

superior yield of 81% whereas the cyclisation did not work with the phenyl derivative. One diastereomer **138i** was observed in 56% yield when *cis*-1,2-disubstituted alkene was subjected to the cyclisation conditions. However, the cyclisation reaction of tri-substituted alkene was unsuccessful (Scheme 62).



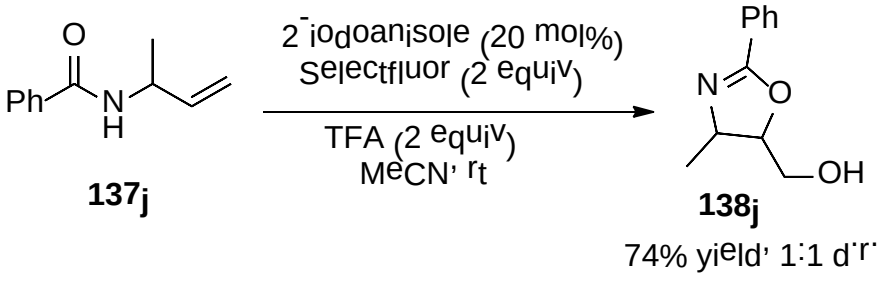
Scheme 62

With a desire to prepare more substituted products, amides **137j** and **137k** were prepared by a known literature procedure.[70,71] *N*-Alkenyl phthalimides **140j** and **140k** were synthesised by the reaction of alkenyl halides **139** with potassium phthalimide using K_2CO_3 in DMF at 140 °C. Compounds **140j** and **140k** were treated with ethylenediamine in ethanol at 78 °C to give the free alkenylamines which were directly converted to the amides **137j** and **137k** by addition of the acid chloride to provide the products in good yield (Scheme 63).



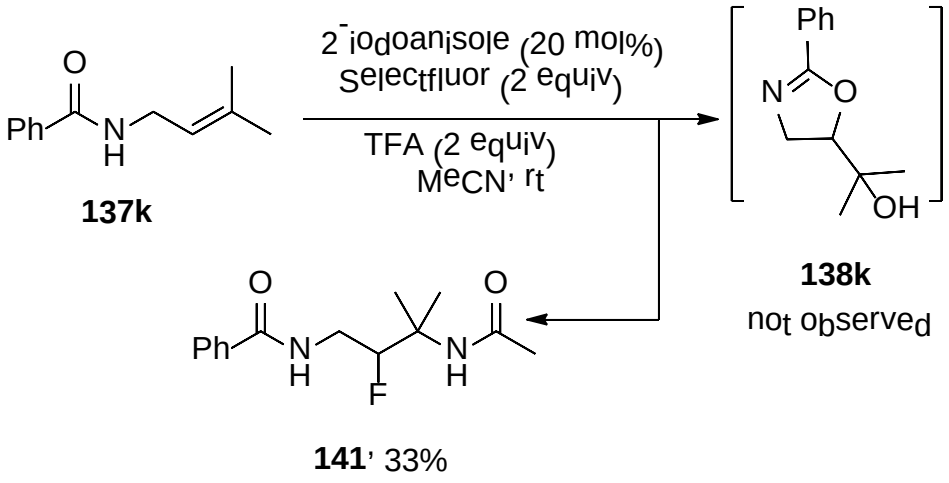
Scheme 63

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



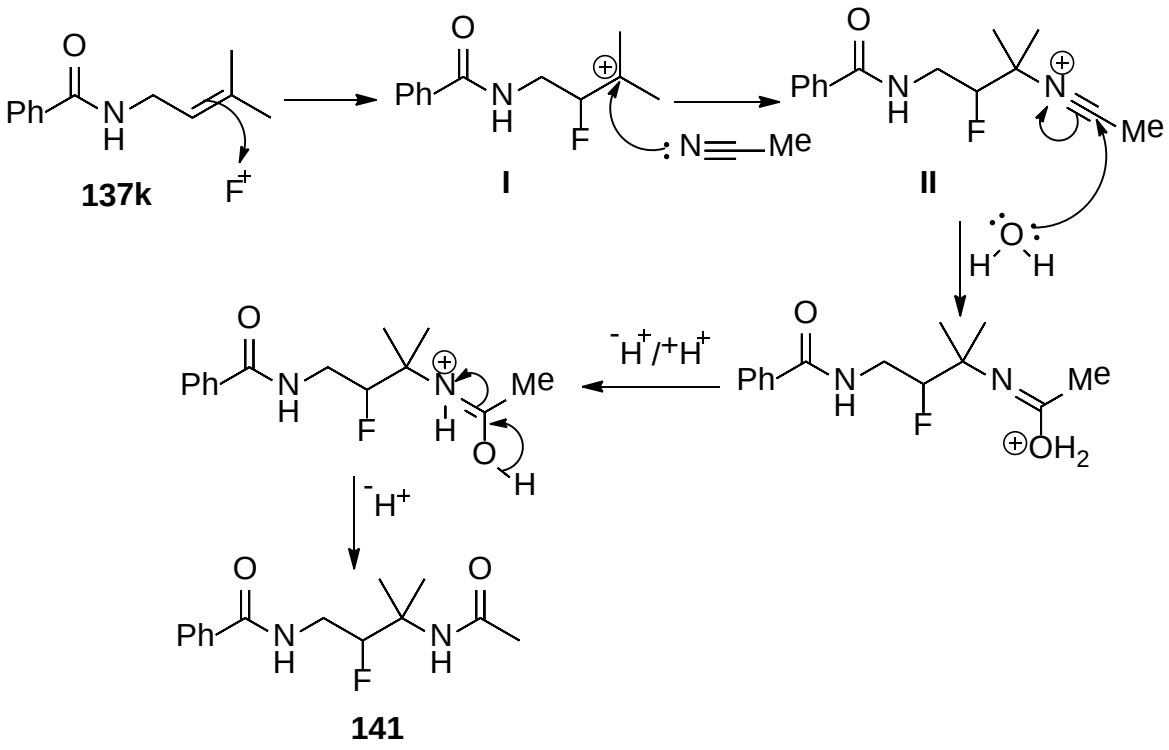
Scheme 64

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



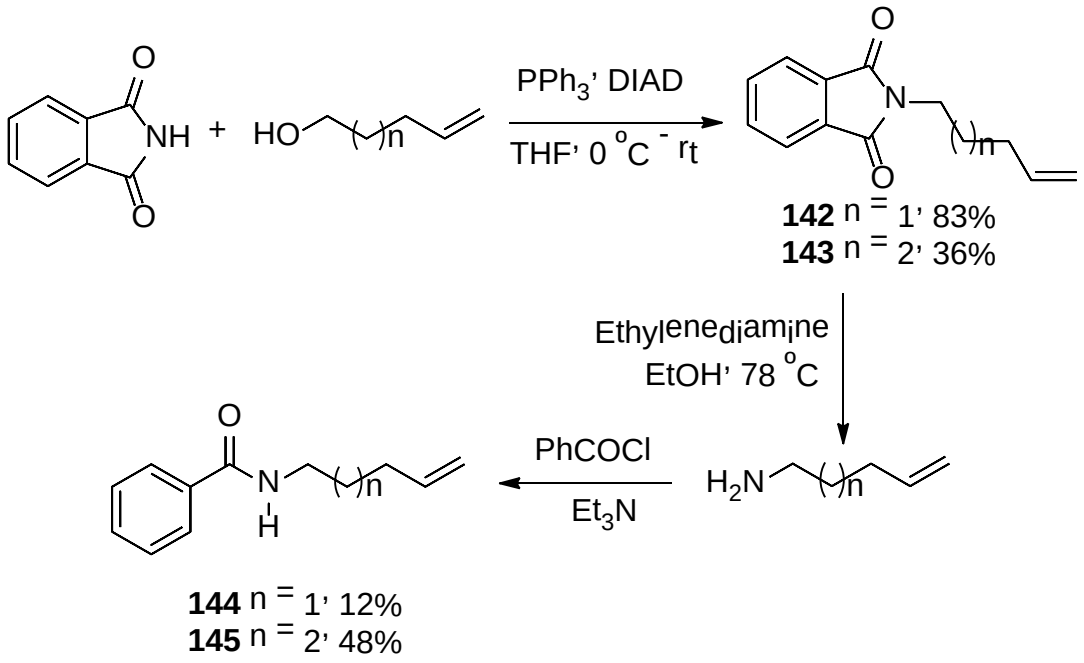
Scheme 65

A plausible reaction mechanism for this reaction is proposed in Scheme 66. First, fluorine cation produced from Selectfluor attacks the double bond generating intermediate **(I)** followed by insertion of the acetonitrile into intermediate **(I)** (a Ritter reaction) producing nitrilium ion **(II)** which undergoes hydrolysis to the corresponding amide **141** upon aqueous work-up.



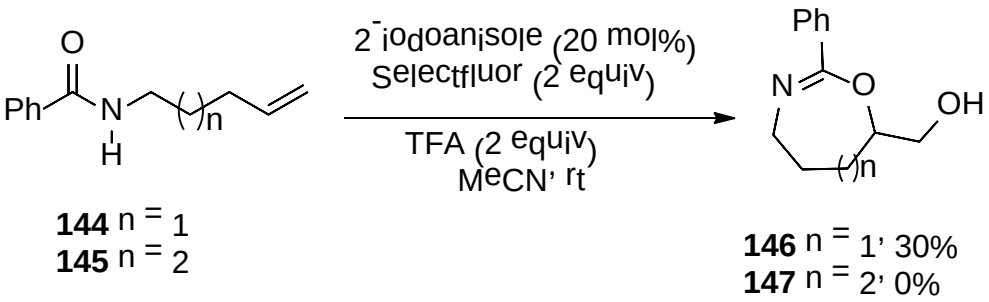
Scheme 66

Pleased with the formation of five- and six-membered rings using our catalytic conditions, the scope of the process was wished to expand to include seven- and eight-membered ring formation. Substrates **144** and **145** were prepared according to the literature procedure reported by Michael and Cochran.[72] *N*-Alkylation of phthalimide with the corresponding alcohol under Mitsunobu conditions produced **142** and **143** in good yield. This was cleaved with ethylenediamine in ethanol at 78 °C to give free alkenylamines which were used directly in the second step to prepare **144** and **145** by addition of the benzoyl chloride to provide the products in moderate yield (Scheme 67).



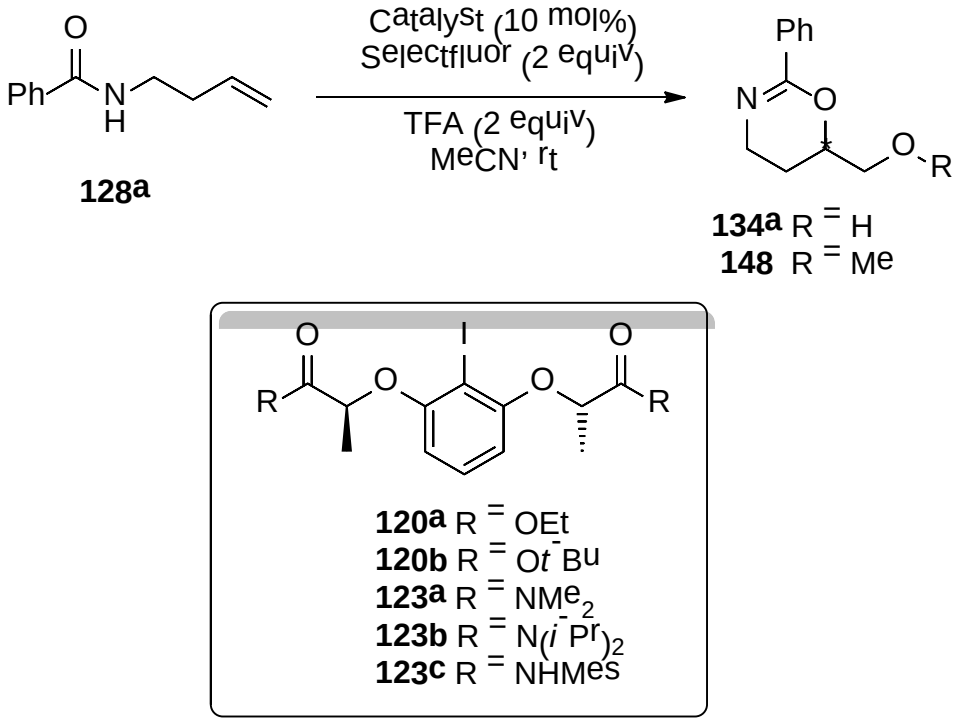
Scheme 67

Then, the cyclisation reaction of **144** and **145** was attempted using our standard conditions. The seven-membered ring **146** was successfully formed in 30% yield. However, the eight-membered ring **147** was not formed (Scheme 68).



Scheme 68

With an effective cyclisation process in hand, it was turned the attention to the use of chiral iodoarene catalysts in order to see if high levels of enantioselectivity were possible (Scheme 69).



Scheme 69

The work on iodoarenes **120a**, **120b**, **123a**, **123b** and **123c** was focussed as these chiral iodoarene afforded the best enantioselectivities in the cyclisation of the ester analogues and have been shown to be effective in several enantioselective oxidation reactions of styrene derivatives.[13] The results of this study of precatalysts is summarised in Table 8.

The use of dimethylamide catalyst **123a** led to formation of **134a** in very good yield with moderate enantioselectivity of 64% ee (entry 1). Interestingly, the amount of catalyst could be lowered to 10 mol% without a drop in yield. Varying the temperature of the cyclisation was also attempted in the hope of improving selectivity. Performing the reaction at 50 ^{o}C and at -10 ^{o}C afforded the product in low selectivity in the former case and about the same in the latter (entries 2 and 3). In the same way, lower selectivity was obtained when bistrifluoromethanesulfonimide was used instead of TFA (entry 4). Also, when methanol was used as a solvent instead of performing acetonitrile only the formation of methyl ether **148** was observed but in low yield and low selectivity (26%) (entry 5). However, performing the

reaction with 1:1 or 2:1 acetonitrile/methanol mixture as solvent led to separable mixtures of **134a** and **148** being formed (entries 6 and 7). In this case, the enantioselectivity of ether **148** was 62% this was the same as the highest enantioselectivity recorded for **134a**. After that, a few other related catalysts **120-123** were screened but unfortunately no improvement in selectivity was observed. With diisopropylamide catalyst **123b**, complete conversion to ether **148** with enantiomeric excess 50% ee was observed by changing the solvent to a 1:2 mixture of MeCN and MeOH (entry 9) instead of MeCN that afforded the desired product with very low conversion therefor the enantioselectivity was not determined (entry 8). Both pr-catalysts mesityl amide **123c** and ethers **120a** provided the desired product in moderate yields and enantioselectivites (entries 10-11). With *t*-butyl ester catalyst **120b** and the mixed solvent system lower selectivity was observed for both products **134a** and **148** but a swap in the major enantiomer formed was noted (entry 12).

Entry	Catalyst	Solvent	Yield %[a] **134a**	ee %[b] **134a**	Yield %[a] **148**	ee %[b] **148**
1	**123a**	MeCN	86	64	0	-
2[c]	**123a**	MeCN	75	34	0	-
3[d]	**123a**	MeCN	10	58	0	-
4[e]	**123a**	MeCN	11	26	0	-
5	**123a**	MeOH	0	-	10	26

6	**123a**	1:1 MeCN/MeOH	37	42	28	48
7	**123a**	1:2 MeCN/MeOH	51	52	34	62
8	**123b**	MeCN	<5	n.d.	0	-
9	**123b**	1:2 MeCN/MeOH	0	-	99	50
10	**123c**	MeCN	53	50	0	-
11	**120a**	MeCN	23	44	0	-
12	**120b**	1:1 MeCN/MeOH	49	30	64	32

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis.
[c] Reaction performed at 50 ºC. [d] Reaction performed at -10 ºC.
[e] Bistrifluoromethanesulfonimide used instead of TFA.

Table 8

At this point, thinking about developing some novel catalyst structures but based on the pioneering work of others was decided. Specifically, it were intrigued by the possibility of using chiral vinyl iodides as catalysts instead of aryl iodides following on from the seminal work of Wirth [73] using achiral vinyl iodides (Figure 5).

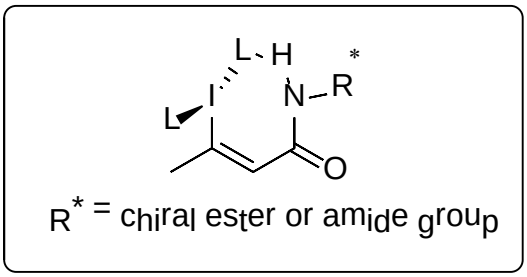
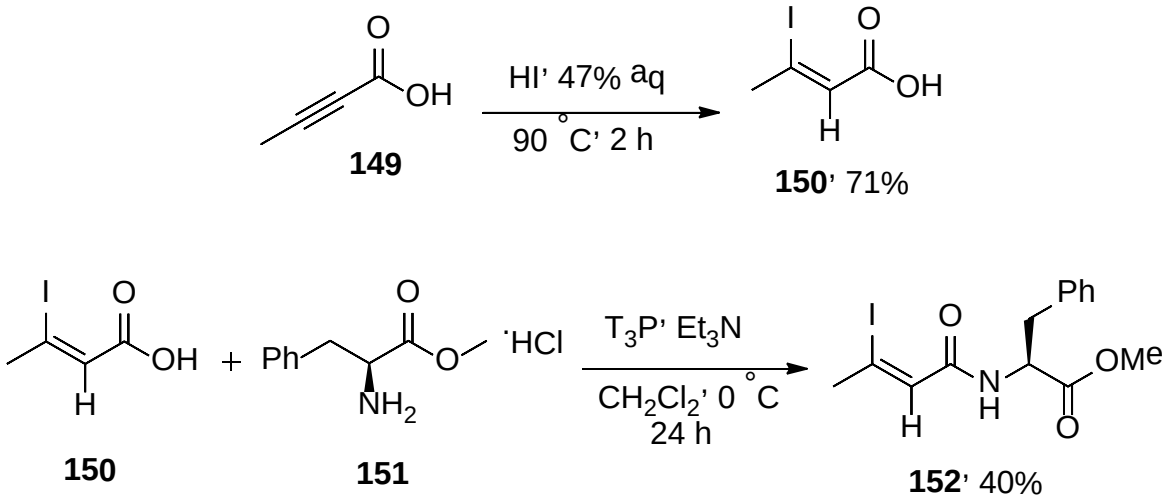


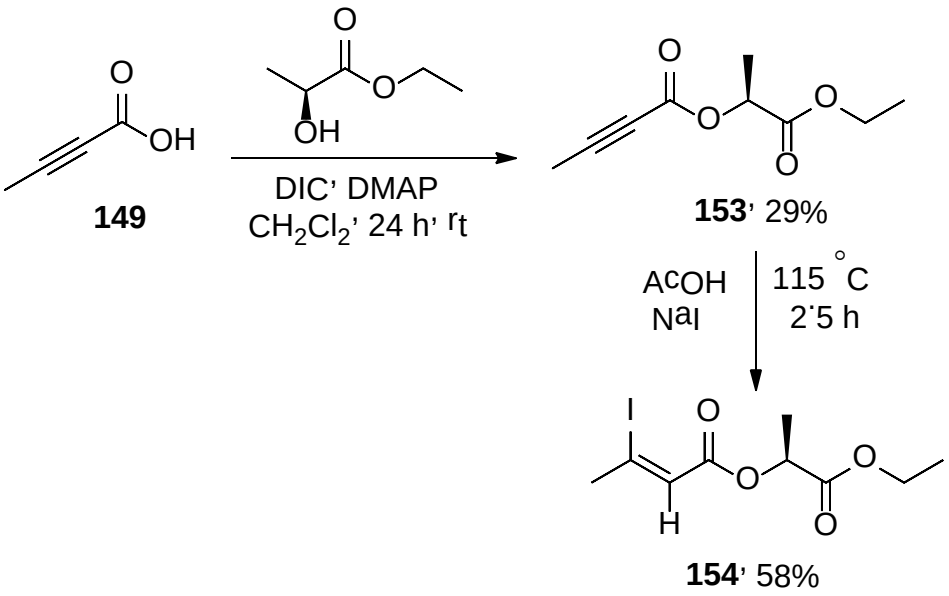
Figure 5

It was envisaged that a hydrogen-bond between the N-H and the ligand oxygen would enable formation of a macrocyclic ring similar to that reported for the Ishihara-Fujita catalyst (Scheme 9) and Figure 4. The work was initiated with the preparation of chiral amide **152**. The first step was the treatment of but-2-ynoic acid **149** with 47% aq. HI solution at 90 ºC which resulted in the formation of (*Z*)-3-iodobut-2-enoic acid **150** in 71% yield.[73] In the next step, amide **152** was prepared accordingly to the procedure reported by Moran.[74] (*Z*)-3-Iodobut-2-enoic acid **150** was coupled with (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride using T_3P which provided the corresponding amide **152** in 40% yield (Scheme 70).



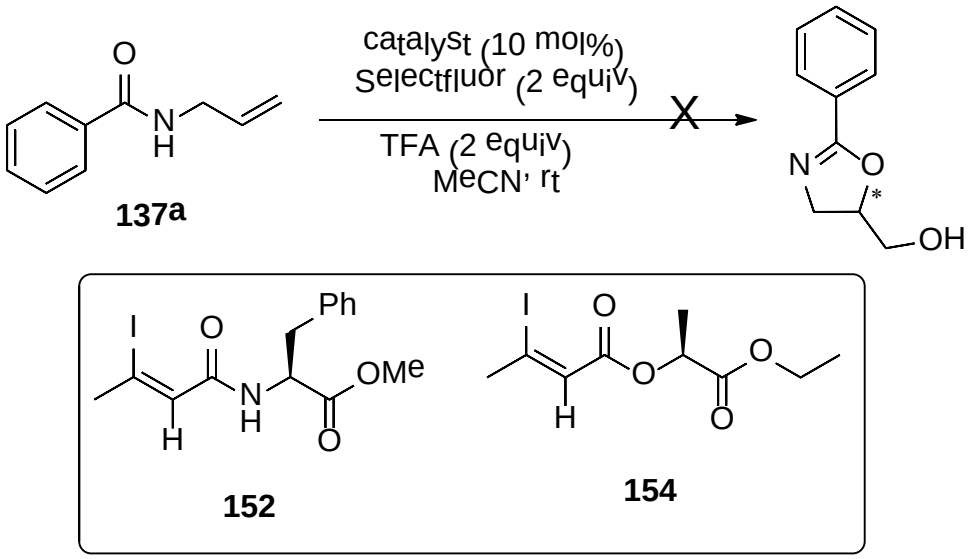
Scheme 70

In addition, the ester analogue **154** was prepared by a similar pathway in two steps. First, ester **153** was prepared according to a literature procedure[75] via esterification of but-2-ynoic acid **149** with (L)-lactic acid ethyl ester using DMAP and DIC in 29% yield. Then the alkynyl ester **153** was stereo- and regioselectively transformed into β-iodo-alkenyl ester **154** by AcOH in the presence of NaI to provide **154** in moderate yield (58%) (Scheme 71).[76]



Scheme 71

Lastly, these new catalysts **152** and **154** were applied in the cyclisation reaction of *N*-allylbenzamide substrate **137a** for the preparation of five-membered rings but, unfortunately there was no product found by ^{1}H NMR analysis of the crude mixture in both cases. The starting material was recovered (Scheme 72).



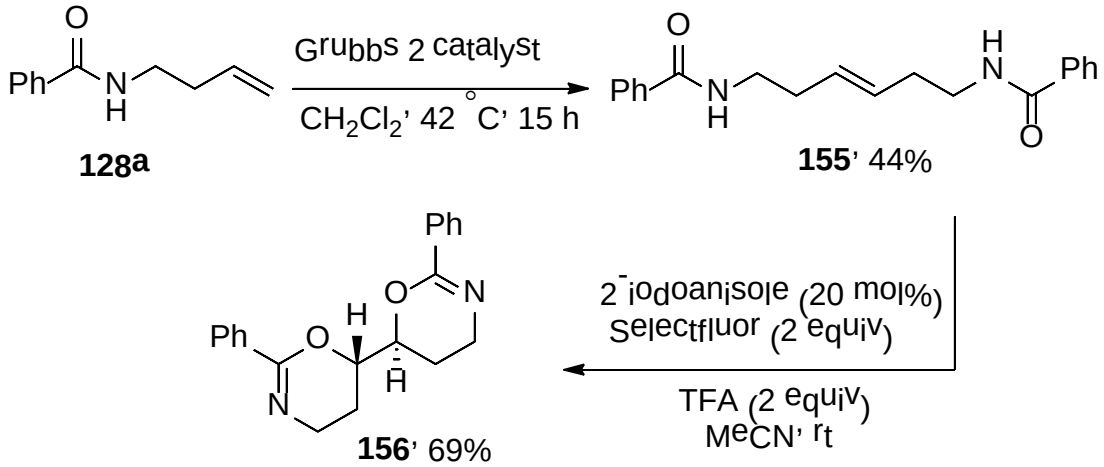
Scheme 72

3.2.1. Conclusion and future work

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

Future work

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

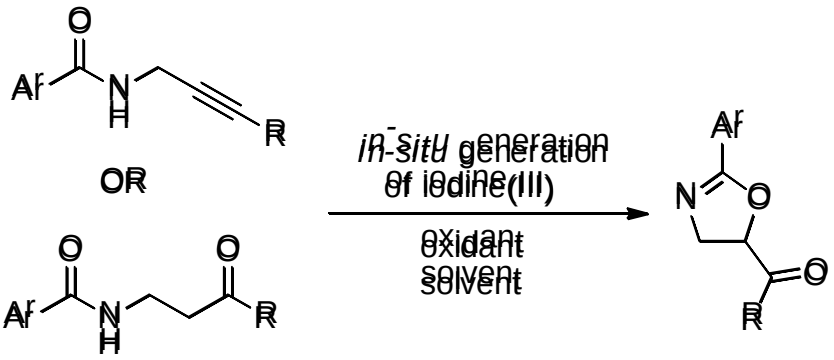


Scheme 73

Future work will focus on the development of this tandem cyclisation process to generate products with a mixture of ring sizes and substituent.

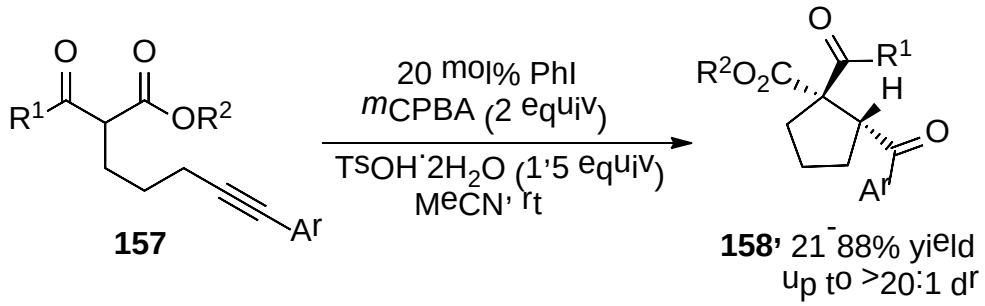
3.3. Cyclisation Reactions of propargyl amides and β-amidoketones

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



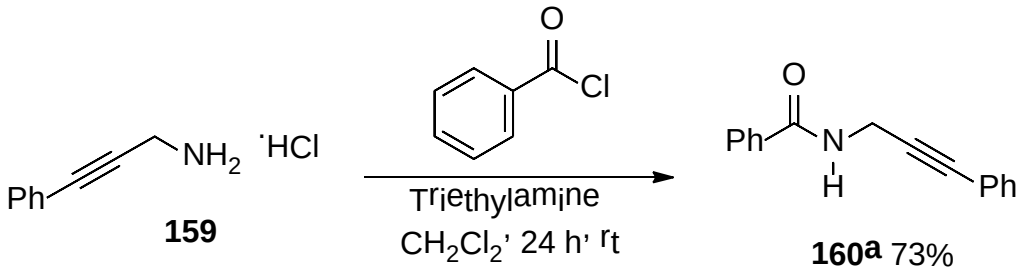
Scheme 74

Previously, the Moran group reported a catalytic procedure for the diastereoselective intramolecular cyclisation of δ-alkynyl β-ketoesters using iodobenzene under oxidative conditions (*m*CPBA as the oxidant in the presence of *p*-TsOH in MeCN at room temperature) that generated iodine(III) species *in situ*. These iodine(III) species mediated the cyclisation of δ-alkynyl β-ketoesters **157** to provide cyclopentanes **158** in moderate to high yields with excellent diastereoselectivity (Scheme 75).[79]



Scheme 75

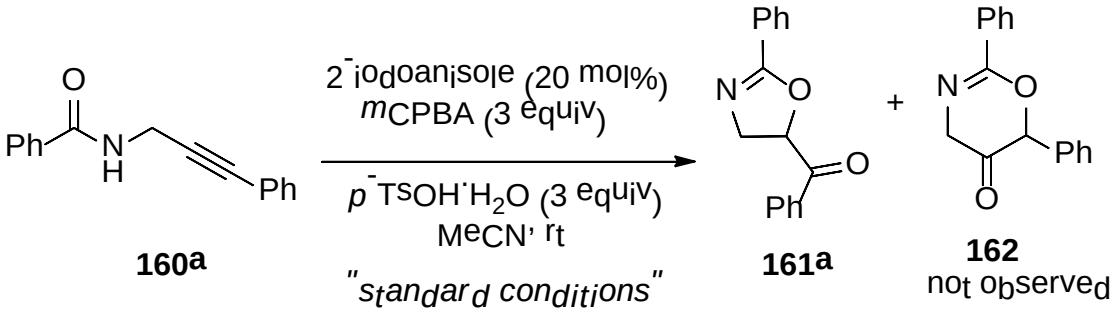
Initially, alkyne substrate **160** was synthesised in good yield (73%) by a known literature procedure[80] via the amidation of propargyl amine using benzoyl chloride in CH_2Cl_2 in the presence of triethylamine (Scheme 76).



Scheme 76

With *N*-(3-phenylprop-2-yn-1-yl)benzamide **160** in hand, its cyclisation was investigated using reaction conditions previously reported. Representative results are shown in Table 9. In agreement with our previous results with *N*-alkenylamides the use of 2-iodoanisole instead of iodobenzene provided the desired oxazine heterocycles **134** in high yield. For that reason we decided to use 2-iodoanisole as precatalyst and *m*CPBA as stoichiometric oxidant in the presence of *p*-TsOH in acetonitrile at room temperature, after reaction for 12 h, the cyclised product **161a** was formed in 92% yield as determined by ^{1}H NMR analysis of the crude reaction mixture (entry 1). Whereas, subjecting iodobenzene as precatalyst the yield for **161a** decreased to 60% (entry 2). It was evidenced that, the 2-iodoanisole was the best iodoarenes for this type of the cyclisation. In contrast, the reaction did not proceed in the absence of iodoarene catalysts and the starting material **160a** was completely recovered (entry 3). In the same way, a small amount of product (<5%) was detected when the Oxone was used as oxidant (entry 4). Switching the acid to TFA dropped the yield of **161a** significantly to 19% (entry 5). In addition, only 37 % yield for **161a** was obtained by switching the solvent to less polar solvent as CH_2Cl_2 (entry 6). To study the effect of the number of equivalents of oxidant and/or acid various ratios were investigated 2 equiv *m*CPBA and 2 equiv TsOH.H_2O, 1:1 and

3:1 afforded the desired product with low yields (entries 7-9). Notably, the formation of the six-membered ring was not observed under any conditions studied.



Scheme 77

Entry	deviations from "standard conditions"	Yield %[a]
1	none	92 (73)[b]
2	iodobenzene instead of 2-iodoanisole	60
3	no 2-iodoanisole	0
4	Oxone instead of *m*-CPBA	<5
5	TFA instead of TsOH.H_2O	19
6	CH_2Cl_2 instead of MeCN	37
7	2 equiv *m*CPBA and 2 equiv TsOH.H_2O	54
8	1 equiv *m*CPBA and 1 equiv TsOH.H_2O	44
9	3 equiv *m*CPBA and 1 equiv TsOH.H_2O	41

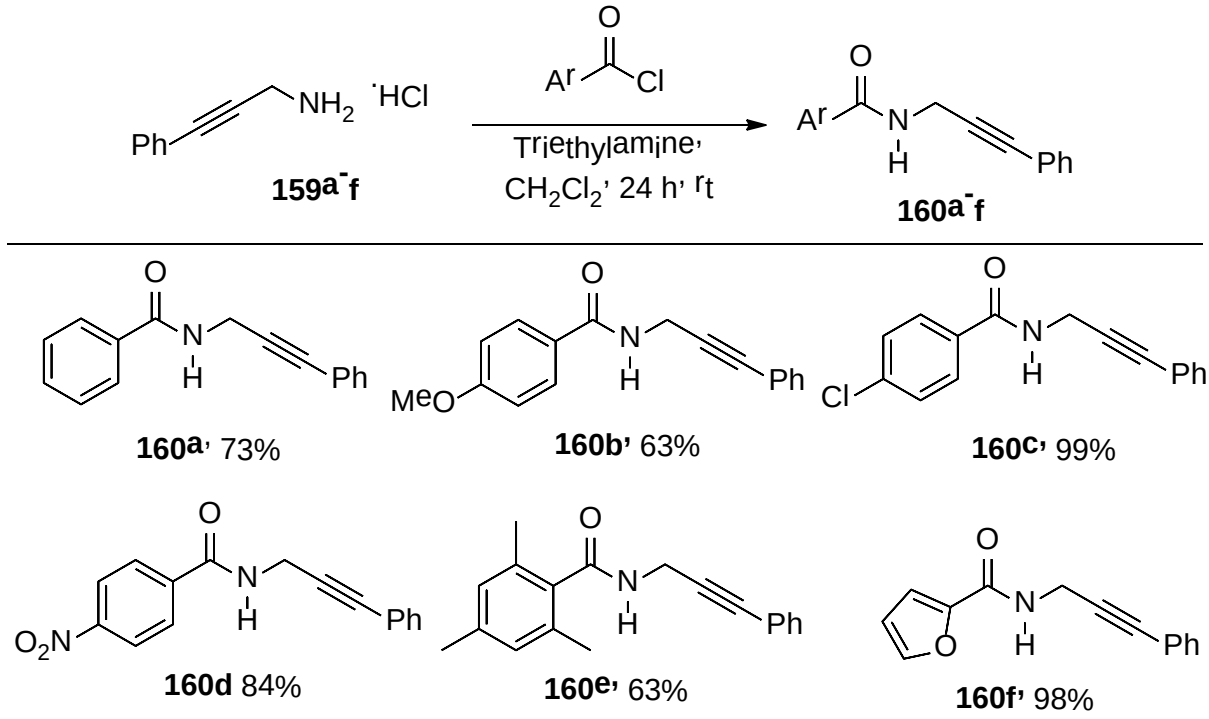
a) Yield determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

b) Yield of isolated compound.

Table 9

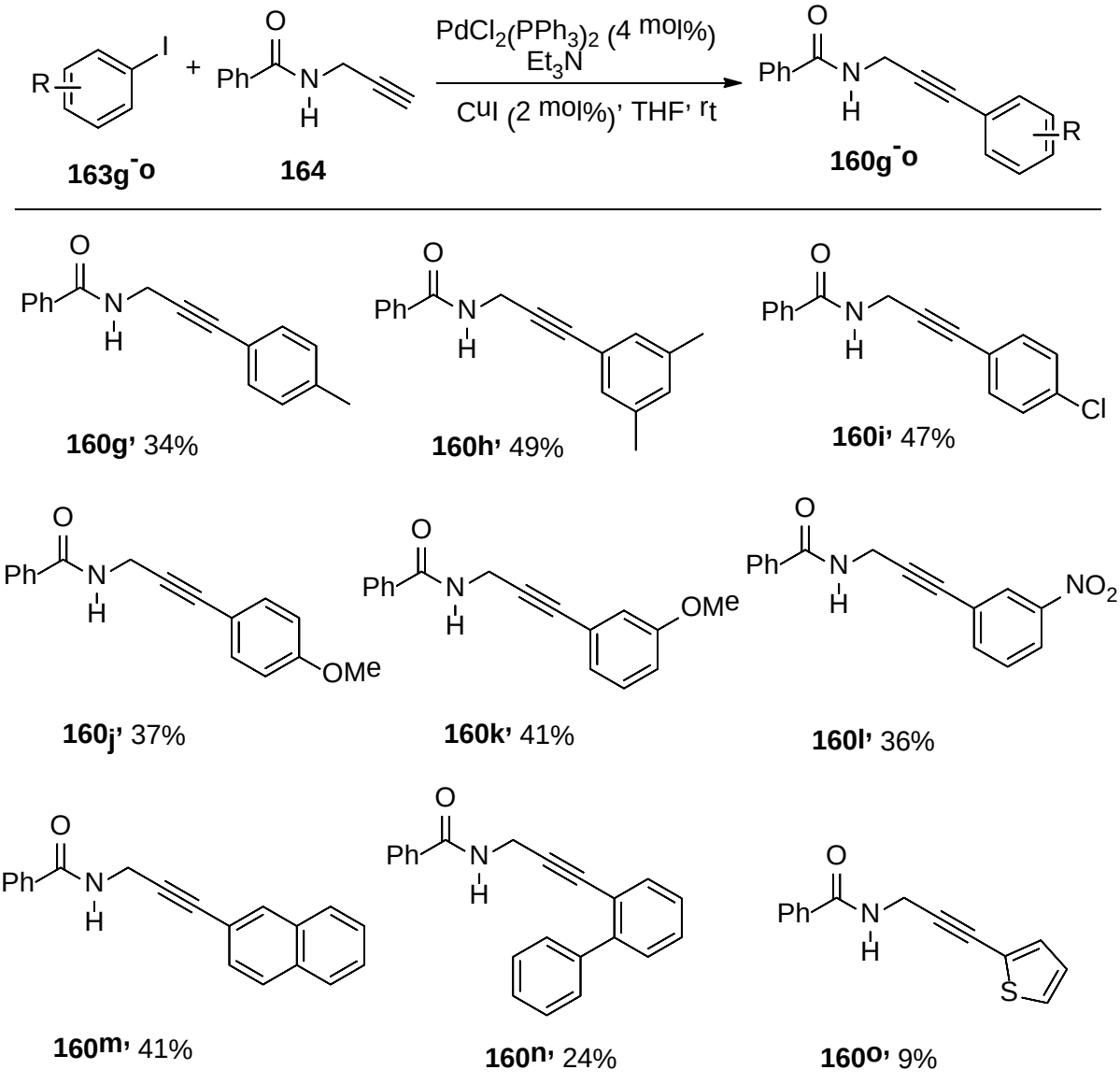
With the suitable reaction conditions established, the scope and generality of the cyclisation process for different propargyl amides **160** was set out to extend**.**

Initially, various propargyl amides substrates **160a-f** were synthesised in moderate to good yield following the procedure reported by Frank Rominger,[80] started from the reaction of 3-arylprop-2-yn-1-amine hydrochloride **159a-f** with benzoyl chloride in CH_2Cl_2 in the presence of trimethylamine at room temperature. As illustrated in Scheme 78, all of the desired alkyne amides were obtained in good to excellent yields. The propargyl amide was obtained in good yield (73%) when the aryl group was a phenyl ring. In the case of aryl groups containing electron-donating groups (OMe and Me) the amide products were obtained in good yields. However, electron-withdrawing groups (NO_2 and Cl) at the *para* position of the phenyl ring afforded the amides with good to excellent yields (84-99%). Additionally, a heterocyclic substrate containing 2-furyl a substituent provided the corresponding amide in excellent yield.



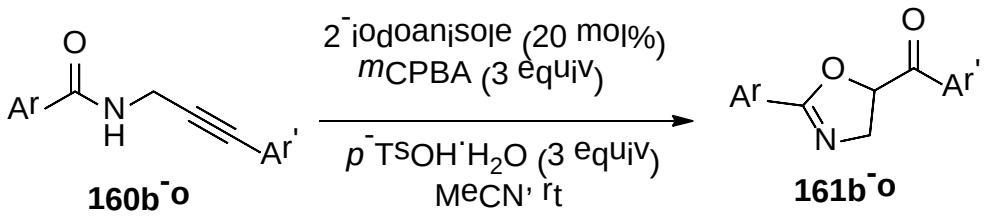
Scheme 78

In addition, alkyl-substituted propargylic amides substrates **160g-o** were synthesised by a Sonogoshira reaction from the appropriate aryl iodide and propargylamides with a palladium catalyst $PdCl_2(PPh_3)_2$ and with CuI as co-catalyst in THF in the presence of Et_3N at room temperature (Scheme 79).[81] In general these substrates were isolated in moderate yields with the exception of the 2-thienyl product **160o** which was afforded in very low yield. Under these conditions, relatively high Pd loadings were required to achieve moderate conversions of amide.



Scheme 79

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



Scheme 80

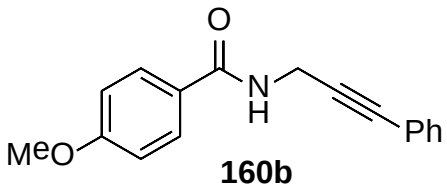
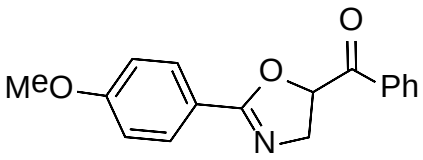
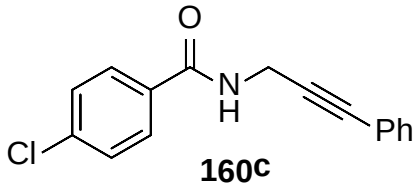
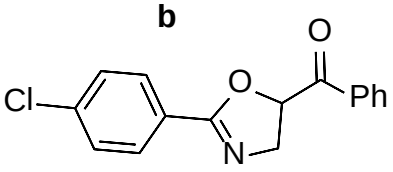
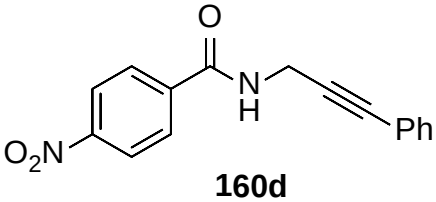
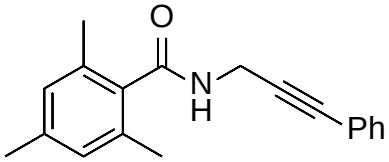
entry	substrate	product	yield %
1	 **160b**	 **161b**	50
2	 **160c**	 **161c**	75
3	 **160d**	no reaction	-
4	 **160e**	no reaction	-

Table 10

Similarly, substrates with different alkyne substituents were examined and were cyclised giving the corresponding 2-oxazoline products in varying yields depending on the position of the substitution on the alkyne as shown in Table 11. Alkyl substituents on the phenyl ring led to diminished yields (entries 1and 2). Chlorine and methoxy were well tolerated at the *para* position and the corresponding 2-oxazoline derivatives were produced in 52 and 68% yield respactivly (entries 3 and 4). However, when the functional groups methoxy and nitro were in the *meta* position, the yields were lower than their *para*-substituted in case of methoxy group (entries 5) whereas in the case of nitro group, the reaction did not occurred (entries 6). This can be explained by the electron-withdrawing nitro group reduces the nucleophilicity of the amide and prevents the cyclisation from occurring.

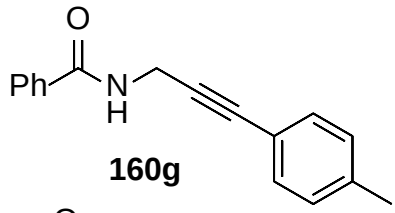
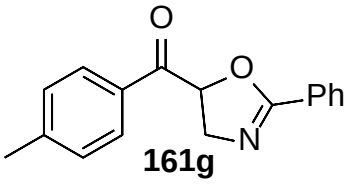
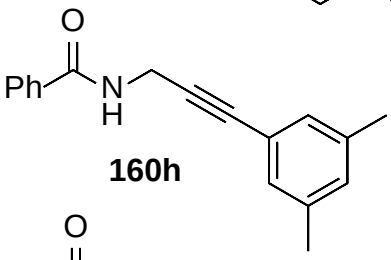
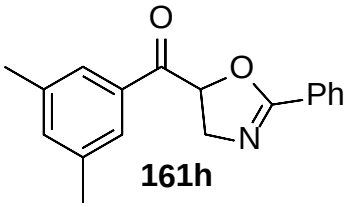
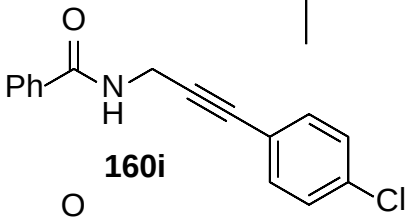
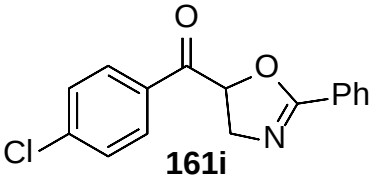
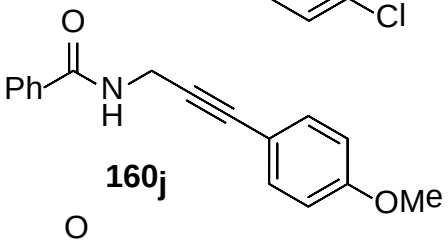
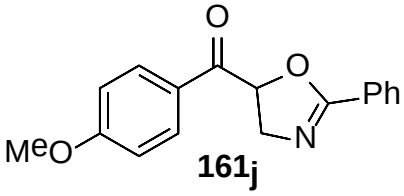
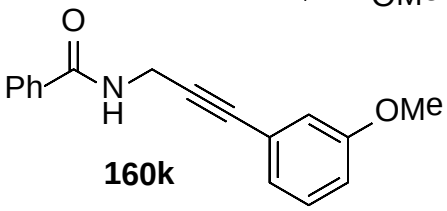
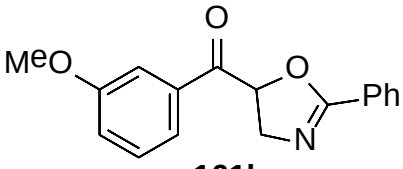
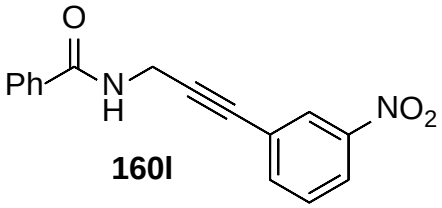
entry	substrate	product	yield %
1	 **160g**	 **161g**	35
2	 **160h**	 **161h**	<5
3	 **160i**	 **161i**	68
4	 **160j**	 **161j**	52
5	 **160k**	 **161k**	14
6	 **160l**	no reaction	-

Table 11

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

and the cyclised product **160n** was obtained in 82% yield, when compound **160n** with biphenyl substituent on the alkyne moiety was subjected to reaction conditions (entry 3). However, the cyclisation failed to produce the 2-oxazoline when a thienyl group was attached to the alkyne (entry 4).

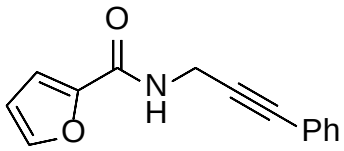
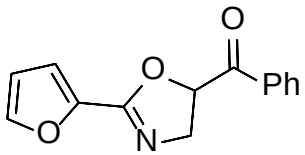
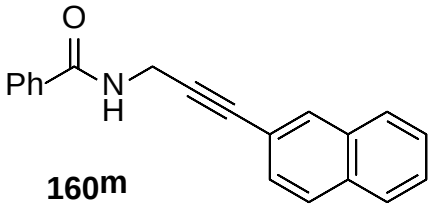
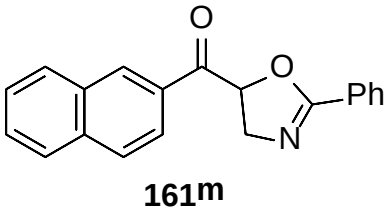
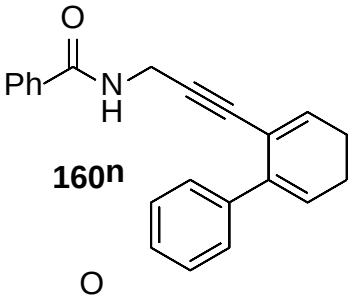
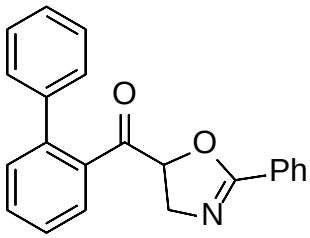
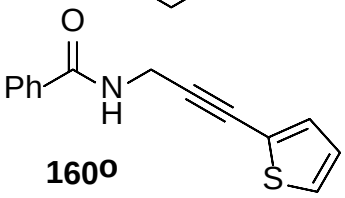
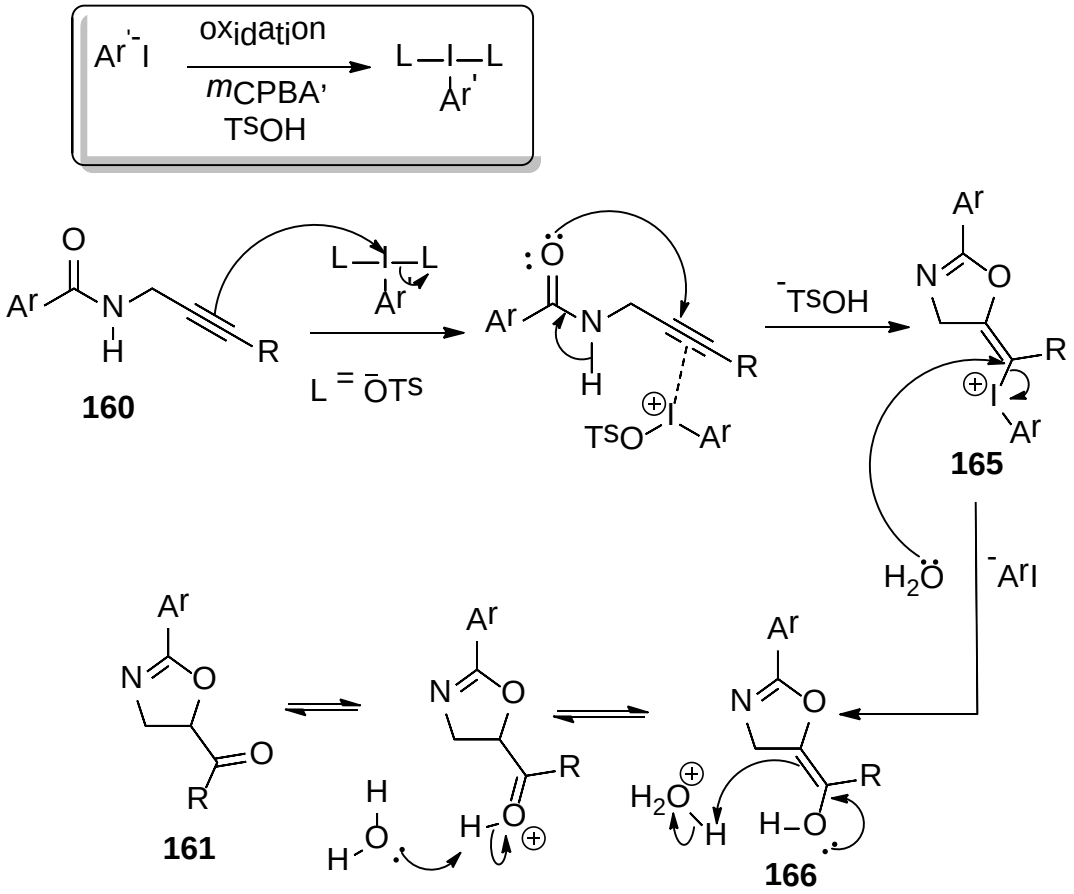
entry	substrate	product	yield %
1	 **160f**	 **161f**	66
2	 **160m**	 **161m**	75
3	 **160n**	 **161n**	82
4	 **160o**	no reaction	-

Table 12

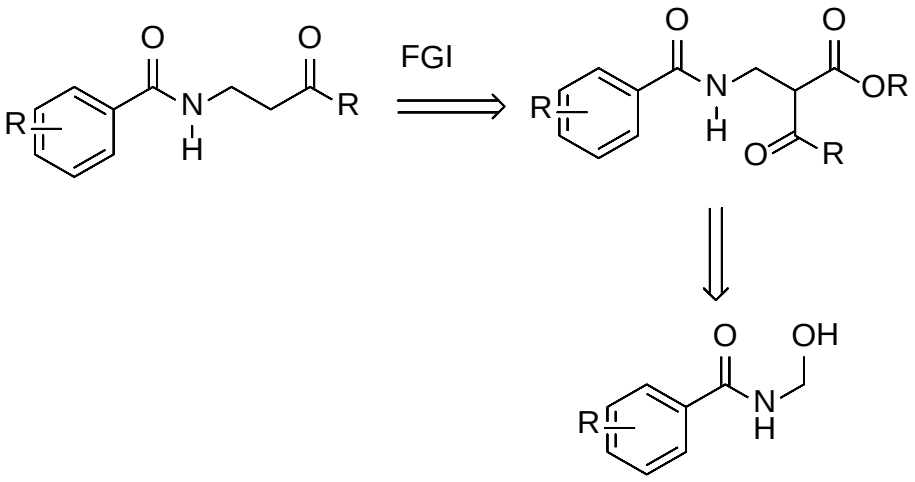
The plausible reaction pathway for the cyclisation of propargyl amides is illustrated in Scheme 81. The initial step is the active hypervalent iodine(III) species is generated *in-situ* from oxidation of the aryl iodide by *m*CPBA and TsOH. The next step is the electrophilic iodine(III) species activates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

loss of the iodoarene form alkenyl(aryl)iodine intermediate **165** generates enol **166**. Tautomerisation of the resulting enol can provide the oxazoline product **161.**



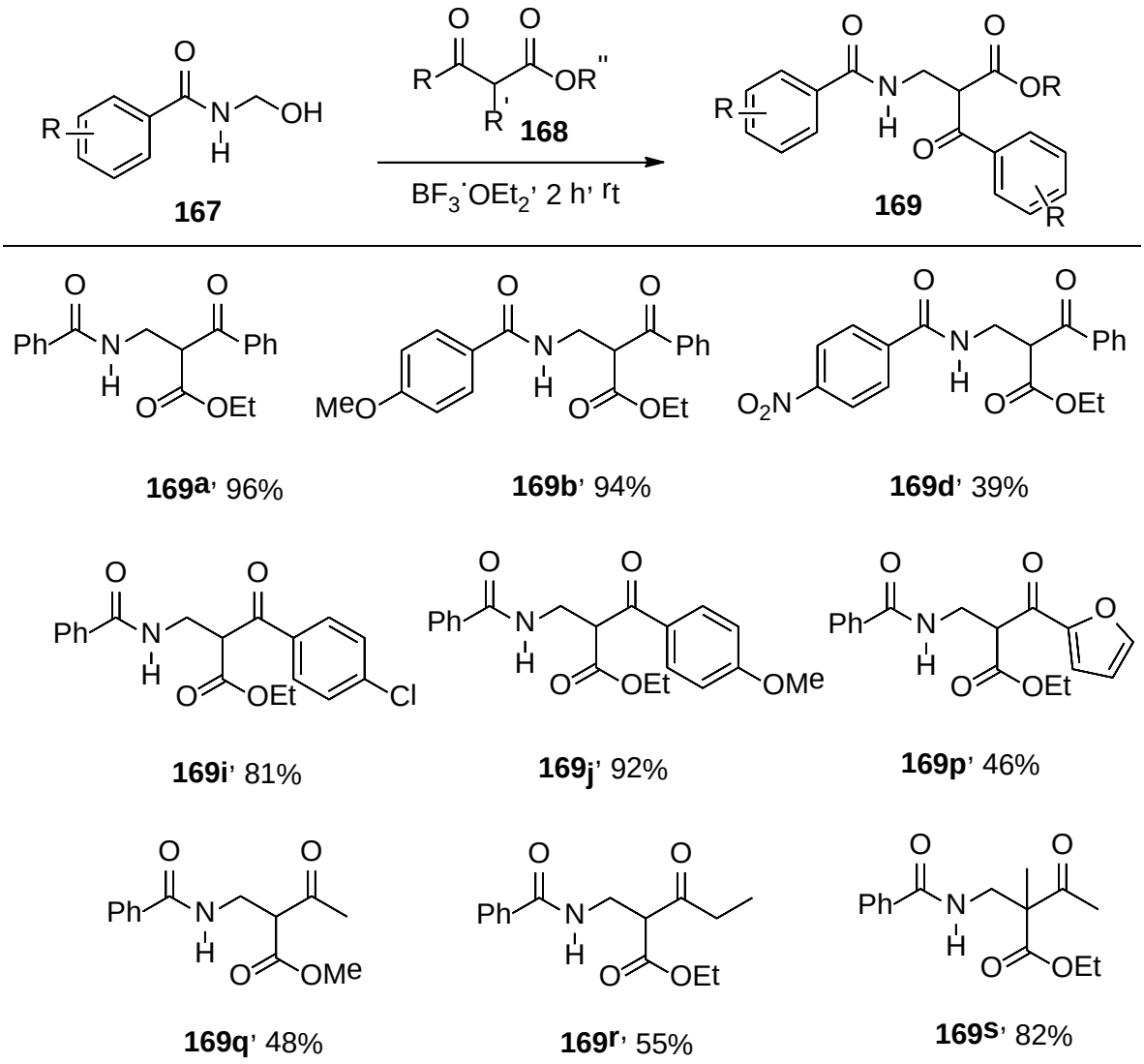
Scheme 81

With these results in hand, β-amidoketones **172** were selected to test our iodoarene-catalysed cyclisation strategy as the products would provide an alternative approach to 2-oxazoline formation. These are readily prepared by alkylation of the corresponding β-ketoester followed by decarboxylation (Scheme 82).



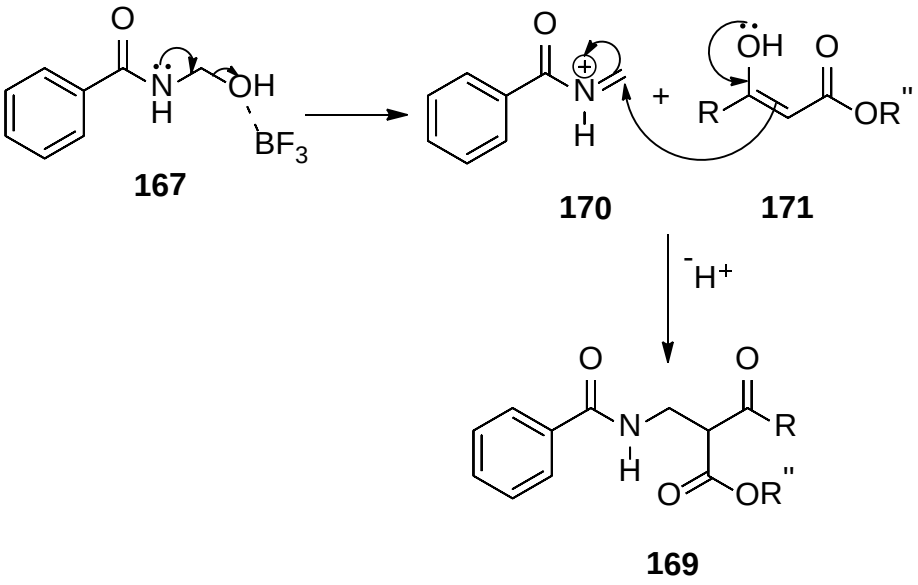
Scheme 82

Firstly, following a literature procedure reported by Wang,[82] compounds **169** were prepared in good to high yields by the alkylation of the corresponding β-ketoester using *N*-(hydroxylmethyl)benzamide in the presence of boron trifluoride etherate (Scheme 83). All the desired products were obtained in moderate to excellent yields. With a phenyl ring in both the amide moiety and in the β-ketoester the respective product **169a** was isolated in 96% yield. Similarly, an excellent yield of 94% was obtained when the phenyl ring at the α-position of the amide group was substituted with a *para*-methoxy group whereas a *para*- nitro group led to low yield of product. The corresponding α-benzamido β-keto esters **169i** and **169j** were obtained in 81 and 92% yield respectively when the β-ketoester phenyl ring was substituted with the moderately electron-withdrawing *para*-chloro and *para*-methoxy groups. 2-Furyl substituted β-keto ester **169p** was also prepared in 46% yield. Other α-benzamido aliphatic β-ketoesters **169q-s** were also prepared in yields ranging from 48 to 82%.



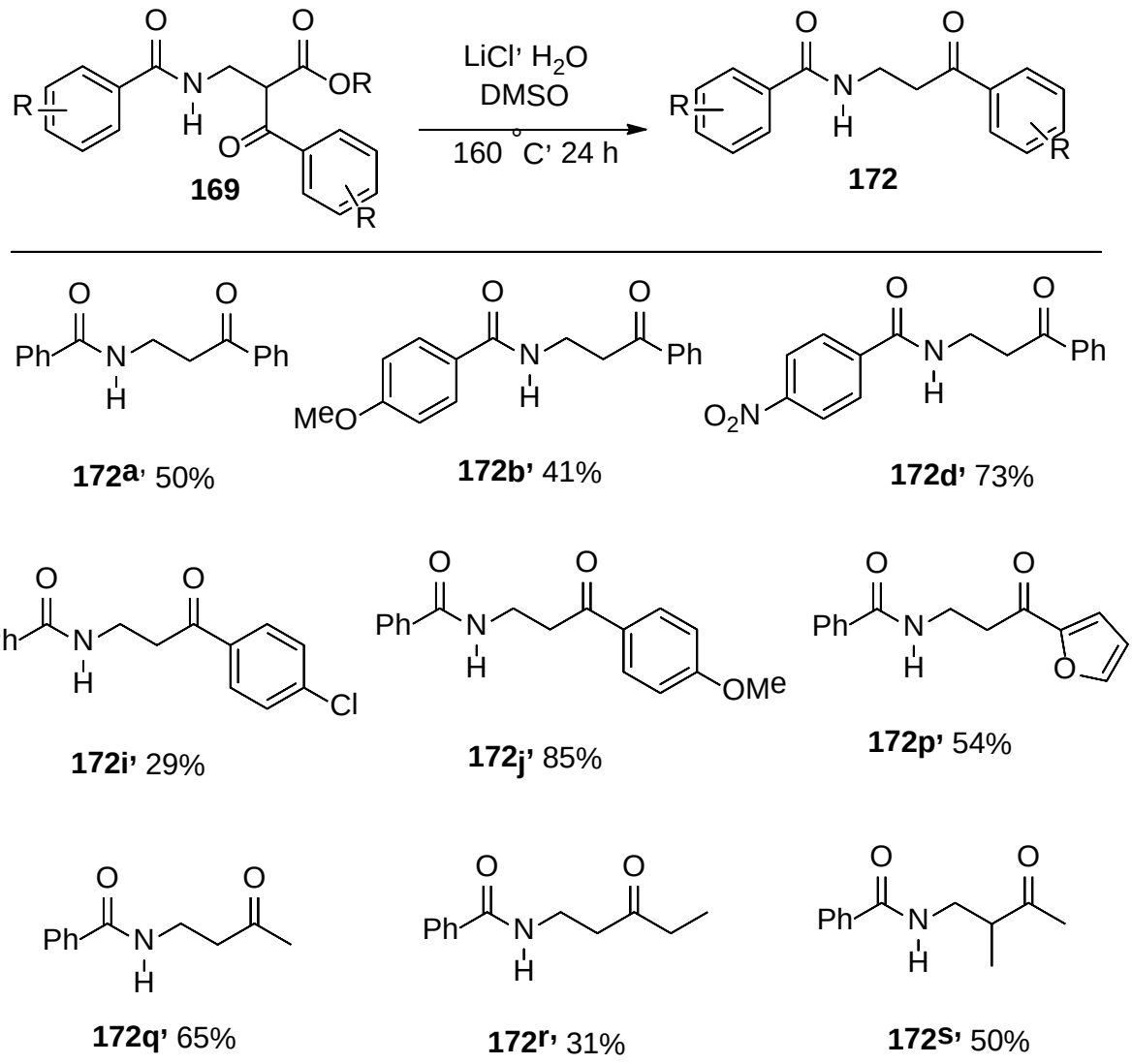
Scheme 83

A plausible mechanism for the reaction is described in Scheme 84. First the Lewis acid BF_3 activates the hydroxyl group making it a good leaving group which results in the formation of iminium cation intermediate **170**. Nucleophilic attack of enolate **171** results in the formation of α-benzamido β-keto esters **169**.



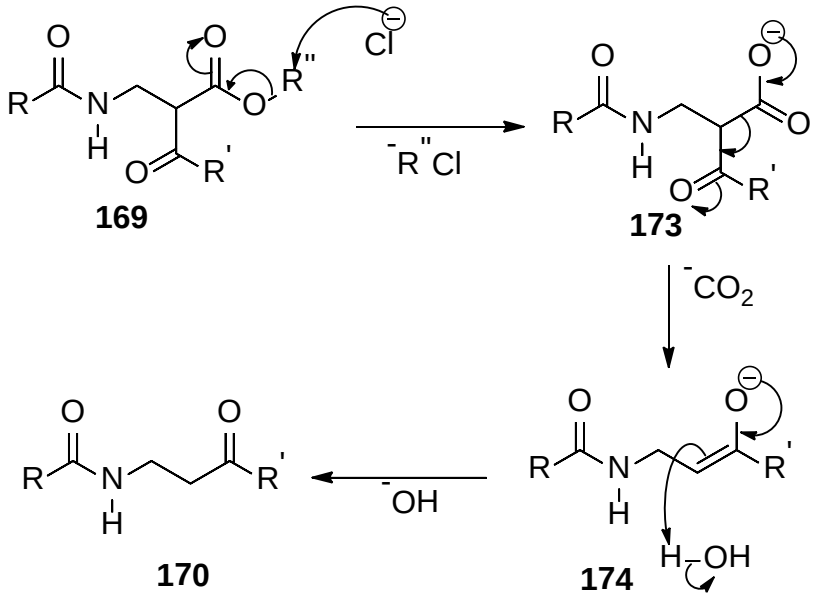
Scheme 84

The next step in the syntheses of β-amidoketones **172** was the decarboxylation of substrates **169** via a known procedure developed by Kaku,[83] by treatment of compounds **169a-s** with DMSO, LiCl and water under reflux for 24 h (Scheme 85). Both alkyl- and aryl β-amidoketones were prepared in moderate to good yields. The β-amidoketone **172a** was obtained in 50% yield, and **172b** was obtained in 41% when the phenyl ring on the amide group was substituted with a *para*-methoxy group while the presence of a *para*-nitro group led to a superior 73% yield. Modification of the aryl ring next to the ketone with *para*-chloro, *para*-methoxy and 2-furyl groups, led to the corresponding β-amidoketones **172i, 172j** and **172p** being prepared in 29%, 85% and 54% yields respectively. In addition, switching the aryl rings next to the ketone with alkyl groups afforded the corresponding β-amidoketones **172q-s** in yields ranging from 31 to 65%.



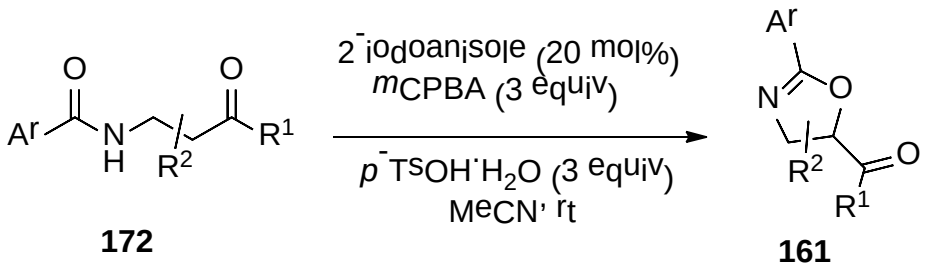
Scheme 85

A plausible mechanism for the Krapcho decarboxylation[84] reaction is shown in Scheme 86. The reaction follows an S_N2 mechanism. Chloride ion attacks the alkyl carbon resulting in the elimination of an alkyl halide which provides an anionic intermediate **173** which undergoes decarboxylation to provide enolate intermediate **174** which is protonated to the final product **172**.



Scheme 86

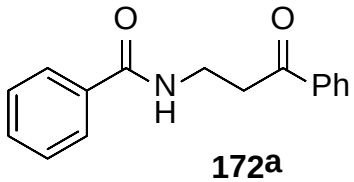
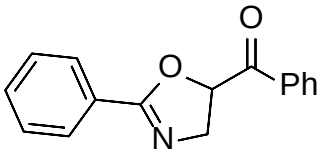
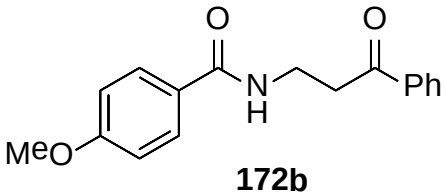
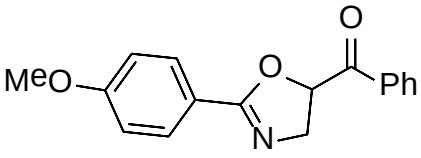
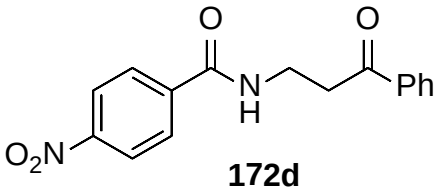
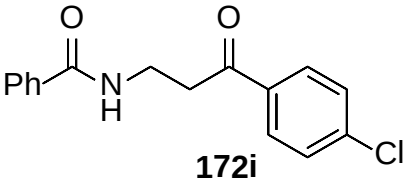
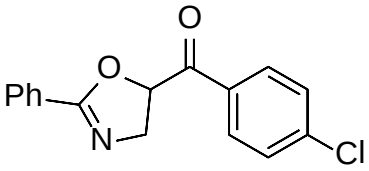
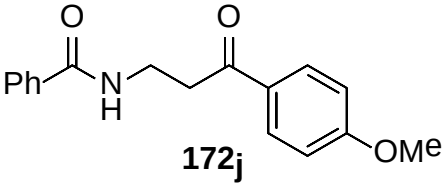
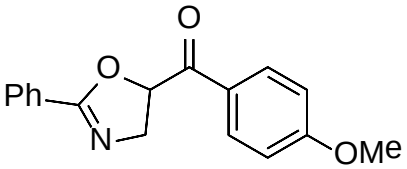
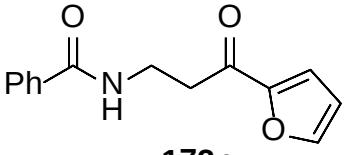
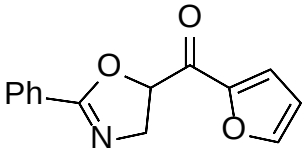
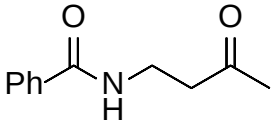
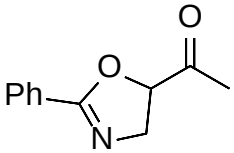
The cyclisation of β-amidoketones **172** was successful under the same conditions as propargyl amides **160** (Scheme 87). In accordance with the results for the propargyl amides, iodobenzene was an inferior pre-catalyst to 2-iodoanisole and subjecting other oxidants, acids and solvents led to lower yields of **161**.



Scheme 87

The scope of the β-amidoketone substrates and the functional group compatibility was investigated under our optimal cyclisation conditions (Table 13). A variety of β-amidoketones having electron-donating and electron-withdrawing groups on the amide aryl ring were tested. The cyclisation of *N*-(3-oxo-3-phenylpropyl)benzamide **172a** afforded 2-oxazoline in good yield (77%) (entry 1). Similarly, substrate **172b** having a *p*-methoxy

substituent afforded the product **161b** in 77 % yield (entry 2). However, the expected oxazoline was not observed when substrate **172d** with a *p*-nitro group was subjected to the reaction conditions (entry 3). Presumably, the nitro group lowered the nucleophilicity of the amide. Next, substrates with electron-donating and electron-withdrawing substituents in the *para*-position of the ketone aryl ring were successfully tolerated in this cyclisation. In the case of the *p*-Cl substituent, the corresponding 2-oxazoline **172i** was isolated in high yield (84%) compared to the *p*-OMe substituent **172j** which gave the corresponding 2-oxazoline **161j** in 46% yield (entries 4 and 5). A 2-furyl group was also tolerated and the desired cyclisation product **161p** was isolated in excellent yield (95%) (entry 6). Alkyl ketone substrates were also successfully converted in to 2-oxazolines with moderate to good yields. For example, the substrates **172q** and **172r** with methyl and ethyl groups underwent cyclisation to give the 2-oxazolines in 63% and 56% yields, respectively (entries 7 and 8). Interestingly, the presence of a methyl group adjacent to the ketone led to the corresponding 2-oxazoline **161s** being isolated in 75% yield (entry 9).

entry	substrate	product	yield %
1	 **172a**	 **161a**	77
2	 **172b**	 **161b**	77
3	 **172d**	no desired product	-
4	 **172i**	 **161i**	84
5	 **172j**	 **161j**	46
6	 **172p**	 **161p**	95
7	 **172q**	 **161q**	63

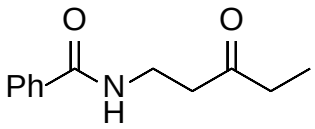
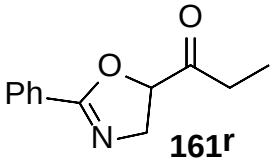
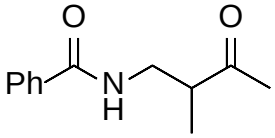
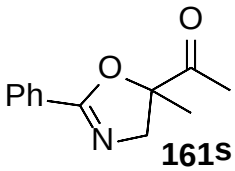
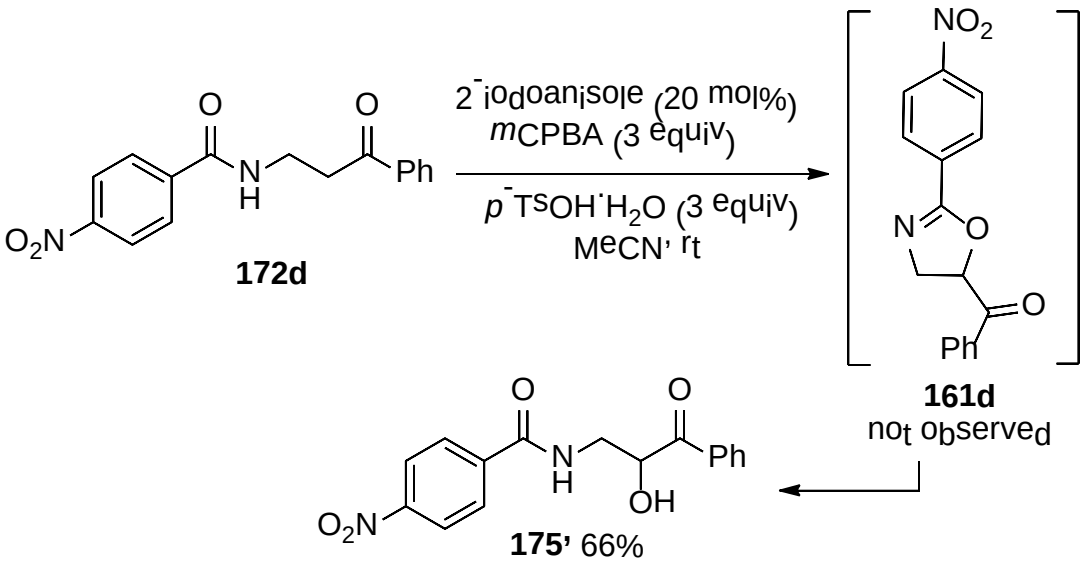
entry	substrate	product	yield %
8	 **172r**	 **161r**	56
9	 **172s**	 **161s**	75

Table 13

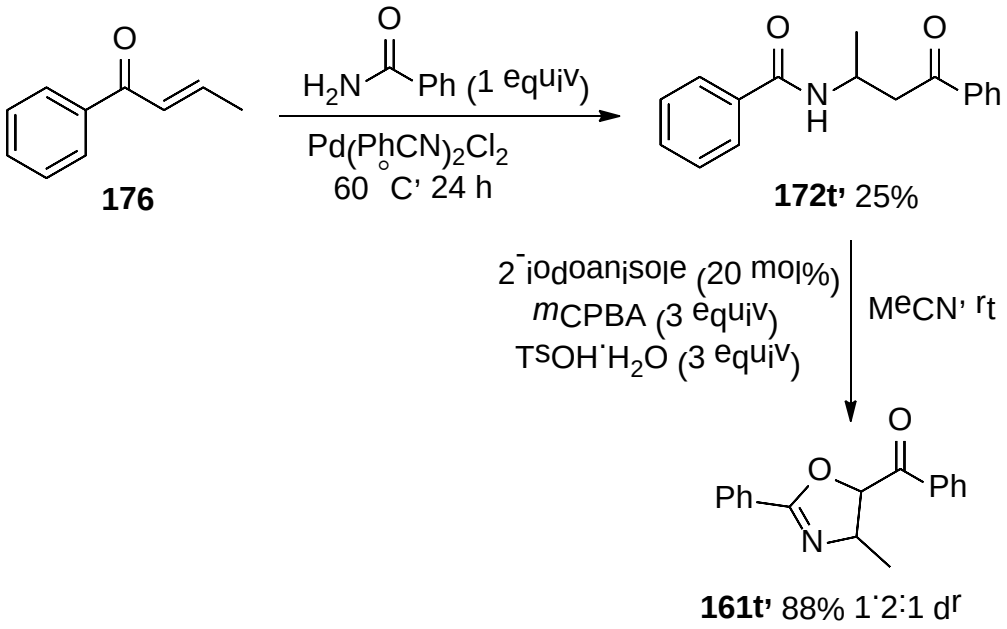
Unexpectedly, *p*-nitrophenylamide, **172d** did not yield the cyclised product. Instead, alcohol **175** was isolated in 66% yield. It is possible that, the product **161d** may have formed under the reaction conditions but it was instantly hydrolysed due to the influence of the electron-withdrawing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



Scheme 88

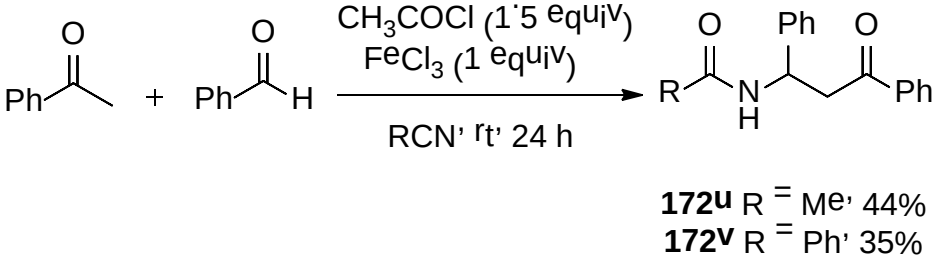
In addition, the effect of introducing substituents on the tether of the β-amidoketones was investigated to explore how these affected the cyclisation reaction.

Compound **172t** was prepared following the procedure reported by Takasu,[85] by conjugate addition reaction of benzamide with 1-phenylbut-2-en-1-one using a catalytic amount of $Pd(PhCN)_2Cl_2$. Then, the cyclisation reaction was attempted using our conditions. Cyclisation was very efficient although no diastereoselectivity was observed (Scheme 89).



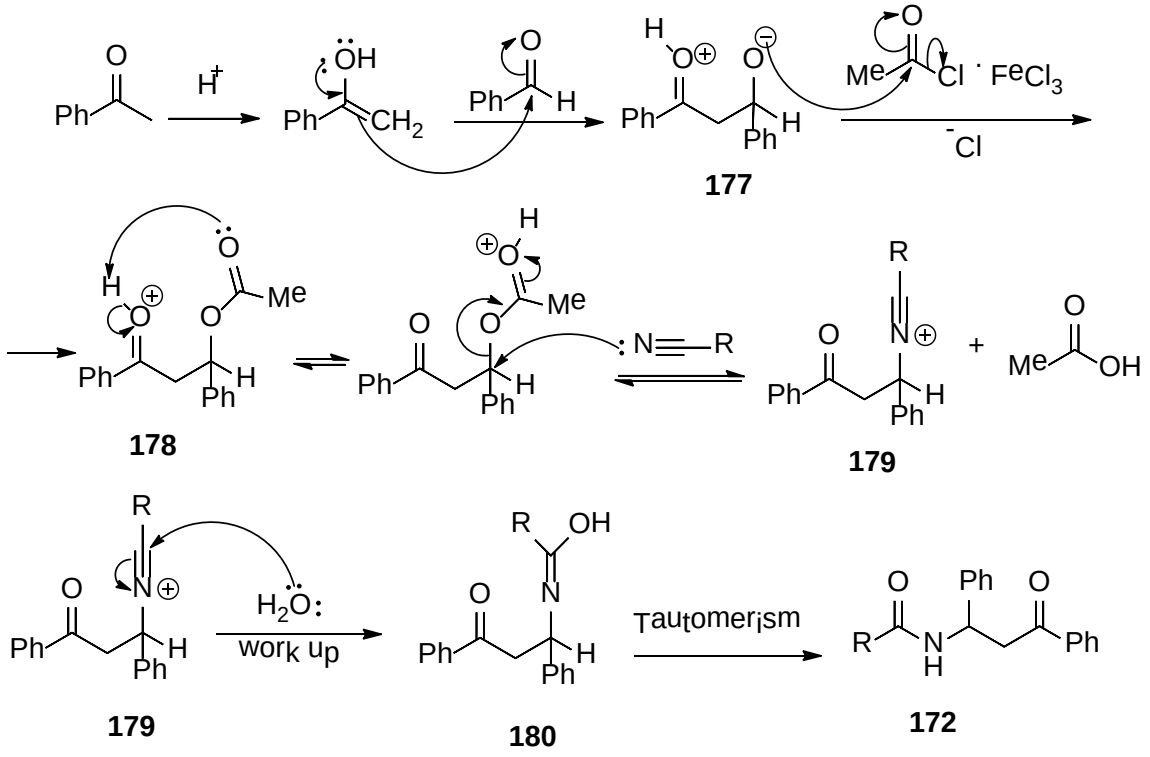
Scheme 89

Amides **172u** and **172v** were prepared in moderate yields via the procedure developed by Khan and coauthors.[86] Accordingly, acetophenone, benzaldehyde, and various nitriles were treated with acetyl chloride and $FeCl_3$ at room temperature (Scheme 90).



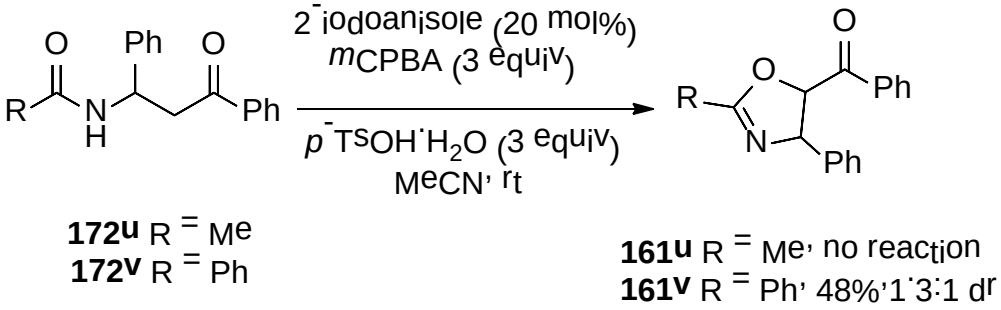
Scheme 90

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



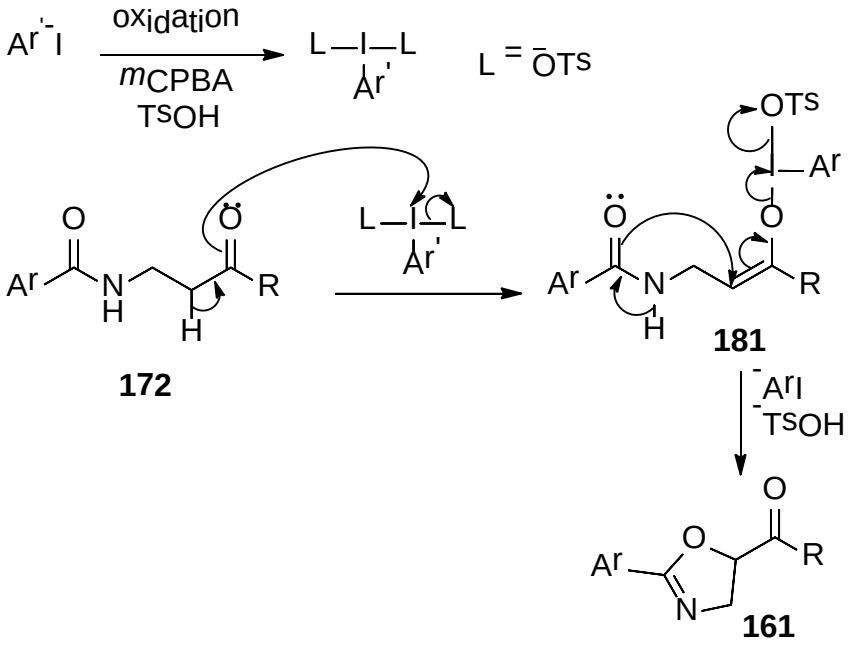
Scheme 91

Then both amides **172u** and **172v** were treated with our standard reaction conditions, but unfortunately with amide **172u** there was no product observed, whereas with **172v** a moderate yield of the desired cyclised product **161v** was observed. Unfortunately, no diasteroselectivity was observed in the formation of **161v** but interestingly, switching the acid from trifluoroacetic acid to *p*-toluenesulfonic acid improved the selectivity for **161v** to 5:1, albeit with loss of yield (Scheme 92).



Scheme 92

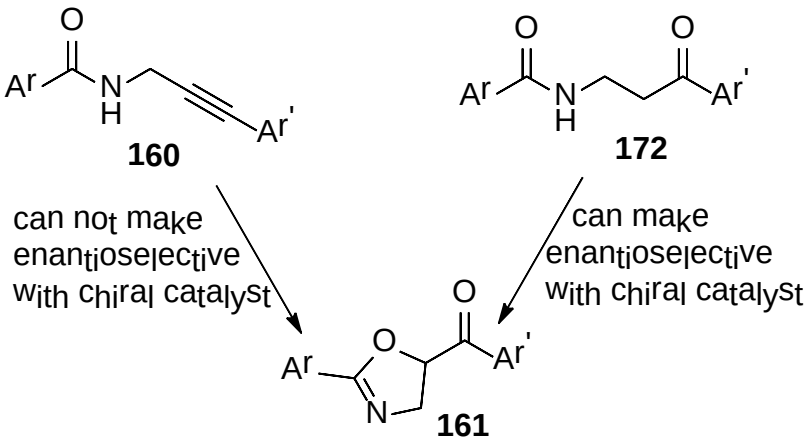
A plausible reaction mechanism for this cyclisation is proposed in Scheme 93. First, 2-iodoanisole is oxidised to generate the active iodine(III) species by utilising *m*CBPA and *p*-TsOH. Second, the active iodine(III) species activates the carbonyl ketone leading to the formation of iodine(III)-enolate **181.** The next step is the oxygen of the amide moiety attacks the enolate intermediate **181** which results in a 5-*exo*-*trig* cyclisation providing the oxazoline product **161** with reductive elimination of the iodoarene.



Scheme 93

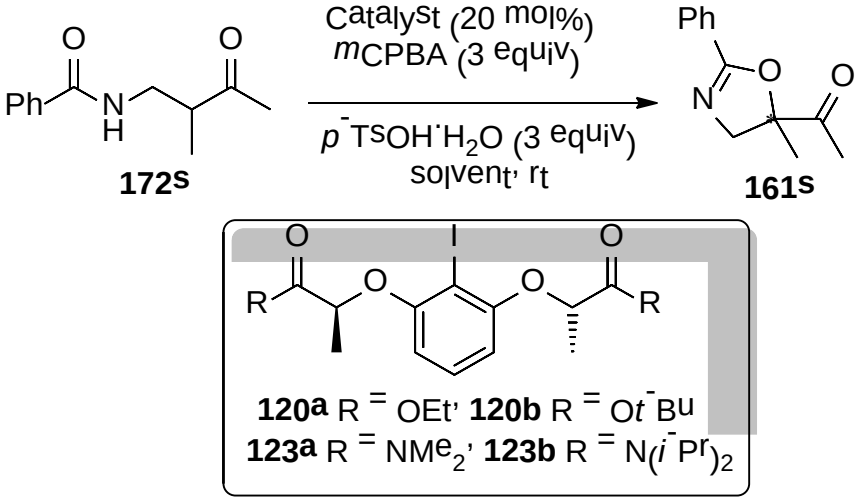
The catalytic cyclisation reaction of both propargyl amides **160** and β-amidoketones **172** using 2-iodoanisole are successfully achieved providing the oxazoline products **161** with

moderate to good yields however the reaction with β-amidoketones shows superior substrate scope. In addition, the cyclisation of propargyl amides **160** cannot be rendered enantioselective by the use of a chiral iodoarene whereas the enantioselective cyclisation of β-amidoketones **170** should be possible using a chiral iodoarene (Scheme 94).



Scheme 94

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



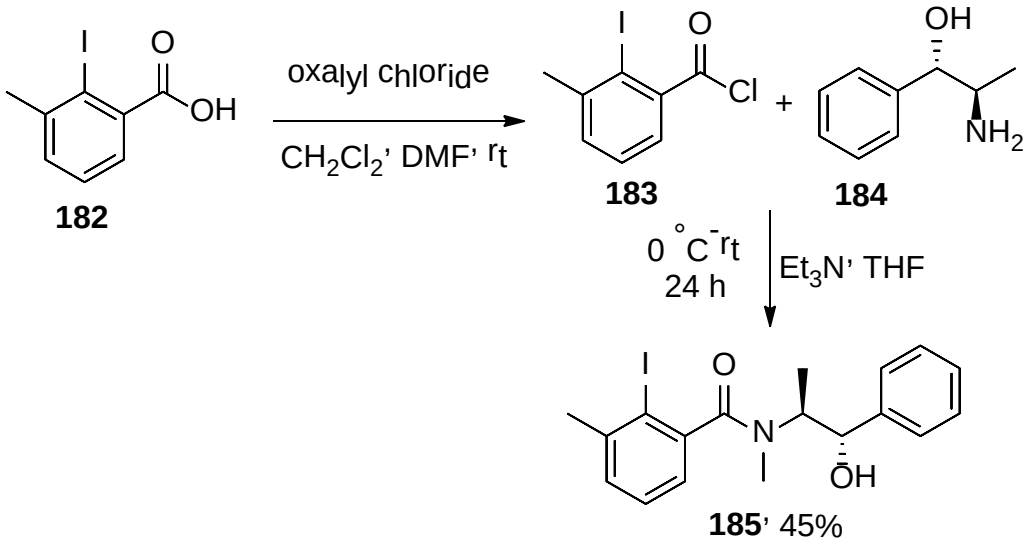
Scheme 95

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

Entry	Catalyst	Solvent	Yield %	ee %
1	**120a**	MeCN	91	11
2	**120b**	MeCN	82	14
3	**120b**	MeCN:MeOH (1:1)	42	10
4	**123a**	MeCN	94	9
5	**123b**	MeCN	67	5

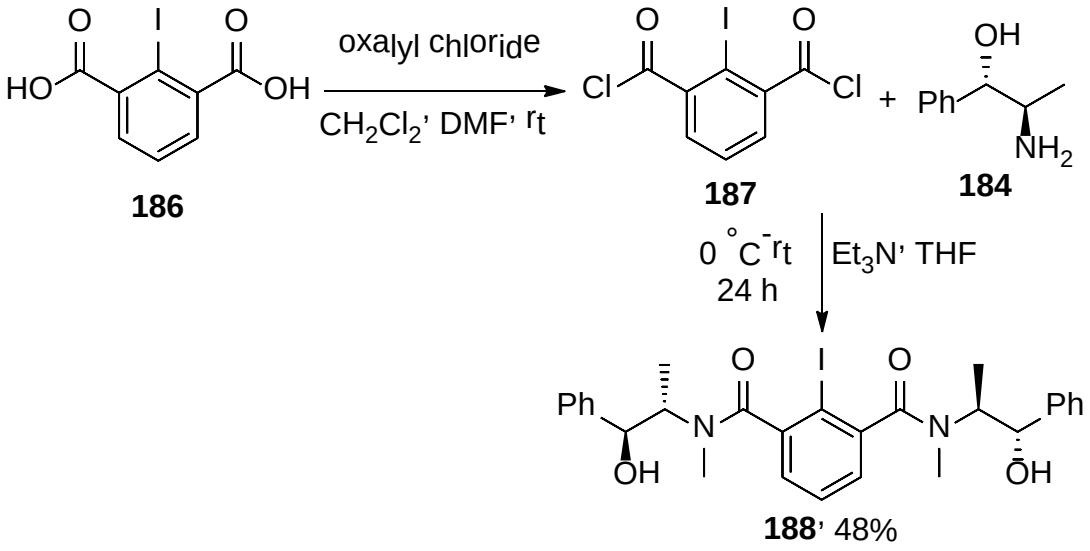
Table 14

Considering the mechanistic similarities between the process by Moran and Rodríguez illustrated earlier (Scheme 15) and the one under investigation, it was decided to test their catalyst and a new C_2-symmetric chiral iodoarene **188**. First, pseudoephedrine derivative **185** was prepared by converting 2-iodo-3-methylbenzoic acid **182** to 2-iodo-3-methylbenzoyl chloride **183** and then adding a solution of (1*S*,2*S*)-pseudoephedrine hydrochloride **184**. In line with the published procedure, **185** were isolated in moderate yield as a mixture of four rotamers (Scheme 96).[37]



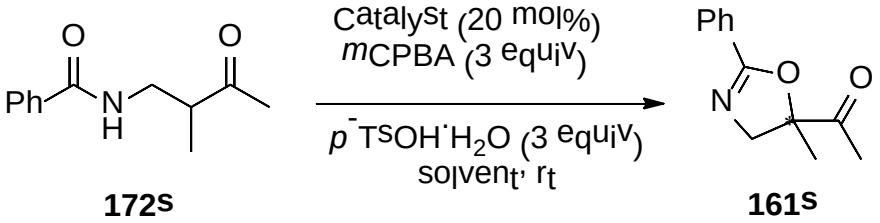
Scheme 96

Second, the new chiral iodoarene **188** was synthesised in a similar manner as pseudoephedrine derivative **185** but from commercially available 2-iodoisophthalic acid **186**. This was converted into 2-iodoisophthaloyl dichloride **187** which was then added slowly to a solution of (1*S*,2*S*)-pseudoephedrine hydrochloride **184**. Gratifyingly, the desired compound **188** was obtained as a white solid in 48% yield (Scheme 97).



Scheme 97

Next, the cyclisation reaction of **172t** was attempted using pseudoephedrine derivative **185** and new catalyst **188** under our conditions (Table 15). Employing pseudoephedrine derivative **185** provided almost racemic product with low yield when MeCN was used as a solvent (entry 1). The cyclisation of **172s** did not occur when the solvent was changed to methanol (entry 2). In contrast, using our new catalyst bispseudoephedrine derivative **188** led to very poor conversion of the starting material **172s** into **161s** when MeCN was used as a solvent; consequently, the selectivity was not determined (entry 3). However, no cyclised product was observed when utilising other solvents such as MeOH, CH_2Cl_2 and DMSO. It was apparent that **188** exhibited very poor solubility in all of these solvents, which probably explains the lack of conversion to product (entry 4,5 and 6).



172s **161s**

Scheme 98

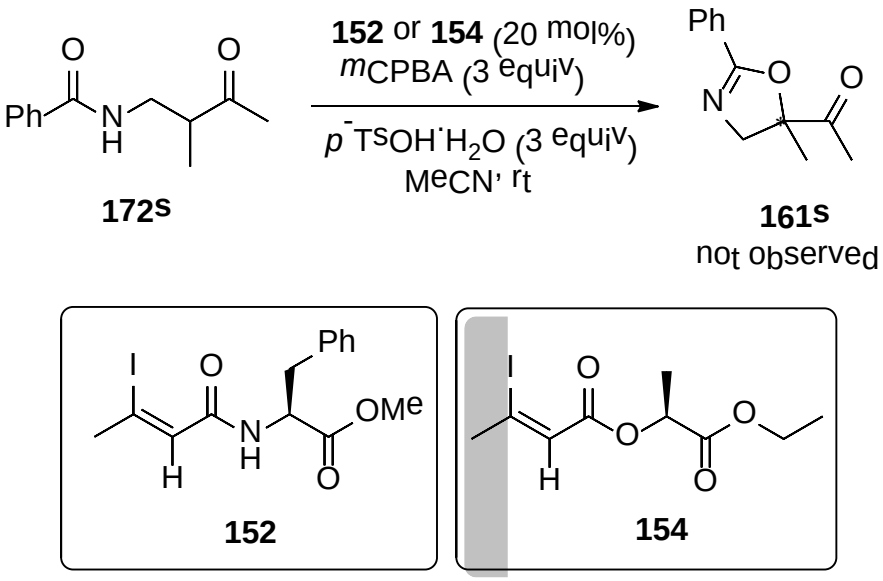
Entry	Catalyst	Solvent	Yield %	ee %
1	**185**	MeCN	39	4
2	**185**	MeOH	N.R.	-
3	**188**	MeCN	<5	N.D.
4	**188**	MeOH	N.R	-
5	**188**	CH_2Cl_2	N.R.	-

6	**188**	DMSO	N.R.	-

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

Table 15

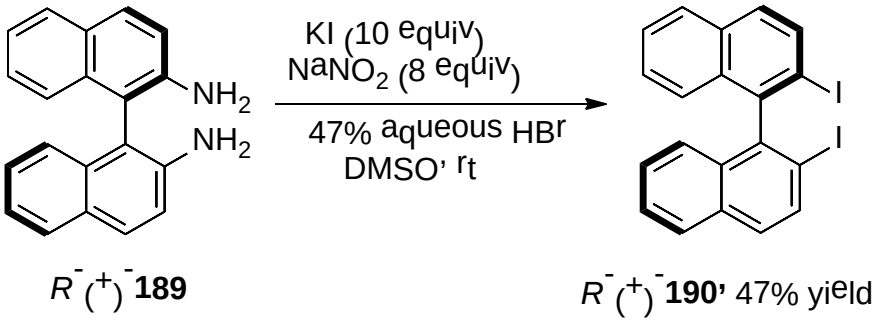
Next, we applied the new catalysts **152** and **154** in our cyclisation reaction but, unfortunately the cyclisation of **172s** did not occur when employing our new chiral organoiodines **152** and **154** and this was confirmed by ^{1}H NMR analysis of the crude mixture in both cases. The starting material was recovered in both cases (Scheme 99).



Scheme 99

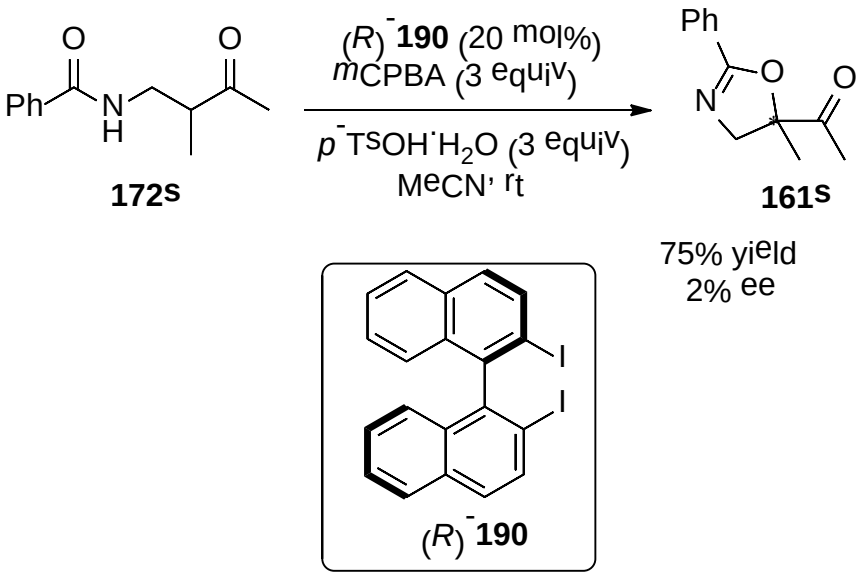
At this point, other types of chiral iodoarenes were decided to test in the cyclisation reaction and to see whether both the selectivity and yield could be improved.

The efficacy of bis-iodide (*R*)-**190** as a catalyst was decided to investigate in the cyclisation of **172s**. It was synthesised according to the to the literature procedure.[87] (*R*)-(+)-2,2'-Diamino-1,1'-binaphthyl **189** was treated with potassium iodide and sodium nitrite and then added 47% aqueous HBr to provide the catalyst (*R*)-**190** in 47% yield (Scheme 100).



Scheme 100

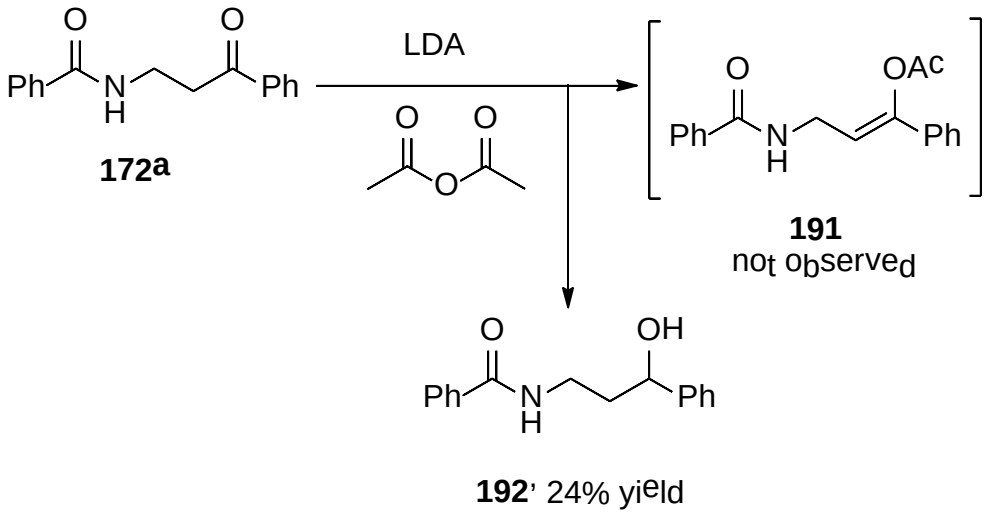
Using 20 mol% of **50** under our conditions led to formation of cyclised product **161s** in high yield but with essentially no enantioselectivity (Scheme 101).



Scheme 101

Next, the β-amidoketone **172a** was decided to convert to the corresponding enol acetates in a bid to improve the enantioselective cyclisation inspired by the work reported by Basdevant and Legault.[40] It was anticipated that treatment of β-amidoketones **172a** with LDA followed by acetic anhydride would generate enol acetate **191**. Unfortunately, the expected product was not observed and the β-amidoalcohol **192** was obtained in 24% yield (Scheme 102). It seemed that, after the formation of the enolate the acetic anhydride was not reacted as a

nucleophile and the enolate intermediate was reduced to provide β-amidoalcohol **191** instead of the corresponding enol acetates **190**. The reductive transformation of **172a** into **192** merits further investigation to improve both yield and range of example.



Scheme 102

3.3.1. Conclusion and future work

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

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

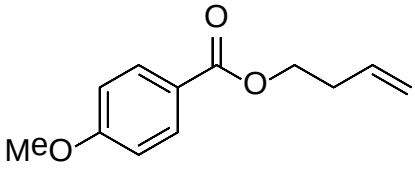
Experimental

General experimental

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR was recorded at 100 MHz in $CDCl_3$ unless otherwise stated with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.4 ppm). Mass spectrometry (m/z) was performed in ESI mode, with only molecular ions being reported. Infrared (IR) spectra ν_{max} are reported in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Melting points were determined on a Stuart SMP10. All purchased reagents were used as received without further purification. Petroleum ether refers to the fraction boiling at 40-60 ^{o}C. The solvents used were hexane ethanol and 2-propanol (all of HPLC grade purity, Fisher Scientific). HPLC analysis was performed with analytical chiral columns Chiralpak IA and Chiralpak IB wath UV detector at 254 nm.

Experimental for Tetrahydrofuranylation Reactions

Synthesis of but-3-en-1-yl 4-methoxybenzoate, 115b:[88]



According to literature procedure reported by Harried *et al*.[67] To a solution of 4-methoxybenzoyl chloride (3.0 g, 17.5 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.2 g,

1.75 mmol) in CH_2Cl_2 (30 mL), was added 3-butanol (1.5 mL, 17.5 mmol). The mixture was cooled to 0 °C and Et_3N (2.5 mL, 17.5 mmol) was added slowly. The resulting mixture was stirred overnight at room temperature. The resulting mixture was treated with 5% solution of HCl (20 mL) and $NaHCO_3$ (0.5 M, 20 mL) and washed with brine (10 mL) then extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under vacuum to give the product as a yellow oil (3.39 g, 93% yield).

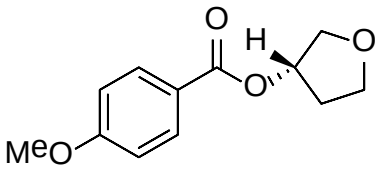
IR: 2961 (w), 1707 (m), 1605 (m), 1510 (m), 1248 (m) cm^{-1}

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{15}NO_3^+$ 207.1016, found 207.1017.

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



To a stirred solution of **115b** (0.1 g, 0.48 mmol) and **123b** (0.03g, 0.05 mmol) in a 2:1 mixture of methanol/acetonitrile (3 mL) was added Selectfluor (0.34 g, 0.97 mmol) followed by bis(trifluoromethane)sulfonamide (0.27 g, 0.97 mmol) and water (0.04 mL, 2.42 mmol). The reaction was allowed to stir at room temperature overnight. The mixture was washed with water (2 × 5 mL) and brine then extracted with EtOAc (2 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The residue

was purified by flash chromatography on silica gel (eluent: petroleum ether 40-60/EtOAc 20:1 to 5:1) to give **125a** as a colourless oil (0.04g, 35% yield, 57% ee).

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

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

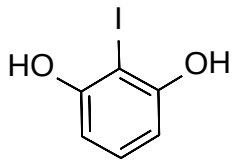
^{1}H NMR: δ 2.09-2.19 (1H, m), 2.21-2.32 (1H, m), 3.86 (3H, s), 3.88-4.05 (4H, m), 5.48-5.55 (1H, m), 6.91 (2H, d, J = 9.0 Hz), 7.99 (2H, d, J = 9.0 Hz).

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{12}H_{15}O_4^+$ 223.0965, found 223.0965.

Procedure for preparation of chiral iodoarenes:

2-Iodobenzene-1,3-diol, 118:[68]



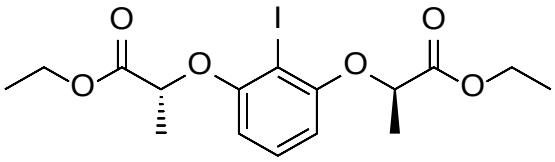
According to literature procedure reported by Tsujiyama and coauthors.[68] Resorcinol **117** (5.50 g, 49.9 mml) was added to deionised water (30 mL). The solution was placed in an ice bath and iodine (19.0 g, 74.9 mmol) and $NaHCO_3$ (6.70 g, 79.9 mmol) were added in one portion. The resulting mixture was stirred at room temperature for half an hour. The precipitate was filtered and the filtrate was extracted twice with diethyl ether (2 × 50 mL), dried over $MgSO_4$, and concentrated to give **118** as a white solid (4.7 g, 40% yield), m.p 106-109 ºC (lit.[89] m.p. 107-109 ºC).

^{1}H NMR: δ = 5.45 (2H, s), 6.55 (2H, d, J = 8.0 Hz), 7.10 (1H, t, J = 8.0 Hz).

^{13}C NMR: δ 77.5, 107.5 (2C), 130.5, 155.9 (2C).

HRMS (m/z): $[M]^+$ calcd for $C_6H_5IO_2^+$ 235.9334, found, 235.9333.

((2*R*,2′*R*)-Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoate, 120a:[27]



A solution of **118** (0.50 g, 2.12 mmol) was dissolved in THF (20 mL) with PPh_3 (1.4 g, 5.3 mmol) and (-)-ethyl lactate (0.6 mL, 5.3 mmol) in an ice bath (0 °C) under N_2. Diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 1.04 mL, 5.3 mmol) was added slowly, and the mixture was stirred for 1h in ice bath. The mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum and purified by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/EtOAc) which afforded **120a** as a colourless oil (1.27 g, 73% yield).

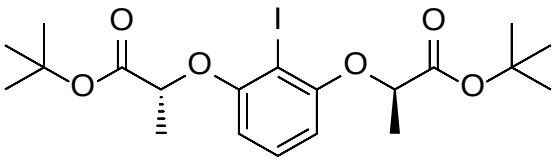
IR: 2984 (w), 1749 (m), 1586 (w), 1458 (m), 1248 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{16}H_{22}IO_6^+$ 437.0456, found 437.0454.

((2*R*,2′*R*)-Di-tert-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoate, 120b:[77]



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

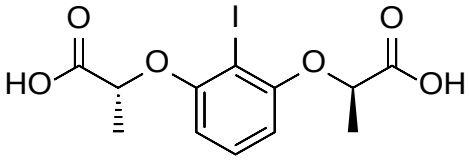
IR: 2984 (w), 1727 (s), 1581 (w), 1455 (s), 1235 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{20}H_{30}IO_6^+$ 493.1009, found 493.1042.

((2*R*,2′*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))dipropanoic acid, (121)[27]



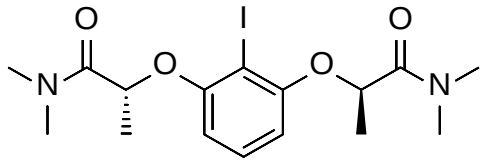
To a solution of **120a** (1.1g, 2.5 mmol) in THF (7 mL) and MeOH (7 mL) was added 2 M NaOH (7 mL) and left to stir at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with HCl (1M, 20 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuum to give analytically pure **121** as a white solid (3.4 g, 97% yield).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.58 (6H, d, J = 6.7 Hz), 4.88 (2H, q, J = 6.8 Hz), 6.42 (2H, d, J = 8.8 Hz), 7.24 (1H, t, J = 8.1 Hz).

^{13}C NMR (DMSO-d6, 100 MHz): δ 19.3 (2C), 73.7 (2C), 80.5, 106.8 (2C), 130.6, 158.7 (2C), 173.6 (2C).

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{16}H_{22}IO_6^+$ 380.9757, found 380.9755.

((2*R*,2′*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*,*N* dimethylpropanamide), 123a:[77]



To a solution of **121** (0.87 g, 2.29 mmol) in CH_2Cl_2 (10 mL) and 1 drop of DMF was added oxalyl chloride (1.57 mL, 18.3 mmol) and the mixture was stirred overnight under N_2. The resulting mixture was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (6 mL) at 0 °C and dimethylamine hydrochloride (0.34 g, 4.17 mmol) was added. After 0.5 h, Et_3N (1.16 mL, 8.34 mmol) was added. After stirring overnight, the reaction mixture was poured into HCl (1 M, 20 mL) and extracted with brine and CH_2Cl_2 (25 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed in vacuum to give the pure product as a white solid (0.54 g, 59% yield).

Melting point: 195-197 ºC

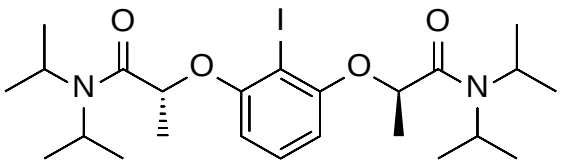
IR: 2939 (w), 1650 (m), 1587 (m), 1460 (m), 1345 (w) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{16}H_{24}IN_2O_4^+$ 435.0775, found 435.0796.

(2*R*,2′*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*,*N*-diisopropylpropanamide), 123b:[77]



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

Melting point: 125-128 ºC.

IR: 2967 (w), 1642 (m), 1622 (s), 1584(m), 1128 (m) cm^{-1}.

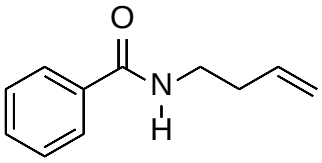
^{1}H NMR: δ 0.90 (6H, d, J = 6.4 Hz), 1.18 (6H, d, J = 6.8 Hz), 1.28 (6H, d, J = 6.8 Hz), 1.40 (6H, d, J = 6.8 Hz), 1.66 (6H, d, J = 6.8 Hz), 3.23-3.35 (2H, m), 4.46-4.59 (2H, m), 4.82 (2H, q, J = 6.8 Hz), 6.52 (2H, d, J = 8.6 Hz), 7.08-7.16 (1H, m).

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{24}H_{40}IN_2O_4^+$ 547.2027, found 547.2024.

Experimental for Amide Cyclisation Reactions

Synthesis of *N*-(but-3-en-1-yl)benzamide, 128a:[90]



According to literature procedure reported by Dvořák,[69] a solution of 1-amino-3-butene hydrochloride (0.5 g, 4.7 mmol) and triethylamine (1.3 mL, 9.3 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, then benzoyl chloride (0.6 mL, 5.11 mmol) was added dropwise and the

mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and filtered. The solvent from the filtrate was removed under vacuum, and the residue was dissolved in ether (20 mL) and again filtered and concentrated under vacuum. To the crude product NaOH (3 M, 20 mL) was added and the resulting mixture was stirred overnight at room temperature. The resulting mixture was extracted with diethyl ether twice (2 × 30 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum to give **128a** as a light yellow oil (0.65 g, 80% yield).

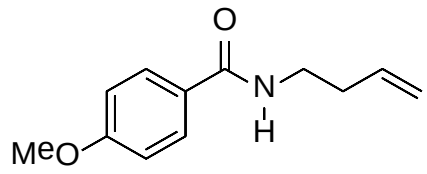
IR: 3314 (br), 3077 (w), 2978 (w), 2931 (w), 1640 (s), 1541 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+Na]^+$ $C_{11}H_{13}NONa+$ 198.0889, found 198.0905.

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



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

Melting point: 63-65 ºC

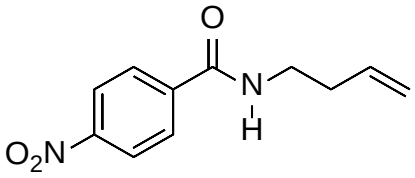
IR: 3312 (br), 3081 (w), 2836 (w), 1629 (m), 1606 (s), 1502 (m) cm^{-1}.

^{1}H NMR: δ 2.36 (2H, q, J = 6.6 Hz), 3.49 (2H, q, J = 6.4 Hz), 3.82 (3H, s), 5.06-5.19 (2H, m), 5.75-5.88 (1H, m), 6.26 (1H, br), 6.89 (2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.8 Hz).

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

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

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



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

Melting point: 94-96 ºC.

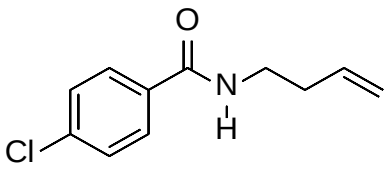
IR: 3284 (br), 3112 (w), 2940 (w), 1633 (m), 1596 (w), 1509 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{11}H_{13}N_2O_3^+$ 221.0921, found 221.0920.

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



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

Melting point: 73-74 ºC.

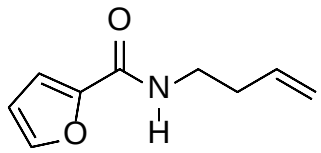
IR: 3298 (br), 3022 (w), 2945 (w), 1636 (s), 1538 (s), 1277 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{11}H_{13}Cl^{35}NO_2^+$ 210.0680, found 210.0675.

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



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

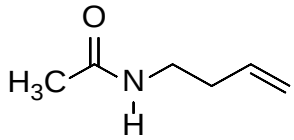
IR: 3297 (br), 2980 (w), 1639 (m), 1592 (m), 1300 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_9H_{12}NO_2^+$ 166.0863, found 166.0860.

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



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

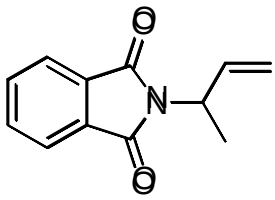
IR: 3289 (br), 3079 (w), 2929 (w), 1633 (m), 1552 (m) cm^{-1}.

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

^{13}C NMR: δ 23.2, 33.7, 38.9, 117.1, 135.4, 170.9.

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_6H_{12}NO^+$ 114.0913, found 114.0916.

Preparation of 2-(but-3-en-2-yl)isoindoline-1,3-dione, 140j:[91]



Prepared a ccording to a literature procedure reported by Minakata and coauthors.[70] To a stirred solution of potassium phthalimide (2.6 g, 14.1 mmol) and potassium carbonate (0.50 g, 3.64 mmol) in dry DMF (25 mL) at room temperature was added 3-chloro-1-butene (1.84 mL, 18.2 mmol). The flash was fitted with a reflux condenser and heated to 140 ºC overnight under N_2 atmosphere. The mixture was cooled to room temperature and ice cold water was poured into the mixture with rapid stirring. The resulting white precipitate was collected by filtration and rinsed with cold water giving **140j** as a white solid (1.7 g, 61% yield), m.p 87-88 ºC (lit. m.p. 86-87 ºC).

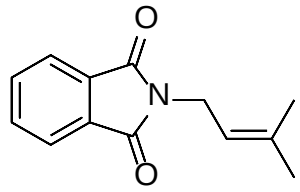
IR: 3460 (br), 1769 (m), 1698 (s), 1469 (m), 1383 (s), 1139 (m), 715 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{12}H_{12}NO_2^+$ 202.0863, found 202.0866.

Synthesis of 2-(3-methylbut-2-en-1-yl)isoindoline-1,3-dione, 140k:[92]



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

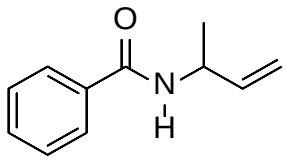
IR: 3034 (br), 2902 (w), 1765 (m), 1697 (s), 1425 (m), 1382 (s), 718 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{13}H_{14}NO_2^+$ 216.1019, found 216.1022.

***N*-(But-3-en-2-yl)benzamide, 137j:**[91]



According to literature procedure reported by Trost *et al.*[71] To a solution of **140j** (1.0 g, 4.9 mmol) in ethanol (16 mL) was added ethylenediamine (0.7 mL, 9.9 mmol) and the solution was heated to reflux for 4 h. The resulting mixture was cooled to room temperature and the solid was removed by filtration through a pad of celite. The solid was washed with ethanol (20 mL) and the combined washings were washed with water (10 mL) then brine (10 mL) then extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were dried over anhydrous $MgSO_4$ and were used immediately to prepare **137j** which was prepared according to the procedure for **128a** using benzoyl chloride (0.64 mL, 5.47 mmol) to yield **137j** a white solid (0.26 g, 29% yield), m.p 87-88 ºC (lit. m.p. 86-87 ºC).

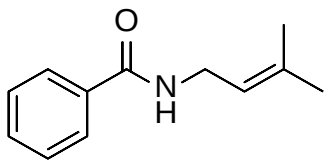
IR: 3296 (br), 2972 (w), 1632 (m), 1537 (s), 692 (s) cm^{-1}.

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

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

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

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



This compound was prepared according to the procedure for **137j** using **140k** (2.0 g, 9.3 mmol) and benzoyl chloride (1.19 mL, 1.02 mmol) giving **137k** as a light yellow oil (0.84 g, 48% yield).

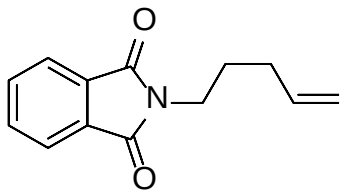
IR: 3303 (br), 1633 (s), 1533 (s), 1488 (m), 1289 (m), 1050 (m), 692 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{16}NO^+$ 190.1226, found 190.1228.

Synthesis of 2-(pent-4-en-1-yl)isoindoline-1,3-dione, 142:[93]



Prepared according to the literature procedure reported by Michael and Cochran.[72] To a solution of triphenylphosphine (6.0 g, 23.2 mmol) in THF (25 mL), diethyl azodicarboxylate (DIAD) (4.6 mL, 25 mmol) was added dropwise at 0 °C under a N_2 atmosphere and stirred for 5 min. Then, 4-penten-1-ol (2.40 mL, 23.2 mmol) was added dropwise and stirred for 5 min. Lastly, phthalimide (3.4 g, 23.2 mmol) was added in one portion and the ice bath was removed. The mixture was stirred overnight. Then *n*-hexane was added and the reaction mixture was filtered. The filtrate was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/ EtOAc) gave **142** as a colourless oil (4.09 g, 83% yield).

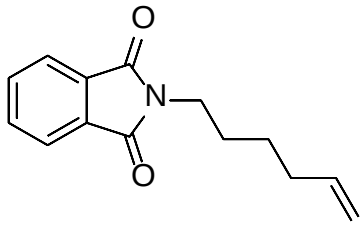
IR: 2939 (w), 1772 (m), 1702 (s), 1640 (w), 1437 (m), 1393 (s), 1071 (m), 716 (s) cm^{-1}.

^{1}H NMR: δ 1.74 (2H, pent, *J* = 7.3 Hz), 2.07 (2H, q, *J* = 7.4 Hz), 3.65 (2H, t, *J* = 7.3 Hz), 4.93 (1H, dd, *J* = 10, 1.5 Hz), 5.02 (1H, ddd, *J* = 17, 3.4, 1.6 Hz), 5.77 (1H, ddt, *J* = 17, 10, 6.6 Hz), 7.67 (2H, dd, *J* = 5.5, 2.9 Hz), 7.79 (2H, dd, *J* = 5,5, 2.9 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{13}H_{14}NO_2^+$ 216.1019, found 216.1020.

Synthesis of 2-(Hex-5-en-1-yl)isoindoline-1,3-dione, 143[94]



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

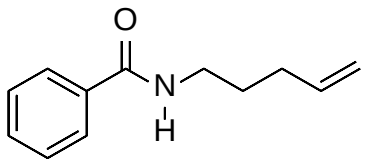
IR: 2936 (w), 1771 (m), 1703 (s), 1640 (w), 1466 (m), 1394 (s), 1039 (w), 717 (s) cm^{-1}.

^{1}H NMR: δ 1.37 (2H, pent, *J* = 7.6 Hz), 1.59 (2H, pent, *J* = 7.6 Hz), 1.99 (2H, q, *J* = 7.4 Hz), 3.58 (2H, t, *J* = 7.4 Hz), 4.83 (1H, d, *J* = 10 Hz), 4.90 (1H, dd, *J* = 17, 1.6 Hz), 5.67 (1H, ddt, *J* = 17, 10, 6.5 Hz), 7.61 (2H, dd, *J* = 5.5, 3.1 Hz), 7.72 (2H, dd, *J* = 5,5, 3.1 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{16}NO_2^+$ 230.1176, found 230.1179.

Synthesis of *N*-(pent-4-en-1-yl)benzamide, 144:[95]



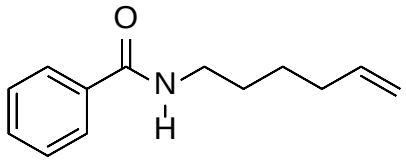
This compound was prepared according to the procedure for **137j** using **142** (1.0 g, 9.3 mmol) and benzoyl chloride (1.19 mL, 1.02 mmol) giving **144** as a yellow wax (0.21 g, 12% yield).

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{16}NO^+$ 190.1226, found 190.1228.

Synthesis of *N*-(hex-5-en-1-yl)benzamide, 145:[96]



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

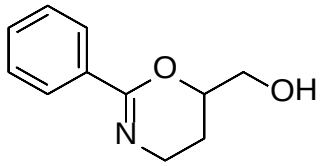
IR: 3298 (br), 3064 (w), 2929 (w), 1632 (s), 1539 (s) cm^{-1}.

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

^{13}C NMR: δ 26.5, 29.4, 33.7, 40.3, 115.2, 127.2 (2C), 128.8 (2C), 131.6, 135.1, 138.7, 167.9.

HRMS: m/z calc'd for $[M+H]^+$ $C_{13}H_{18}NO^+$ 204.1383, found 204.1391

Representative procedure for 2-iodoanisole-catalysed cyclisation: Synthesis of (2-phenyl-5, 6-dihydro-4*H*-1, 3-oxazin-6-yl) methanol, 134a:[77]



To a stirred solution of **128a** (0.1 g, 0.57 mmol) and 2-iodoanisole (1.5 μL, 0.11 mmol) in acetonitrile (4 mL) was added Selectfluor (0.41 g, 1.14 mmol), followed by TFA (9.1 μL, 1.14 mmol). The reaction was stirred overnight at room temperature. The mixture was washed with NaOH (2 M, 5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel (eluent: 4:1 EtOAc/petroleum ether 40-60) to give **134a** as a colourless oil (0.06 g, 48% yield).

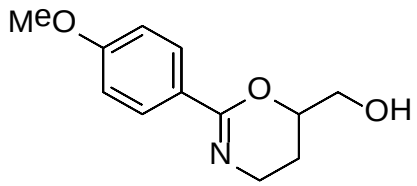
IR: 3220 (br), 2931 (w), 2860 (w), 1648 (s), 1352 (m) cm^{-1}.

1H NMR: δ 1.68-1.90 (2H, m), 3.50 (1H, br), 3.51 (1H, ddd, J = 17, 11, 5.3 Hz), 3.64 (1H, ddd, J = 17, 5.3, 2.5 Hz), 3.71 (1H, dd, J = 12, 5.7 Hz), 3.77 (1H, dd, J = 12, 4.0 Hz), 4.20-4.28 (1H, m), 7. 33 (2H, t, J = 7.4 Hz), 7.39 (1H, t, J = 7.4 Hz), 7.86 (2H, d, J = 7.4 Hz),

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{11}H_{14}NO_2^+$ 192.1019, found 192.1029.

Synthesis of (2-(*p*-methoxyphenyl)-5,6-dihydro-4*H*-1,3-oxazin-6-yl)methanol, 134b:[77]



This compound was prepared according to the procedure for **134a** using **128b** (0.1 g, 0.52 mmol) giving **134b** as a yellow oil (0.07 g, 58% yield).

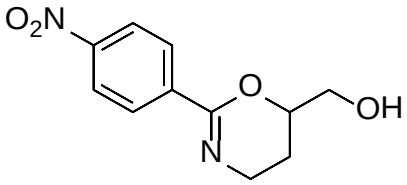
IR: 3155 (br), 2933 (w), 2858 (w), 1646 (m), 1511 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{12}H_{16}NO_3^+$ 222.1125, found 222.1126.

Synthesis of (2-(*p*-nitrophenyl)-5,6-dihydro-4*H*-1,3-oxazin-6-yl)methanol, 134c:[77]



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

Melting point: 148-150 ºC.

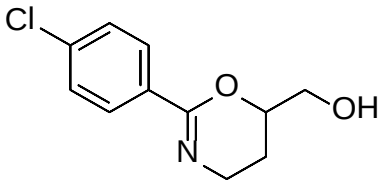
IR: 3264 (br), 3107 (w), 2865 (w), 1651 (m), 1513 (m), 1337 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{11}H_{13}N_2O_4^+$ 237.0870, found 237.0877.

Synthesis of (2-(*p*-chlorophenyl)-5,6-dihydro-4*H*-1,3-oxazin-6-yl)methanol, 134d:[77]



This compound was prepared according to the procedure for **134a** using **128d** (0.1 g, 0.48 mmol) giving **134d** as a colourless oil (0.072 g, 68% yield).

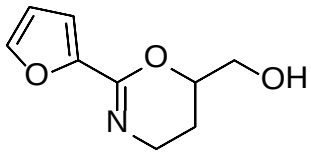
IR: 3189 (br), 2982 (w), 2859 (w), 1723 (w), 1645 (m), 1275 (m) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{11}H_{13}N^{35}ClO_2^+$ 226.0629, found 226.0639.

4.2.11 Synthesis of (2-(furan-2-yl)-5,6-dihydro-4*H*-1,3-oxazin-6-yl)methanol, 134e:[77]



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

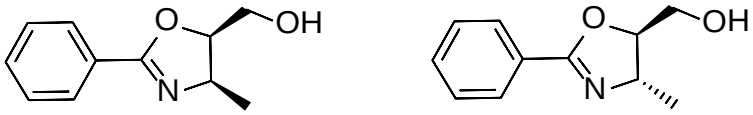
IR: 3078 (br), 2994 (w), 1664 (m), 1570 (m), 1481 (m), 1288 (m) cm^{-1}.

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

^{13}C NMR: δ 23.7, 42.5, 65.4, 75.8, 111.5, 112.0, 144.6, 147.4, 149.4.

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_9H_{12}NO_3^+$ 182.0812, found 182.0820

Synthesis of (4-methyl-2-phenyl-4,5-dihydrooxazol-5-yl)methanol, 134j:[77]



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

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

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

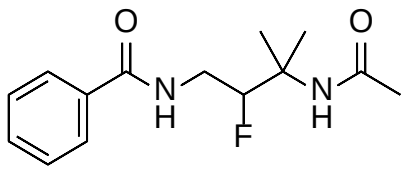
^{13}C NMR (major isomer): δ 21.6, 62.8, 63.8, 87.3, 127.8, 128.5 (2C), 128.6 (2C), 131.8, 163.3.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{11}H_{14}NO_2^+$ 192.1019, found 192.1026.

***N*-(3-Acetamido-2-fluoro-3-methylbutyl)benzamide, 141:**



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

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

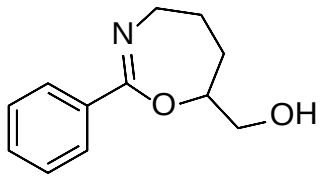
^{1}H NMR: δ 1.42 (2×3H, s), 1.94 (3H, s), 3.40-3.54 (1H, m), 3.96 (1H, dddd, J = 33, 14, 6.9, 2.8 Hz), 4.99 (1H, ddd, J = 49, 8.6, 2.8 Hz), 5.72 (1H, s), 6.70 (1H, br), 7.43 (2H, t, J = 7.4 Hz), 7.50 (1H, t, J = 7.4 Hz), 7.78 (2H, d, J = 7.8 Hz).

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

^{19}F NMR: δ -194.13 ppm.

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{14}H_{20}FN_2O_2^+$ 267.1503, found 267.1506.

Synthesis of (2-phenyl-4,5,6,7-tetrahydro-1,3-oxazepin-7-yl)methanol, 146:[77]



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

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

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

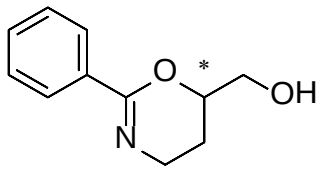
^{13}C NMR: δ 25.4, 28.9, 51.5, 61.9, 67.6, 127.4 (2C), 128.7 (2C), 130.6, 136.9, 172.6.

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{16}NO_2^+$ 206.1176, found 206.1180.

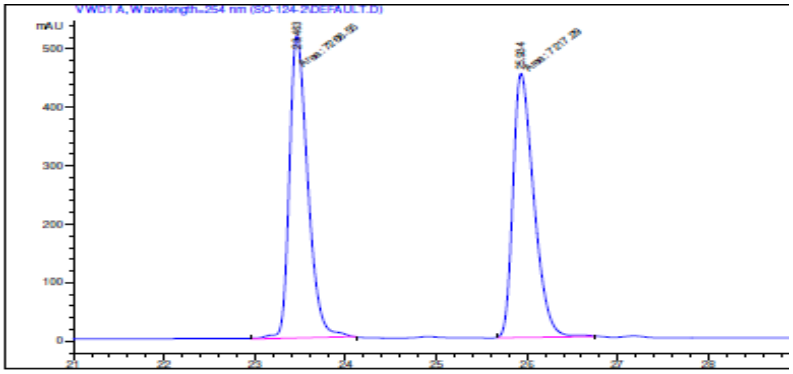
Representative procedure for chiral iodoarene-catalysed cyclisation

Amide **128a** (1 equiv) was dissolved in solvent and chiral iodoarene (0.1 equiv) was added, followed by trifluoroacetic acid (2 equiv) and Selectfluor (2 equiv). The mixture was stirred overnight at room temperature, then aqueous NaOH solution (2 M) was added and the mixture extracted with CH_2Cl_2. The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/EtOAc) to furnish **134a** or **148**.

(2-Phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)methanol, 134a:[77]



HPLC: chiralpak IA 254 nm hexane/EtOH gradient (100:0 to 80:20 over 25 min), 1 mL/min.

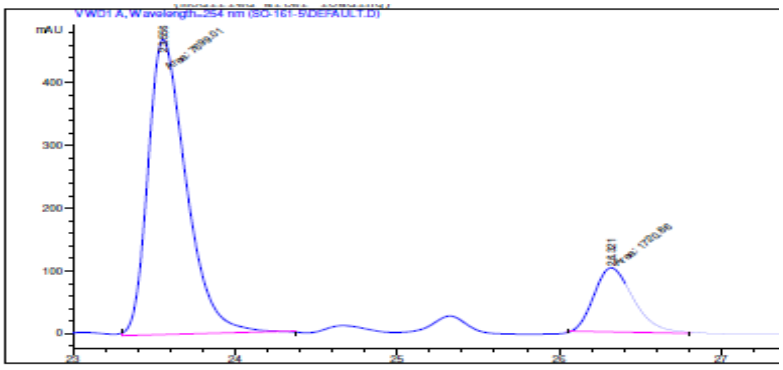


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.463	MM	0.2342	7268.54736	517.18182	50.1769
2	25.934	MM	0.2663	7217.28857	451.74106	49.8231
Totals :				1.44858e4	968.92288	



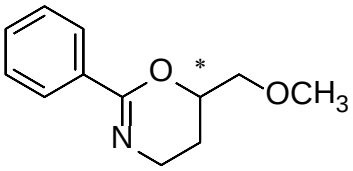
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.556	MM	0.2727	7699.01367	470.55386	81.7316
2	26.321	MM	0.2811	1720.86060	102.02901	18.2684
Totals :				9419.87427	572.58288	

6-(Methoxymethyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine, 148:[77]



Up to 0.12 g, 99%. Colourless oil.

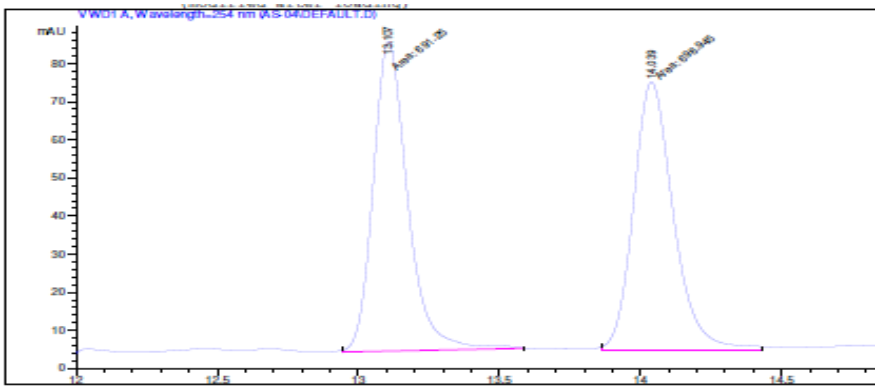
IR: 2927 (br), 2860 (w), 1651 (s), 1346 (w), 1274 (m) cm^{-1}.

^{1}H NMR: δ 1.74-1.86 (1H, m), 1.90-2.04 (1H, m), 3.46 (3H, s), 3.53-3.77 (4H, m), 4.37-4.46 (1H, m), 7.32-7.44 (3H, m), 7.91 (1H, d, *J* = 7.5 Hz).

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

HRMS: *m/z* calc'd for $[M+H]^+$ $C_{12}H_{15}NO_2^+$ 206.1176, found 206.1185

HPLC: chiralpak IA 254 nm hexane/EtOH gradient (100:0 to 80:20 over 25 min), 1 mL/min.

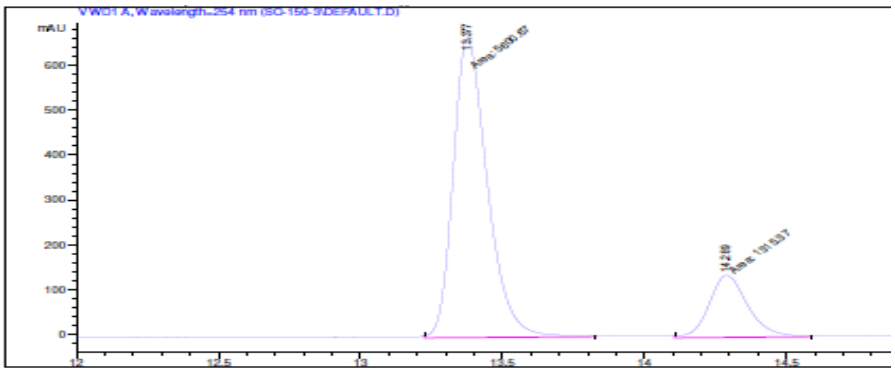


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.107	MM	0.1415	691.25024	81.41743	49.7233
2	14.039	MM	0.1648	698.94452	70.70022	50.2767
Totals :				1390.19476	152.11765	



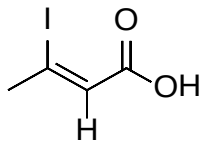
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.377	MM	0.1394	5600.67432	669.62781	80.9809
2	14.289	MM	0.1578	1315.36902	138.89790	19.0191
Totals :				6916.04333	808.52571	

(*Z*)-3-Iodobut-2-enoic acid, 150:[97]



Following the literature procedure reported by Wirth and coauthors,[73] a 47% aq. HI solution (3.65 mL, 22.8 mmol) was added dropwise to 2-butynoic acid **149** (1.5 g, 17.8 mmol). The solution was heated at 90 ºC with stirring for 2h. After cooling to r.t, a 5% aq. $Na_2S_2O_3$ (6 mL) solution was added. The organic phase was separated, and the aqueous phase was extracted with (2 × 30 mL) Et_2O. The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **150** as a white solid (2.69 g, 71% yield), m.p 100-102 ºC (lit. m.p. 111 ºC).

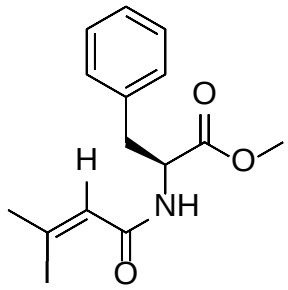
IR: 2246 (w), 1671 (m), 1613 (s), 1428 (m), 1216 (s), 1084 (m), 861 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_4H_6IO_2^+$ 212.9407, found 212.9407.

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



1-Propanephosphonic acid anhydride solution (T_3P; 50% in DMF, 2.07 mL, 7.08 mmol, 3 equiv) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. Triethylamine (1.97 mL, 14.2

mmol, 6 equiv) and (*Z*)-3-iodobut-2-enoic acid **150** (0.50 g, 2.36 mmol, 1 equiv) were added. The reaction mixture was left to stir at 0 °C for 0.5 h, then (*L*)-methyl 2-amino-3-phenylpropanoate hydrochloride (0.51 g, 2.36 mmol, 1 equiv) was added. After stirring overnight at room temperature, the reaction was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash chromatography (1:1 petroleum ether/EtOAc) to provide **152** as a yellow oil (0.35 g, 40% yield).

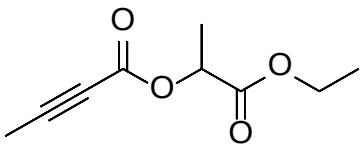
IR: 2980 (br), 2970 (m), 1745 (m), 1667 (s), 1539 (m), 1211 (s), 700 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{14}H_{17}INO_3^+$ 374.0248, found 374.0244.

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



Following the literature procedure reported by Kennedy and Hall,[75] a solution of 2-butynoic acid (1.0 g, 1.2 mmol, 1 equiv), L-ethyllactate (1.4 mL, 1.2 mmol, 1.1 equiv), DIC (2.2 mL, 1.4 mmol, 1.2 equiv) and DMAP (0.2 g, 0.2 mmol, 0.2 equiv) in CH_2Cl_2 (20 mL) were stirred at room temperature under N_2 for two days. The resulting mixture was diluted with water (120 mL), the layers separated and the aqueous layers subsequently extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were washed with aq. $NaHCO_3$ (2 x 30 mL), and brine (60 mL)

then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 petroleum ether/EtOAc) to provide **153** as a yellow oil (0.63 g, 29% yield).

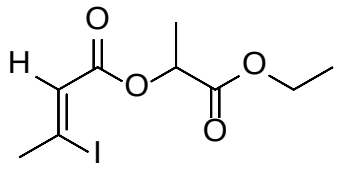
IR: 2981 (br), 2241 (m), 1743 (m), 1711 (s), 1448 (w), 1250 (s), 746 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_9H_{13}O_4^+$ 185.0808, found 185.0813.

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



Following the literature procedure reported by Piers and coauthors,[76] a flask was charged with a mixture of **153** (0.20 g, 1.09 mmol, 1 equiv), NaI (0.26 g, 1.74 mmol, 1.6 equiv) and glacial acetic acid (0.46 mL, 7.27 mmol, 6.7 equiv) under N_2. The mixture was stirred at 115 °C for 2 h. The mixture was cooled down to room temperature, quenched with water (20 mL) and subsequently extracted with Et_2O (3 x 10 mL). The organic layers were washed with 5% solution of Na_2CO_3 (15 mL), saturated solution of $Na_2S_2O_3$ (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 petroleum ether/EtOAc) to provide **154** as a yellow oil (0.19 g, 58% yield).

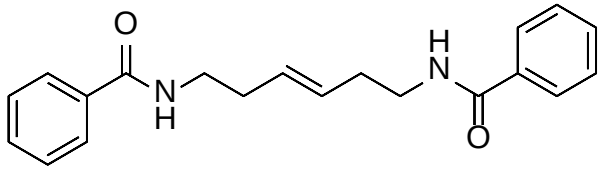
IR: 3358 (br), 2968 (m), 1731 (s), 1625 (m), 1377 (w), 1189 (s), 950 (m) cm^{-1}.

^{1}H NMR: δ 1.26 (3H, t, J = 7.2 Hz), 1.50 (3H, d, J = 7.1 Hz), 2.74 (3H, s), 4.19 (2H, qd, J = 7.0, 2.2 Hz), 5.15 (1H, q, J = 7.1 Hz), 6.40 (1H, s).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_9H_{14}IO_4^+$ 312.9931, found 312.9937.

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



Second generation Grubbs catalyst, (0.024 g, 0.029 mmol, 0.05 equiv) was add to a stirring solution of **128a** (0.1 g, 1.71 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL). The mixture was refluxed for overnight at 42 °C under N_2. The resulting mixture was filtrate through ped of cilete and washed by CH_2Cl_2 (10 mL). The filtrate was dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to provide **155** as a light brown solid (0.082g, 44% yield).

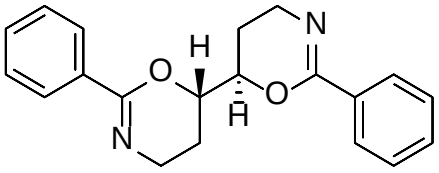
IR: 3324 (br), 2359 (w), 1632 (s), 1536 (s), 1488 (m), 1294 (m), 692 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{20}H_{23}N_2O_2^+$ 323.1754, found 323.1753.

2,2'-Diphenyl-5,5',6,6'-tetrahydro-4H,4'H-6,6'-bi(1,3-oxazine), 156



To a stirred solution of **155** (0.05 g, 0.16 mmol) and 2-iodoanisole (0.0041 mL, 0.062 mmol) in acetonitrile (2 mL) was added Selectfluor (0.110 g, 0.62 mmol), followed by TFA (0.025 mL, 0.62 mmol). The reaction was allowed to stir at room temperature overnight. The mixture was washed with 2 M NaOH (2 × 5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash chromatography (1:3 petroleum ether/EtOAc) to give **156** as light yellow wax (0.0341 g, 69% yield).

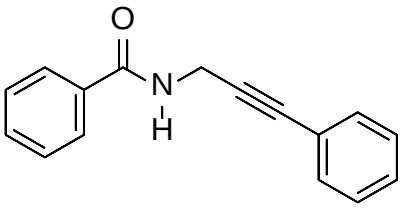
IR: 2859 (br), 2359 (w), 1651 (s), 1445 (m), 1344 (m), 1111 (s), 699 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M+H]^+$ $C_{20}H_{21}N_2O_2^+$ 321.1598, found 321.1599.

Representative procedure: Preparation of 4-chloro-*N*-(3-phenylprop-2-yn-1-yl)benzamide, 160a:[98]



Following the literature procedure reported by Rominger and coauthors,[80] benzoyl chloride (0.23 mL, 1.8 mmol) was added dropwise to an ice cooled solution of 3-phenyl-2-propyn-1-amine.HCl (0.30 g, 1.8 mmol) and triethylamine (0.50 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred overnight at room temperature. The mixture was washed with water and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum to give **160** as a white solid (0.31 g, 73% yield), m.p 102-104 ºC (lit. m.p. 102-103 ºC).

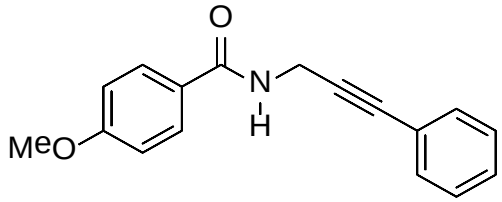
IR: 3308 (br), 3053 (w), 1639 (s), 1529 (s), 1486 (m), 1323 (m), 757 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{14}NO^+$ 236.1071, found 236.1070.

4-Methoxy-*N*-(3-phenylprop-2-yn-1-yl)benzamide, 160b[98]



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

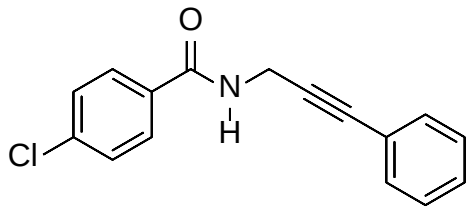
IR: 3246 (br), 1630 (m), 1606 (s), 1552 (s), 1299 (s), 1252 (m), 1025 (s), 692 (s) cm^{-1}.

^{1}H NMR: δ 3.85 (3H, s), 4.84 (2H, d, *J* = 5.1 Hz), 6.44 (1H, br), 6.93 (2H, d, *J* = 8.8 Hz), 7.29-7.34 (3H, m), 7.42-7.47 (2H, m), 7.79 (2H, d, *J* = 8.8 Hz)

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1181.

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



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

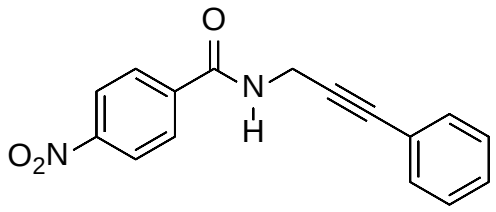
IR: 3257 (br), 3073 (w), 1633 (s), 1545 (s), 1487 (s), 1299 (m), 1093 (m), 751 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{13}{}^{35}ClNO^+$ 270.0680, found 270.0680.

4-Nitro-*N*-(3-phenylprop-2-yn-1-yl)benzamide, 160d:[98]



This compound was prepared according to the procedure for **160a** using 4-nitrobenzoyl chloride (0.33 g, 1.79 mmol) giving **160d** as a light yellow solid (0.42 g, 84% yield), m.p 132-134 ºC (lit. m.p. 131-132 ºC).

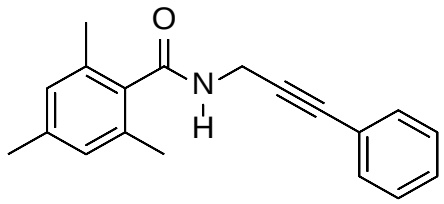
IR: 3288 (br), 3059 (w), 1639 (s), 1602 (w), 1537 (s), 1487 (m), 1262 (m), 626 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{13}N_2O_3^+$ 281.0921, found 281.0921.

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



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

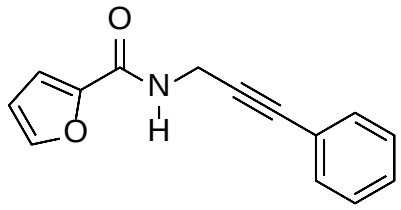
IR: 3255 (br), 1630 (s), 1537 (s), 1442 (w), 1287 (s), 845 (s), 756 (s) cm^{-1}.

^{1}H NMR: δ 2.47 (3H, s), 2.31 (6H, s), 4.46 (2H, d, *J* = 5.3 Hz), 5.89 (1H, br), 6.84 (2H, s), 7.29-7.34 (3H, m), 7.39-7.43 (2H, m)

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

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

***N*-(3-phenylprop-2-yn-1-yl)furan-2-carboxamide, 160f:**[99]



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

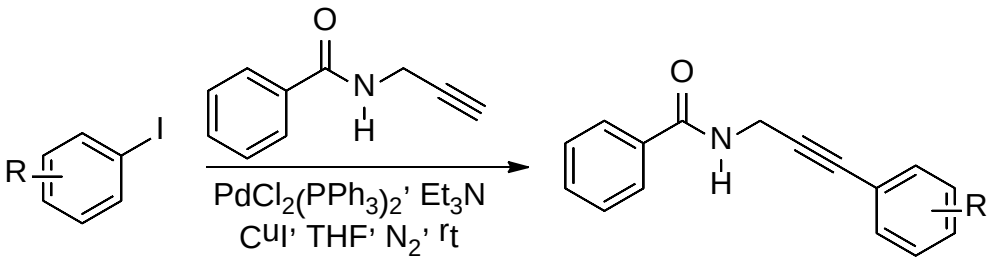
IR: 3205 (br), 3059 (w), 1640 (m), 1574 (s), 1419 (m), 1487 (m), 1323 (s), 754 (s) cm^{-1}.

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

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

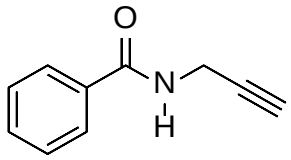
HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{12}N_2O_3^+$ 281.0921, found 281.0921.

General procedure for the Sonogashira-coupling of aryl iodides with propargylamides.



Prepared according to the procedure reported by Cikotiene and coauthors.[81] *N*-(Prop-2-yn-1-yl)benzamide (0.7 g, 6.28 mmol) was added under N_2 to a mixture of the corresponding aryl iodide (3.99 mmol), $PdCl_2(PPh_3)_2$ (0.62 g, 0.88 mmol) and Et_3N (1.84 mL, 13.2 mmol) in THF (10 mL). The mixture was left to stir for 5 min at room temperature followed by addition of CuI (0.08 g, 0.44 mmol). After stirring overnight at room temperature the solvent was removed by rotary evaporation, and the crude product was purified by flash column chromatography (5:1 petroleum ether/EtOAc).

Synthesis of *N*-(prop-2-yn-1-yl)benzamide, 164:[100]



According to literature procedure reported by Ouerghui and coauthors.[100] Propargylamine (4.7 mL, 72.6 mmol), triethylamine (1.3 mL, 9.29 mmol) and DMAP (0.88 g, 7.26 mmol) were dissolved in CH_2Cl_2 (25 mL). The mixture was cooled in an ice bath, then benzoyl chloride (8.4 mL, 72.6 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The mixture was then extracted with 0.1 M aqueous solutions of HCl (2 × 10 mL) and NaOH (2 × 10 mL), washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and the solvent removed under vacuum to give **164** as a white solid (11.1 g, 96% yield), m.p 107-109 ºC (lit. m.p. 106 ºC).

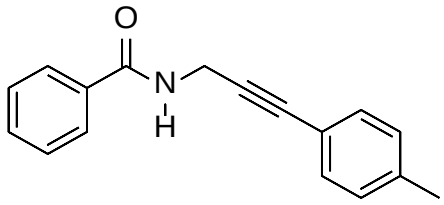
IR: 3288 (br), 3058 (w), 2930 (w), 1639 (s), 1537 (s), 1448 (m), 1047 (m) cm^{-1}.

^{1}H NMR: δ 2.28 (1H, t, *J* = 2.6 Hz), 4.24 (2H, dd, *J* = 5.2, 2.5 Hz), 6.58 (1H, br), 7.42 (2H, t, *J* = 7.3 Hz), 7.50 (1H, t, *J* = 7.3 Hz), 7.79 (2H, d, *J* = 7.6 Hz).

^{13}C NMR: δ 30.1, 72.0, 79.9, 127.4 (2C), 128.5 (2C), 132.1, 134.1, 167.6.

HRMS: m/z calc'd for $[M+H]^+$ $C_{10}H_{10}NO^+$ 160.0757, found 160.0759.

***N*-(3-(*P*-Tolyl)prop-2-yn-1-yl)benzamide, 160g:**[81]



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

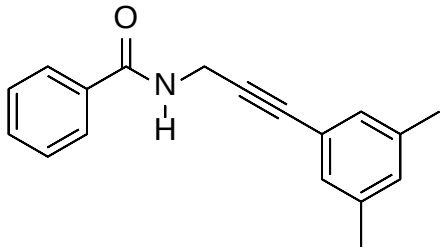
IR: 3294 (br), 1627 (s), 1577 (m), 1522 (s), 1486 (m), 1282 (s), 848 (s), 689 (s) cm^{-1}.

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

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

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

***N*-(3-(3,5-dimethylphenyl)prop-2-yn-1-yl)benzamide, 160h:**



This compound was prepared according to the procedure **A** using iodo-*m*-xylene (0.58 mL, 4.0 mmol) giving **160h** as a brown oil (0.57 g, 49% yield).

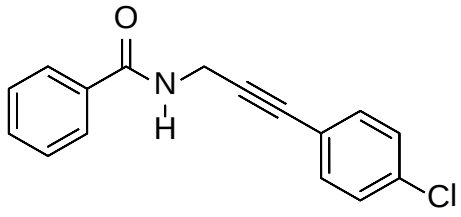
IR: 3295 (br), 2915 (w), 1639 (s), 1525(s), 1484 (m), 1286 (w), 689 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{18}H_{18}NO^+$ 264.1383, found 264.1380.

***N*-(3-(4-Chlorophenyl)prop-2-yn-1-yl)benzamide, 160i:**[81]



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

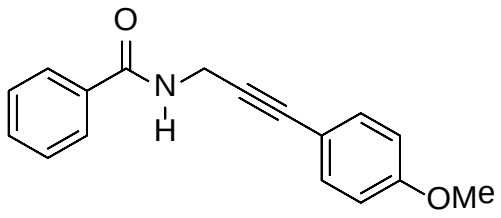
IR: 3271 (br), 1650 (m), 1539 (s), 1486 (s), 1305 (m), 1086 (m), 821 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{13}{}^{35}ClNO^+$ 270.0680, found 270.0682.

***N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)benzamide, 160j:**[81]



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

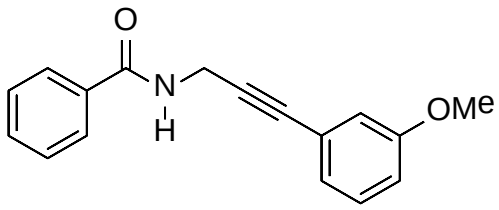
IR: 3311 (br), 1639 (m), 1601 (m), 1542 (s), 1240 (s), 1034 (s), 685 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1176.

***N*-(3-(3-Methoxyphenyl)prop-2-yn-1-yl)benzamide, 160k**



This compound was prepared according to the procedure **A** using 3-iodoanisole (0.48 mL, 3.99 mmol) giving **160k** as a yellow wax (0.48 g, 41% yield).

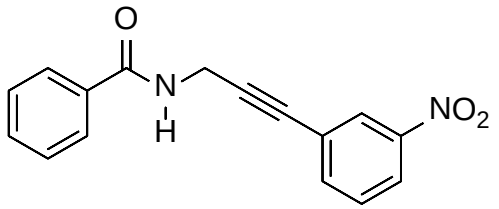
IR: 3308 (br), 3062 (w), 1639 (s), 1526 (s), 1484 (m), 1286 (s), 686 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1175.

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



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

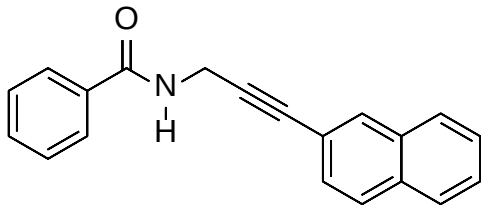
IR: 3376 (br), 3062 (w), 1642 (w), 1514 (s), 1386 (s), 1124 (m), 967 (s) cm^{-1}.

^{1}H NMR: δ 4.49 (2H, d, *J* = 5.5 Hz), 6.82 (1H, br), 7.39-7.54 (4H, m), 7.68 (1H, d, *J* = 7.7 Hz), 7.84 (2H, d, *J* = 7.5 Hz), 8.13 (1H, d, *J* = 8.9 Hz), 8.21 (1H, s).

^{13}C NMR: δ 30.7, 81.3, 88.2, 123.5, 124.7, 126.9, 127.4 (2C), 129.0 (2C), 129.7, 132.2, 134.0, 137.8, 148.3, 167.6.

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{13}N_2O_3^+$ 281.0921, found 281.0920.

***N*-(3-(Naphthalen-2-yl)prop-2-yn-1-yl)benzamide, 160m:**[99]



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

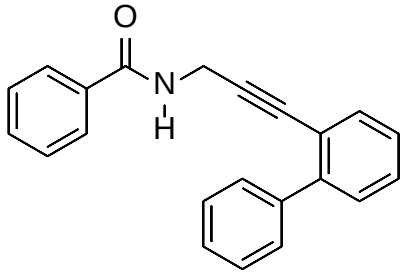
IR: 3385 (br), 2967 (m), 1629 (s), 1530 (m), 1284 (w), 1130 (m), 666 (s) cm^{-1}.

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

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

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

***N*-(3-([1,1'-Biphenyl]-2-yl)prop-2-yn-1-yl)benzamide, 160n:**



This compound was prepared according to the procedure **A** using 2-iodobiphenyl (0.70 mL, 4.0 mmol) giving **160n** as a light brown solid (0.48 g, 24% yield), m. p. 113-115°C.

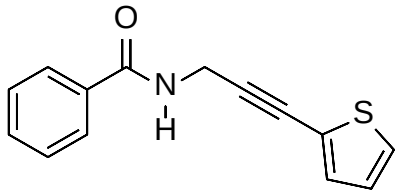
IR: 3290 (br), 1630 (s), 1525(s), 1301 (m), 1077 (w), 690 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{22}H_{18}NO^+$ 312.1383, found 312.1392.

***N*-(3-(thiophen-2-yl)prop-2-yn-1-yl)benzamide, 160o:**[99]



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

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

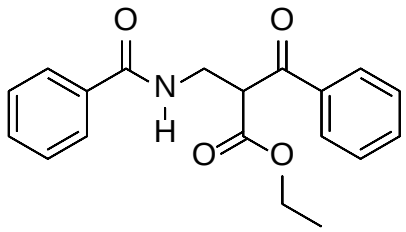
^{1}H NMR: δ 4.51 (2H, d, *J* = 5.2 Hz), 6.36 (1H, br), 6.97 (1H, dd, *J* = 5.5, 3.8 Hz), 7.22 (1H, dd, *J* = 3.7, 1.1 Hz), 7.25 (1H, d, *J* = 4.6 Hz), 7.45 (2H, t, *J* = 7.4 Hz), 7.52 (1H, t, *J* = 7.2 Hz), 7.81 (2H, d, *J* = 7.5 Hz) .

^{13}C NMR: δ 31.2, 77.1, 89.0, 122.5, 127.3, 127.4 (2C), 127.7, 129.0 (2C), 132.2, 132.8, 134.2, 167.4.

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{12}NOS^+$ 242.0634, found 242.0654.

General procedure for the synthesis of starting material (β-amidoketones).

Ethyl 2-(benzamidomethyl)-2-methyl-3-oxopentanoate, 169a:[101]



Following the literature procedure reported by Wang and coauthors,[82] a mixture of *N*-(hydroxylmethyl)benzamide (3 g, 19.8 mmol, 1 equiv) and ethyl benzoyl acetoacetate (3.42 mL, 19.8 mmol) was cooled to 0 °C and $BF_3.OEt_2$ solution (5.0 mL, 39.7 mmol, 2 equiv) was added slowly with stirring. The reaction mixture was left to stir at room temperature for 2 h. The resulting mixture was added to a solution of sodium acetate (6 g) in water (15 mL) mixed well and allowed to separate. The aqueous layer was extracted twice with CH_2Cl_2 (10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed under vacuum giving **169a** as a yellow oil (12.2 g, 96% yield).

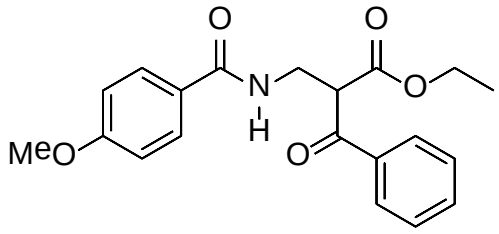
IR: 3339 (br), 2980 (w), 2360 (w), 1732 (m), 1530 (m), 689 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{19}H_{20}NO_4^+$ 326.1387, found 326.1387.

Ethyl 2-((4-methoxybenzamido)methyl)-3-oxo-3-phenylpropanoate, 169b:



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

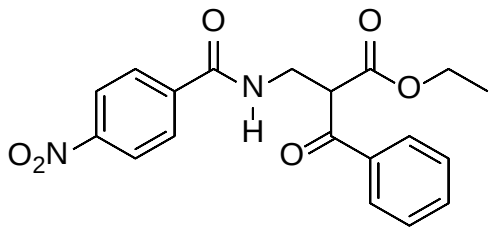
IR: 3341 (br), 2979 (w), 2931 (w), 1731 (m), 1636 (m), 1499 (s) cm^{-1}.

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

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

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

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



This compound was prepared according to the procedure for **169a** using N-(hydroxymethyl)-4-nitrobenzamide (1.8 g, 9.0 mmol, 1 equiv) and ethyl benzoylacetoacetate (1.6 mL, 9.0 mmol, 1 equiv) giving **169d** as a white solid (1.33 g, 39% yield), m. p. 141-144 °C.

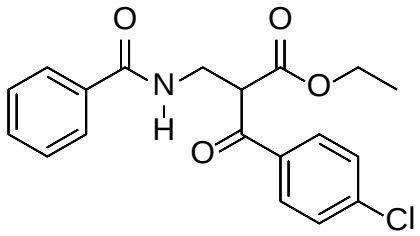
IR: 3376 (m), 3064 (w), 1725 (s), 1666 (m), 1520 (s), 1198 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for calc'd for $[M+H]^+$ $C_{19}H_{19}N_2O_6^+$ 371.1238, found 371.1250.

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



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

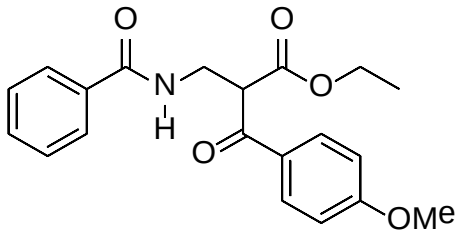
IR: 3342 (br), 3067 (w), 1729 (s), 1639.(s), 1525 (m), 1091 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{19}H_{19}{}^{35}ClNO_4^+$ 360.0997, found 360.0991.

Ethyl 2-(benzamidomethyl)-3-(4-methoxyphenyl)-3-oxopropanoate, 169j:[102]



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

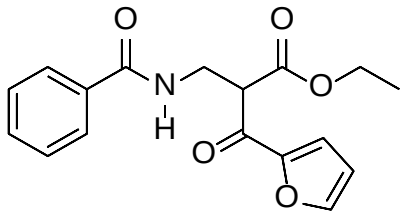
IR: 3399 (br), 2979 (w), 1724 (s), 1653 (m), 1530 (m), 1181 (s) cm^{-1}.

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

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

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

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



This compound was prepared according to the procedure for **169a** using *N*-(hydroxylmethyl)benzamide (1.3 g, 8.2 mmol, 1 equiv) and ethyl-3-(2-furyl)-3-oxopropanoate (1.5 g, 8.2 mmol, 1 equiv) giving **169p** as a white solid (1.2 g, 46% yield), m.p. 110-112 °C.

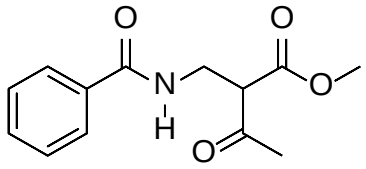
IR: 3364 (br), 3133 (w), 2979 (w), 1723 (m), 1639 (s), 1275 cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{18}NO_5^+$ 316.1179, found 316.1179.

methyl 2-(benzamidomethyl)-3-oxobutanoate, 169q:[82]



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

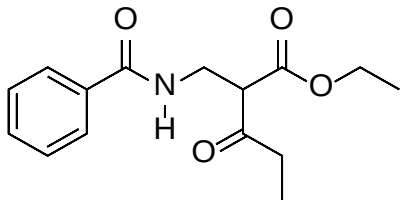
IR: 3308 (br), 1743 (s), 1708 (m), 1635 (s), 1530 (s), 1370 (m), 817 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{13}H_{16}NO_4^+$ 250.1074, found 250.1079.

Ethyl 2-(benzamidomethyl)-3-oxopentanoate, 169r:



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

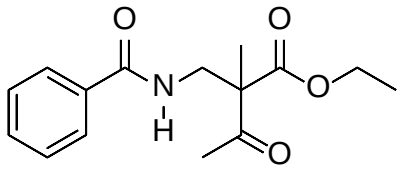
IR: 3363 (br), 2939 (w), 1736 (s), 1630 (m), 1524 (s), 717 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for calc'd for $[M+H]^+$ $C_{15}H_{20}NO_4^+$ 278.1387, found 278.1391.

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



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

IR: 3345 (br), 2985 (w), 1735 (s), 1645 (m), 1525 (m), 1242 (s) cm^{-1}.

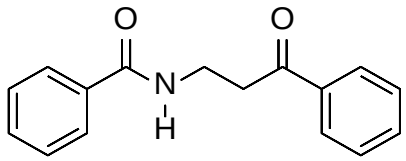
^{1}H NMR: δ 1.06 (3H, t, *J* = 7.1 Hz), 1.28 (3H, s), 2.05 (3H, s), 3.63-3.77 (2H, m), 3.97-4.01 (2H, m), 6.99 (1H, br), 7.21 (2H, t, *J* = 6.3 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 7.56 (2H, d, *J* = 7.4 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{20}NO_4^+$ 278.1348, found 278.1392.

General procedure for the decarboxylation reaction.

***N*-(3-oxo-3-phenylpropyl)benzamide, 172a:**[103]



According to the literature procedure reported by Kaku *et al*,[83] a flask was charged with **169a** (0.40 g, 1.22 mmol, 1 equiv), LiCl (0.12 g, 2.82 mmol), H_2O (1.7 mL) and DMSO (22 mL) at room temperature. The solution was stirred overnight at 160 °C. The resulting solution was cooled to room temperature and diluted with water (20 mL). The mixture was extracted with diethyl ether (20 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to provide a **170a** as a white solid (0.15 g, 50% yield).

Melting point: 90-92 °C.

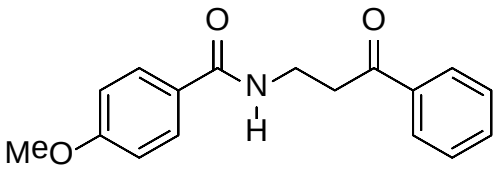
IR: 3239 (br), 3066 (w), 1669 (m), 1553 (m), 1323 (s), 1203 (w), 684 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{16}NO^+$ 254.1176, found 254.1174.

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



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

Melting point: 110-114 °C.

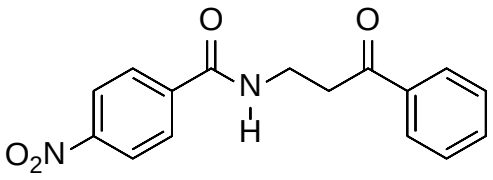
IR: 3395 (br), 2932 (w), 1678 (m), 1503 (m), 1176 (s), 845 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{18}NO_3^+$ 284.1281, found 284.1280.

4-Nitro-*N*-(3-oxo-3-phenylpropyl)benzamide, 172d:



This compound was prepared according to the procedure for **172a** using **169d** (0.29g, 0.78 mmol, 1 equiv) giving **172d** as a white solid (0.17 g, 41% yield).

Melting point: 135-138 °C.

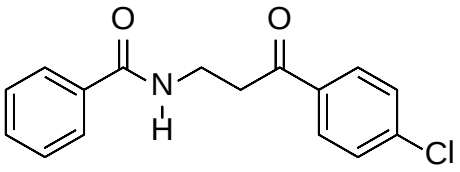
IR: 3364 (br), 2929 (w), 1673 (m), 1518 (s), 1345 (s), 1213 (m), 781 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{15}N_2O_4^+$ 299.1026, found 299.1025.

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



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

Melting point: 119-122 °C.

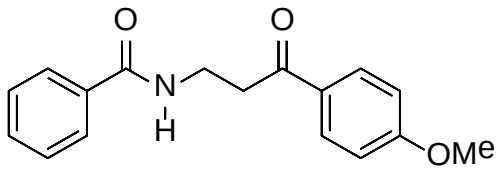
IR: 3237 (br), 2924 (w), 1673 (m), 1297 (m), 1104 (s), 692 (s) cm^{-1}.

^{1}H NMR: δ 3.28 (2H, t, *J* = 5.5 Hz), 3.84 (2H, q, *J* = 5.7 Hz), 7.06 (1H, br), 7.33-7.48 (5H, m), 7.74 (2H, d, *J* = 7.7 Hz), 7.86 (2H, d, *J* = 7.7 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{15}{}^{35}ClNO_2^+$ 288.0786, found 288.0781.

***N*-(3-(4-Methoxyphenyl)-3-oxopropyl)benzamide, 172j:**[81]



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

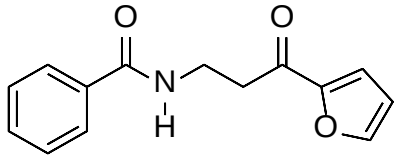
IR: 3363 (br), 2935 (w), 1676 (m), 1599 (m), 1171 (s), 1302 (m), 831 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{18}NO_3^+$ 284.1281, found 284.1279.

***N*-(3-(Furan-2-yl)-3-oxopropyl)benzamide, 172p:**



This compound was prepared according to the procedure for **172a** using **169p** (0.47g, 1.49 mmol, 1 equiv) giving **172p** as a light yellow solid (0.21 g, 54% yield).

Melting point: 92-96 °C.

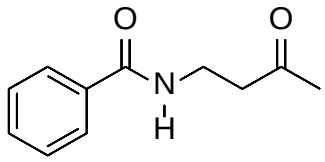
IR: 3362 (br), 2928 (w), 1627 (s), 1522 (s), 1281 (m), 688 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{14}NO_3^+$ 244.0929, found 244.0969.

***N*-(3-oxobutyl)benzamide, 172q:**[104]



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

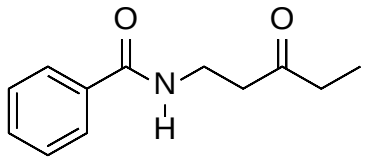
IR: 3332 (br), 2926 (w), 1708 (m), 1637 (s), 1536 (s), 1294 (m), 692 (s) cm^{-1}.

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

^{13}C NMR: δ 30.5, 34.8, 43.2, 127.2 (2C), 128.8 (2C), 128.9, 134.6, 167.7, 209.1.

HRMS: m/z calc'd for $[M+H]^+$ $C_{11}H_{14}NO^+$ 192.1019, found 192.10120.

***N*-(3-Oxopentyl)benzamide, 172r:**



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

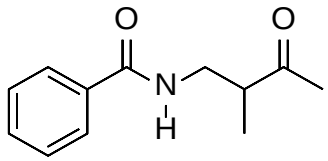
IR: 3306 (br), 2935.8 (w), 1711 (s), 1633 (s), 1537 (s), 1115 (m) cm^{-1}.

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

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

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

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



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

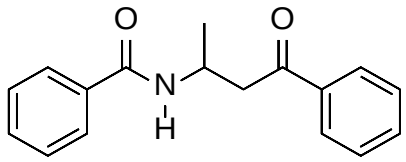
IR: 3359 (br), 2362 (w), 1707 (s), 1645 (m), 1358 (s), 1220 (s) cm^{-1}.

^{1}H NMR: δ 1.17 (3H, d, *J* = 2.5 Hz), 2.15 (3H, s), 2.86-2.96 (1H, m), 3.42-5.51 (1H, m), 3.56-3.65 (1H, m), 6.89 (1H, br), 7.37 (2H, t, *J* = 7.3 Hz), 7.44 (1H, t, *J* = 7.3 Hz), 7.72 (2H, d, *J* = 7.7 Hz).

^{13}C NMR: δ 14.4, 28.5, 41.6, 46.7, 127.0 (2C), 128.4 (2C), 131.4, 134.3, 167.7, 211.9.

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{16}NO_2^+$ 206.1176, found 206.1178.

Synthesis of *N*-(4-oxo-4-phenylbutan-2-yl)benzamide, 172t:[104]



This compound was prepared according to the literature procedure reported by Taskasu, Kiyosei and coauthors[34] a mixture of benzamide (0.66 g, 5.47 mmol, 1 equiv), 1-phenylbut-2-en-1-one (0.80 g, 5.47 mmol, 1 equiv) and $Pd(PhCN)_2Cl_2$ (3.57 mL, 33.1 mmol) was heated to 60 °C for 24 h. The resulting mixture was diluted with $CHCl_3$ and filtrered off. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (5:1 petroleum ether/EtOAc) to give **172t** as a yellow solid (0.67 g, 46% yield)

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

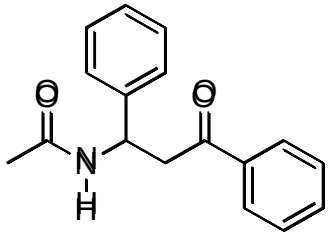
IR: 3308 (br), 3169 (w), 1683 (m), 1634 (m), 1546 (s), 1293 (m), 802 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{18}NO_2^+$ 268.1332, found 268.1333

Synthesis of *N*-(3-oxo-1,3-diphenylpropyl)benzamide, 172u:[86]



Following the literature procedure reported by Khan and coauthors,[86] to a stirred solution of benzaldehyde (0.88 g, 8.32 mmol), acetyl chloride (0.89 mL, 12.5 mmol), and acetophenone (0.97 mL, 8.32 mmol) in acetonitrile (20 mL) was added $FeCl_3$ (1.35 g, 8.32 mmol). The reaction was stirred at room temperature overnight, then quenched with water (50 mL) and extracted with EtOAc (3 × 70 mL). The organic layer was dried over anhydrous $MgSO_4$ and purified by flash chromatography (2:1 petroleum ether/EtOAc) to give **172u** as a white solid (0.98 g, 44%). m.p 104-106 ºC (lit. m.p. 103-105 ºC).

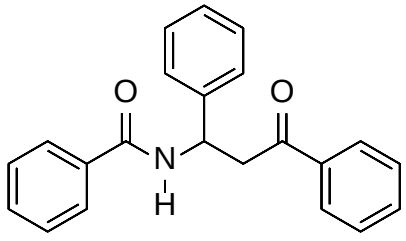
IR: 3323 (br), 2931 (w), 1660 (w), 1378 (m), 1128 (s), 950 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{18}NO_2^+$ 268.1332, found 268.1335.

***N*-(3-oxo-1,3-diphenylpropyl)benzamide, 172v,**[105]



This compound was prepared according to the procedure for **172u** using benzonitrile giving **172v** as a white solid (0.95 g, 35% yield), m.p 153-155 ºC (lit. m.p. 153-154 ºC).

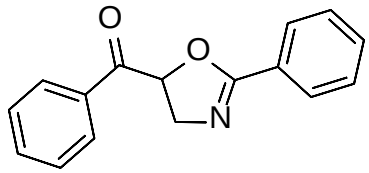
IR: 3361 (br), 3165 (w), 3064 (w), 1625 (s), 1577 (m), 1402 (m) 684 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+Na]^+$ $C_{22}H_{19}NO_2Na^+$ 352.1308, found 352.1304.

Representative procedure for 2-iodoanisole-catalysed cyclisation: synthesis of Phenyl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161a:



160 (0.10 g, 0.43 mmol, 1 equiv) was dissolved in acetonitrile (3 mL) and 2-iodoanisole (11 µL, 0.09 mmol, 0.2 equiv) was added, followed by *m*CBPA (0.29 g, 1.28 mmol, 3 equiv) and *p*-TsOH.H_2O (0.24 g, 1.28 mmol, 3 equiv). The mixture was stirred overnight at room temperature, then aqueous Na_2SO_4 solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) were added and the mixture extracted with CH_2Cl_2 (10 mL × 2). The organic layers were combined and dried with $MgSO_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether/EtOAc) to provide **161a** as a bright yellow solid (0.076 g, 77% yield).

Melting point: 104-108 °C.

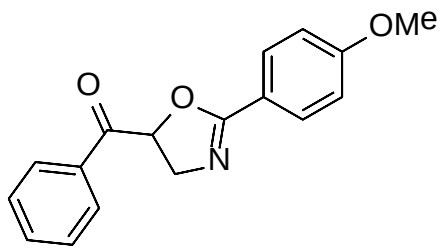
IR: 2922 (br), 2355 (w), 1702 (m), 1650 (s), 1596 (w), 685 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{14}NO_2^+$ 252.0980, found 252.1026.

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



This compound was prepared according to the procedure for **161a** using **172b** (0.10g, 0.35 mmol, 1 equiv) giving **161b** as a yellow solid (0.073 g, 77% yield).

Melting point: 134-137 °C.

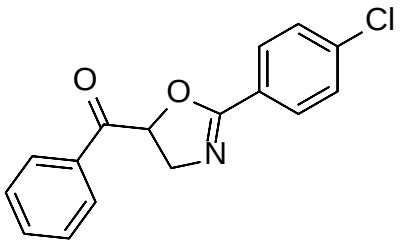
IR: 2924 (br), 2849 (w), 1694 (m), 1604 (m), 1378 (m), 1301 (s), 688 (s) cm^{-1}.

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

^{13}C NMR: δ 55.7, 58.9, 79.9, 114.1 (2C), 119.9, 129.1 (2C), 129.3 (2C), 130.5 (2C), 134.3, 134.5, 162.7, 164.3, 195.5.

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_3^+$ 282.1085, found 282.1123.

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



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

Melting point: 103-107 °C.

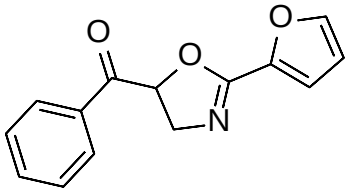
IR: 2927 (br), 1702 (m), 1649 (m), 1488 (m), 1089 (s), 850 (s) cm^{-1}.

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

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

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

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



This compound was prepared according to the procedure for **161a** using **160f** (0.10g, 0.44 mmol, 1 equiv) giving **161f** as a yellow solid (0.071 g, 66% yield).

Melting point: 76-79 °C.

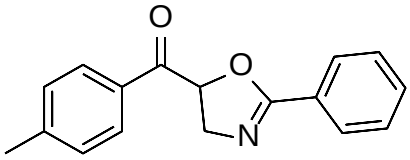
IR: 3111 (br), 2924 (s), 1700 (s), 1672 (s), 1479 (m), 1097 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{12}NO_3^+$ 242.0812, found 242.0818.

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



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

Melting point: 119-122 °C.

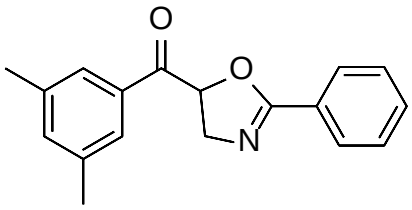
IR: 2924 (br), 1722 (w), 1689 (w), 1577 (w), 1247 (s), 709 (s) cm^{-1}.

^{1}H NMR: δ 2.44 (3H, m), 4.26 (1H, dd, *J* = 15, 7.7 Hz), 4.45 (1H, dd, *J* = 15, 11 Hz), 5.84 (1H, dd, *J* = 11, 7.7 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.42 (2H, t, *J* = 7.7 Hz), 7.49 (1H, t, *J* = 7.4 Hz), 7.89 (2H, d, *J* = 8.1 Hz), 7.99 (2H, d, *J* = 8.1 Hz).

^{13}C NMR: δ 22.2, 58.9, 79.9, 127.4, 128.7 (4C), 128.8 (2C), 129.2 (2C), 130.0, 132.0, 145.4, 164.5, 194.9.

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1176.

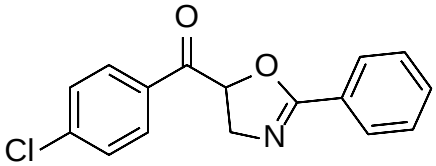
(3,5-Dimethylphenyl)(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161h:



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

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

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



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

Melting point: 106-108 °C.

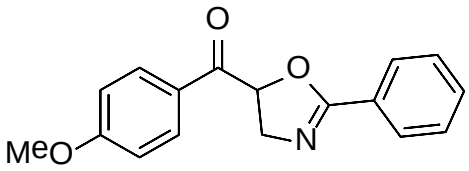
IR: 3063 (br), 2848 (w), 1693 (m), 1586 (m), 1362 (m), 1058 (m), 710 (s) cm^{-1}.

^{1}H NMR: δ 4.31 (1H, dd, *J* = 15, 7.5 Hz), 4.44 (1H, dd, *J* = 15, 11 Hz), 5.78 (1H, dd, *J* = 11, 7.5 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 7.47-7.53 (3H, m), 7.93-7.99 (4H, m).

^{13}C NMR: δ 58.6, 79.9, 127.3, 128.7 (2C), 128.8 (2C), 129.7 (2C), 130.6 (2C), 132.1, 132.9, 140.9, 164.2, 194.4.

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{13}{}^{35}ClNO_2^+$ 286.0629, found 286.6020.

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



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

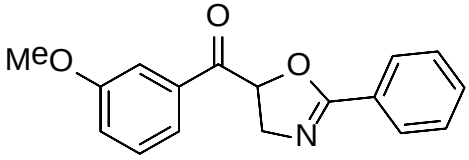
IR: 3324 (br), 2924 (w), 2836 (w), 1740 (m), 1646 (m), 1598 (s), 1169 (m), 695 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_3^+$ 282.1125, found 282.1134.

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



This compound was prepared according to the procedure for **161a** using **160k** (0.05g, 0.19 mmol, 1 equiv) giving **161k** as a Yellowish wax (0.0073 g, 14% yield).

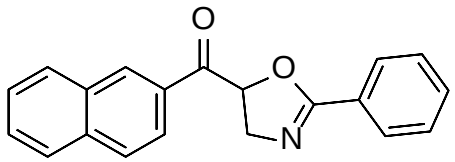
IR: 3326 (br), 2935 (w), 2838 (w), 1744 (m), 1646 (m), 1593 (s), 1170 (m), 695 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_3^+$ 282.1125, found 282.1134.

Naphthalen-2-yl(2-phenyl-4,5-dihydrooxazol-5-yl)methanone, 161m:



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

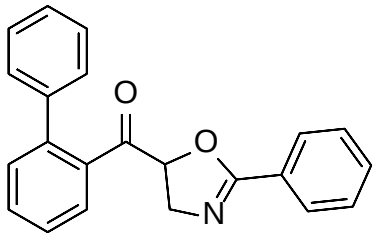
IR: 3339 (br), 2968 (m), 1694 (w), 1650 (m), 1508 (s), 950 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{20}H_{16}NO_2^+$ 302.1176, found 302.1193.

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



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

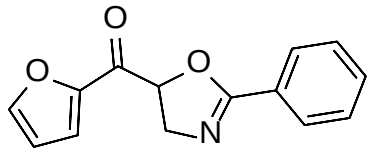
IR: 3055 (br), 2926 (w), 2871 (w), 1698 (m), 1646 (m), 1252 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{22}H_{18}NO_2^+$ 328.1332, found 328.1329.

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



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

Melting point: 75-77 °C.

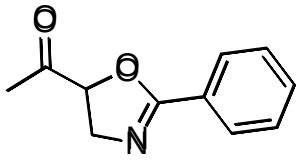
IR: 3335 (br), 2969 (s), 1466 (w), 1378 (m), 1127 (m), 950 (s) cm^{-1}.

^{1}H NMR: δ 4.25 (1H, dd, *J* = 15, 7.8 Hz), 4.47 (1H, dd, *J* = 15, 11 Hz,), 5.61 (1H, dd, *J* = 11, 7.8 Hz), 6.58 (1H, dd, *J* = 3.8, 1.8 Hz), 7.41 (1H, t, *J* = 3.9 Hz), 7.45 (2H, d, *J* = 7.9 Hz), 7.51 (1H, t, *J* = 7.3 Hz), 7.71 (1H, s), 8.00 (2H, d, *J* = 7.7 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{14}H_{12}NO_3^+$ 242.0812, found 242.0804.

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



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

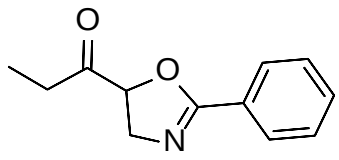
IR: 2937 (br), 1717 (s), 1651 (s), 1254 (m), 1058 (s), 778 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{11}H_{12}NO_2^+$ 190.0863, found 190.0866.

1-(2-Phenyl-4,5-dihydrooxazol-5-yl)propan-1-one, 161r:



This compound was prepared according to the procedure for **161a** using **172r** (0.10g, 0.48 mmol, 1 equiv) giving **161r** as a colourless oil (0.055 g, 56% yield).

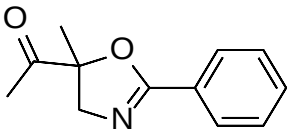
IR: 2969 (br), 1717 (m), 1643 (w), 1451 (w), 1264 (m), 711 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+NH_4]^+$ $C_{12}H_{17}N_2O_2^+$ 221.1285, found 221.1284.

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



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

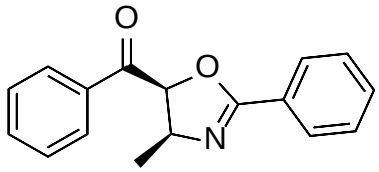
IR: 3335 (br), 2969 (m), 2928 (w), 2359 (m), 1713 (m), 1646 (m), 950 (s) cm^{-1}.

^{1}H NMR: δ 1.58 (3H, s), 2.29 (3H, s), 3.85 (1H, d, *J* = 15 Hz), 4.21 (1H, d, *J* = 15 Hz), 7.44 (2H, t, *J* = 7.5 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.99 (2H, d, *J* = 7.3 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{12}H_{14}NO_2^+$ 204.1019, found 204.1012.

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



This compound was prepared according to the procedure for **161a** using **172t** (0.10g, 0.37 mmol, 1 equiv) giving **161t** as a yellow wax (0.053 g, 54% yield).

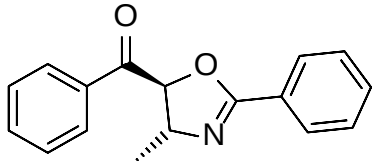
IR: 2925 (br), 1698 (m), 1647 (m), 1448 (m), 1218 (s), 687 (s) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1167.

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



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

Melting point: 71-73 °C.

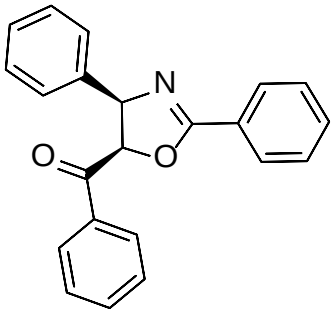
IR: 2925 (br), 1698 (m), 1647 (m), 1448 (m), 1218 (s), 687 (s) cm^{-1}.

^{1}H NMR: δ 1.54 (3H, d, *J* = 6.7 Hz), 4.52 (1H, pent, *J* = 6.6 Hz), 5.39 (1H, d, *J* = 6.7 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 7.50 (1H, t, *J* = 7.8 Hz), 7.52 (2H, t, *J* = 7.8 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.99 (2 x 2H, d, *J* = 7.8 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1167.

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



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

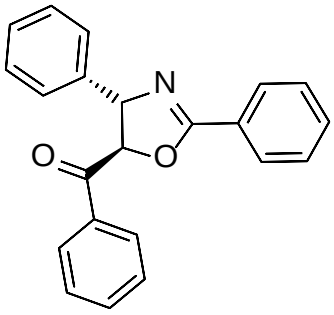
IR: 2918 (br), 1700 (m), 1644 (s), 1447 (m), 1238 (m), 1068 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{22}H_{18}NO_2^+$ 328.1331, found 328.1330.

((*anti*)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl)(phenyl)methanone, 161v:[106]



This compound was prepared according to the procedure for **161a** using **172v** (0.10g, 0.42 mmol, 1 equiv) giving **161v** as a yellow oil (0.041 g, 28% yield).

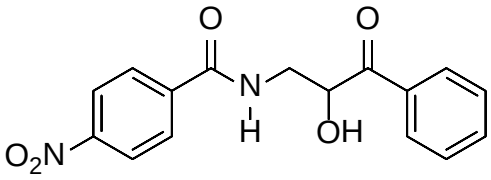
IR: 2918 (br), 1700 (m), 1644 (s), 1447 (m), 1238 (m), 1068 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{22}H_{18}NO_2^+$ 328.1331, found 328.1330.

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



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

Melting point: 75-77 °C.

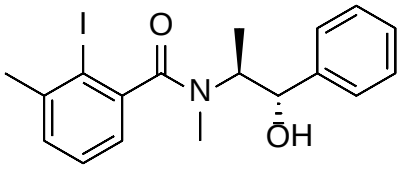
IR: 3405 (br), 2969 (m), 1667 (m), 1535 (m), 1368 (w), 1124 (m), 950 (s) cm^{-1}.

^{1}H NMR: δ 3.33 (1H, ddd, *J* = 13, 8.3, 5.5 Hz), 4.09 (1H, br), 4.24 (1H, ddd, *J* = 10, 6.8, 3.2 Hz), 5.34 (1H, dd, *J* = 7.7, 2.8 Hz), 6.87 (1H, br), 7.57 (2H, t, *J* = 7.7 Hz), 7.68 (1H, t, *J* = 7.7, Hz), 7.95 (2H, d, *J* = 8.7 Hz), 8.12 (2H, d, *J* = 8.2 Hz), 8.29 (2H, d, J = 8.7 Hz).

^{13}C NMR: δ 45.7, 72.8, 124.2 (2C), 128.6 (2C), 129.2 (2C), 129.6 (2C), 133.3, 135.2, 139.8, 150.1, 166.3, 199.4.

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{15}N_2O_5^+$ 315.0936, found 315.0972.

_N_-((1_R_,2_S_)-1-Hydroxy-1-phenylpropan-2-yl)-2-iodo-_N_,3-dimethylbenzamide, 185:[38]



Prepared following the literature procedure reported by Moran and Rodríguez.[37] 2-iodo-3-methylbenzoic acid (0.5 g, 1.9 mmol) was dissolved in CH_2Cl_2 (19 mL) at room temperature and oxalyl chloride (0.32 mL, 3.9 mmol) and DMF (0.01 mL) were added sequentially. The reaction mixture was stirred overnight, then concentrated under vacuum. The residue was dissolved in THF (10 mL) and added dropwise to a solution of (1*S*,2*S*)-pseudoephedrine hydrochloride (0.31 g, 1.6 mmol) and triethylamine (0.5 mL, 3.6 mmol) in THF (10 mL) at 0 ºC. The mixture was allowed to warm to room temperature overnight and then quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (silica gel; 1:1 petroleum ether/EtOAc) provided **185** as a white solid (0.35 g, 45% yield), m.p: 182-186 ºC (lit. m.p. 181-185 ºC).

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

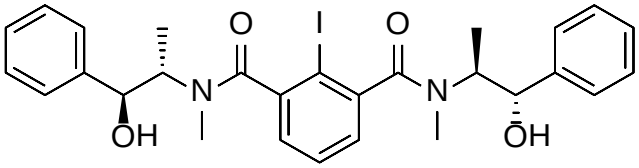
IR (neat): 3330 (br), 2856 (w), 1607 (s), 1412 (m), 1038 (m) cm^{-1}.

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

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

HRMS: m/z calc'd for $[M+H]^{+}$ $C_{18}H_{21}INO_2$ 410.0611, found 410.0611.

***N*^{1},*N*^{3}-bis((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-*N*^{1},*N*^{3}-dimethylisophthalamide, 188:**



Prepared following the literature procedure reported by Moran and Rodríguez.[37] using 2-iodoisophthalic acid (0.5 g, 1.7 mmol) was dissolved in CH_2Cl_2 (20 mL) at room temperature and oxalyl chloride (0.59 mL, 6.85 mmol) and DMF (0.02 mL) were added sequentially. The reaction mixture was stirred overnight, and then concentrated under vacuum. The residue was dissolved in THF (10 mL) and added dropwise to a solution of (1*S*,2*S*)-pseudoephedrine hydrochloride (0.56 g, 2.8 mmol) and triethylamine (1.8 mL, 12.6 mmol) in THF (18 mL) at 0 ºC. The mixture was allowed to warm to room temperature overnight and then quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered and

concentrated. Purification by flash chromatography (silica gel; 1:10 petroleum ether/EtOAc) provided **188** as a white solid (0.48g, 48% yield), m.p 197-200 ^{o}C.

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

IR: 3390 (br), 1611 (s), 1402 (m), 1109 (m), 1046 (m), 699 (s) cm^{-1}.

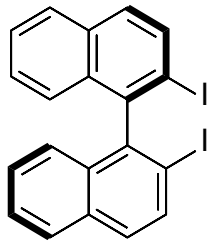
^{1}H NMR (400 MHz, DMSO-d^{6}): δ 0.89-1.14 (6H, m), 2.95 (3H, s), 3.34 (3H, s), 4.39-4.55 (1H, m), 4.58-4.70 (1H, m), 4.77-4.91 (1H, m), 5.45-5.57 (1H, m), 5.59-5.71 (1H, m), 6.77-7.55 (14H, m).

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

^{13}C NMR (100 MHz, DMSO-d^{6}): δ 16.4^{B}, 16.6^{A}, 27.9^{B}, 28.1^{A}, 31.8^{B}, 32.1^{A}, 60.4^{A}, 60.6^{B}, 74.8^{B}, 75.1^{A}, 92.8^{B}, 92.9^{A}, 128.0^{B} (4C), 128.1^{A} (4C), 128.5^{A}, 128.7^{B}, 128.8^{A} (2C), 128.9^{B} (2C), 129.3^{A} (2C), 129.3^{B} (2C), 129.4^{B} (4C), 129.5^{A} (4C), 144.5^{A} (2C), 144.6^{B} (2C), 145.4^{A}, 145.8^{B}, 171.0^{B}, 170.2^{A}, 171.6^{B}, 171.7^{A}.

HRMS: m/z calc'd for $[M+H]^{+}$ $C_{28}H_{32}IN_2O_4$ 587.1401, found 587.1400.

(*R*)-2,2'-Diiodo-1,1'-binaphthyl, 190:[107]



Prepared according to the literature procedure.[87] A mixture of commercial (*R*)-(+)-2,2'-diamino-1,1'-binaphthyl (1 g, 3.52 mmol), potassium iodide (5.87 g, 35 mmol), and sodium nitrite (1.69 g, 28 mmol) were placed in flask charged with N_2. The solids were dissolved in DMSO (60 mL) in a room temperature water bath. Then, 47% aqueous HBr (4.8 mL) was

added dropwise with intense stirring which led to darkening and visible gas evolution. Then, the water bath was removed and the mixture was stirred for 2h. The resulting mixture was poured into 50% aqueous sat. $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (60 mL). The combined organic extracts were washed with 10% aq. $Na_2S_2O_3$ (2 x 30 mL), water (2 x 30 mL), brine (15 mL), and dried over $MgSO_4$. Then, the solvent was removed under vacuum and the residue purified by flash column chromatography on silica gel (eluent: petroleum ether 40-60) which afforded **190** as a white solid (0.83 g, 47% yield), m.p 116-117 ^oC (lit. m.p. 116.5 ^oC).

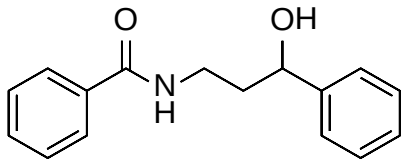
IR: 2970 (br), 1573 (m), 1497 (w), 1265 (m), 1097 (m), 827 (s) cm^{-1}.

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

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

HRMS: *m*/*z* calc'd for $[M-I]^+$ $C_{20}H_{12}I^+$ 378.9978, found 378.9974

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



Following the literature procedure reported by Legault,[40] a solution of diisopropylamine (0.17 mL, 1.2 mmol) in THF (5 mL) under an argon atmosphere at −78 °C was slowly add n-Butyllithium 2.5M (4.7 mL, 1.2 mmol). The mixture was stirred for 30 min, and then *N*-(3-oxo-3-phenylpropyl)benzamide (0.25 g, 0.99 mmol) was added. The resulting mixture was stirred for 45 min, and then acetic anhydride (0.19 mL, 1.97 mmol) was added. The reaction

was stirred 30 min at −78 °C and another 30 min at room temperature. The mixture was poured into saturated $NaHCO_3$ (5 mL), and extracted twice with EtOAc (10 mL). The combined organic layers were washed with brine and dried over MgSO4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1:10 petroleum ether/EtOAc to EtOAc) to provide **192** as a yellow oil (0.06 g, 24% yield).

IR: 3332 (br), 1466 (w), 1378 (m), 1159 (m), 950 (s), 816 (m) cm^{-1}.

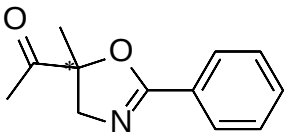
^1H NMR: δ 1.92-2.00 (2H, m), 3.39-3.47 (1H, m), 3.69-3.77 (1H, br), 3.77-3.88 (1H, m), 4.81 (2H, dd, J = 8.5, 4.4 Hz), 7.09 (1H, br), 7.24-7.28 (1H, m), 7.32-7.36 (4H, m), 7.37-7.43 (2H, m), 7.48 (1H, t, J = 7.4 Hz), 7.75 (2H, d, J = 7.8 Hz).

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

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{18}NO_2^+$ 256.1332, found 256.1338.

Representative procedure for chiral iodoarene-catalysed cyclisation

1-(5-Methyl-2-phenyl-4,5-dihydrooxazol-5-yl)ethanon,e 161s



Amide **172s** (1 equiv) was dissolved in solvent and chiral iodoarene (0.1 equiv) was added, followed by *m*CBPA (3 equiv) and *p*-TsOH.H_2O (3 equiv). The mixture was stirred overnight at room temperature, then aqueous Na_2SO_4 solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) were added and the mixture extracted with CH_2Cl_2 (10 mL × 2). The organic layers were combined and dried with $MgSO_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether/EtOAc) to provide **161s.**

ee: 14%, determined by HPLC analysis: chiralpak IB, hexane/IPA gradient (93:7), 1 mL/min. 254 nm; Retention Time (minor) = 5.3 min, Retention Time (major) = 5.8 min.

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