Design and Development of Chiral Iodoarenes and a Novel Iodine(III)-Mediated Carbamate Cyclisation

Department of Chemical Sciences

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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“One, remember to look up at the stars and not down at your feet. Two, never give up work. Work gives you meaning and purpose and life is empty without it. Three, if you are lucky enough to find love, remember it is there and don't throw it away.” — Stephen Hawking

To my beloved son, ***Jayden Reece*** *for his sacrifice,*

in allowing his father to pursue his passion…

Publication(s)

The following publication(s) is/are based on the work presented in this thesis:

Synthesis of Oxazolidinones by a Hypervalent Iodine Mediated Cyclization of *N*-Allylcarbamates

Mirdyul Das, Arantxa Rodríguez, Pui Kin Tony Lo, and Wesley J. Moran, *Adv. Synth. Catal.* **2021**, 363, 1-6

DOI: 10.1002/adsc.202001451

Computationally Assisted Mechanistic Investigation into Hypervalent Iodine Catalysis: Cyclization of *N*-Allylbenzamide

Smaher E. Butt, Mirdyul Das, Jean-Marc Sotiropoulos, and Wesley J. Moran, *J. Org. Chem.* **2019**, 84, 15605−15613

DOI: 10.1021/acs.joc.9b02623

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Finally, I would like to reflect on the loss of two great inspirational chemists both cut down in their prime. Firstly, my beautiful colleague, collaborator, and mentor Dr. Arantxa Rodríguez, who I learned so much from in the laboratory. Secondly, Prof. Kilian Muñiz whose research I closely followed for insight and creative stimulation.

Abbreviations

Ac: acetyl.

Ac_2O: acetic anhydride

AcOH: acetic acid

AcOOH: peroxyacetic acid

ADDP: 1,1'-(azodicarbonyl)dipiperidine

Å: Angstrom (1×10^{-100} m)

Ar: aryl.

ArI: iodoarene.

Et: ethyl.

$BF_3.OEt_2$: boron trifluoride dietherate.

Bn: benzyl.

Boc: *tert*-butoxycarbonyl.

Bz: benzoyl.

Cbz: benzyloxycarbonyl.

CSA: camphorsulfonic acid.

CTAB: cetyltrimethylammonium bromide

d.r.: diastereomeric ratio.

DCM: dichloromethane

DIAD: diisopropyl azodicarboxylate.

DIC: diisopropylcarbodiimide.

DIPEA: diisopropylethylamine.

4-DMAP: 4-dimethylaminopyridine.

DMF: *N,N*-dimethylformamide.

DMP: Dess–Martin periodinane.

DMSO: dimethylsulfoxide.

dppf: 1,1′-bis(diphenylphosphino)ferrocene.

ee: enantiomeric excess.

EDG: electron-donating group.

Et: ethyl.

EWG: electron-withdrawing group.

F: Faraday.

GC: glassy carbon.

h: hour.

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

HMDS: hexamethyldisilazane.

HPLC: high performance liquid chromatography.

HRMS: high resolution mass spectrometry.

HTIB: hydroxy(tosyloxy)iodobenzene.*i*-Pr: isopropyl.

L: ligand.

M: molarity (mol/l).

mA: milliamps

*m*CPBA: 3-chloroperoxybenzoic acid.

Me: methyl.

MeCN: acetonitrile.

MeOH: methanol.

Mes: mesityl.

Min: minute.

mL: millilitre.

MnTIB: [menthyloxy(tosyloxy)iodo]benzene.

mol: mole.

MO: molecular orbital.

m.p.: melting point.

MPa: MegaPascal.

Ms: methanesulfonyl.

MS: mass spectrometry.

MTBE: methyl *tert*-butyl ether.

MTIB: [methoxy(tosyloxy)iodo]benzene.

MW: microwave.

MWD: multiple wavelength detector.

*n*BuLi: *n*-butyllithium.

NMR: nuclear magnetic resonance.

N_2: nitrogen gas.

nm: nanometre.

Nu: nucleophile.

IR: infrared.

OAc: acetate.

OTs: oxy *p*-toluenesulfonate.

Ph: phenyl.

PIDA: phenyliodine(III) diacetate.

PIFA: [Bis(trifluoroacetoxy)iodo]benzene.

PPh_3: triphenyl phosphine.

p-TsOH: *p*-toluenesulfonic acid.

py: pyridine.

rt: room temperature.

R_t: retention time.

SET: single electron transfer.

S_E1: electrophilic substitution.

Selectfluor™: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

S_N1: nucleophilic substitution.

t-AmylOH: 2-methylbutan-2-ol

TBP: tributyl phosphate

t-Bu: *tert* butyl.

Tf: trifluorosulfonyl.

TFA: trifluoroacetic anhydride.

TFE: 2,2,2-trifluoroethanol.

TfOH: triflic acid.

THF: tetrahydrofuran.

TIPS: tri(propan-2-yl)silane.

TLC: thin layer chromatography.

TMSOTf: trimethylsilyl triflate.

TMSOAc: trimethylsilyl acetate.

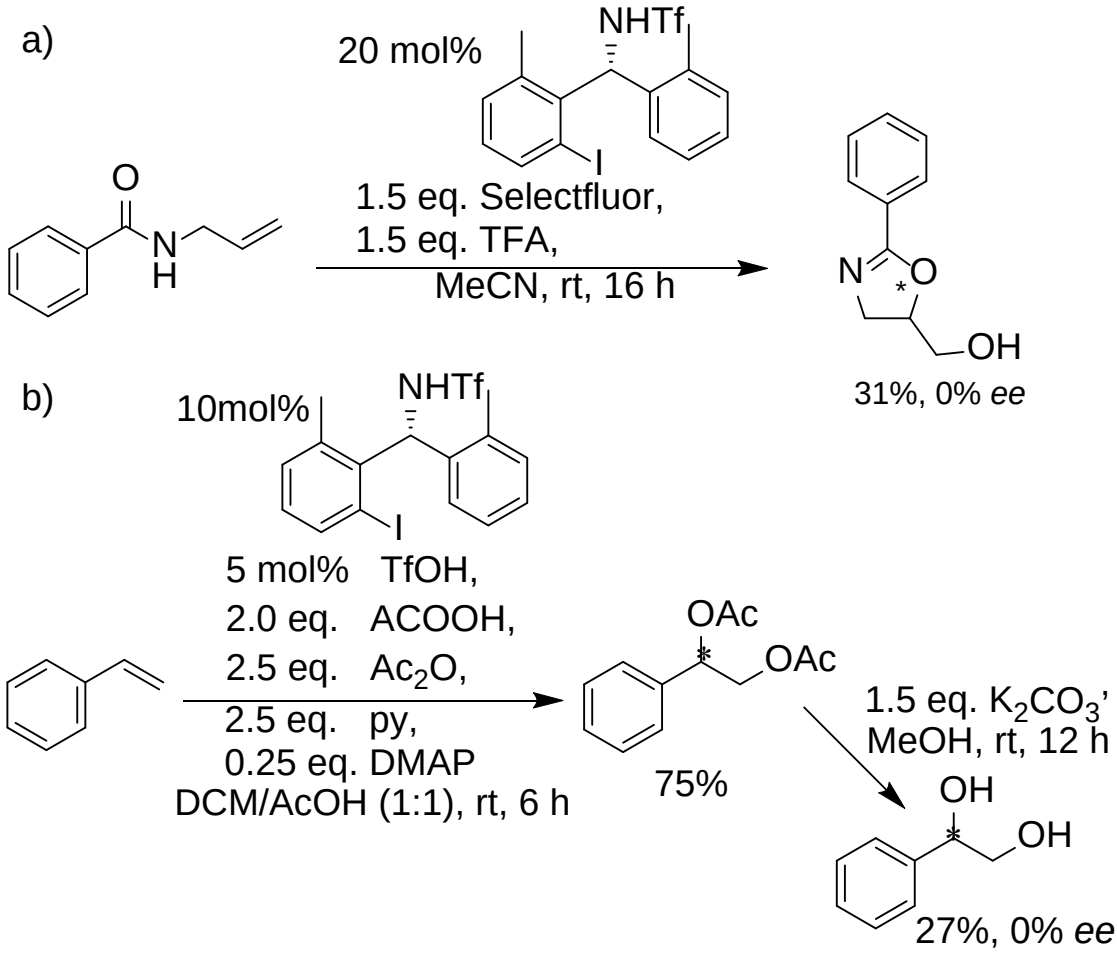
Tol: toluene.

W: Watts.

Abstract

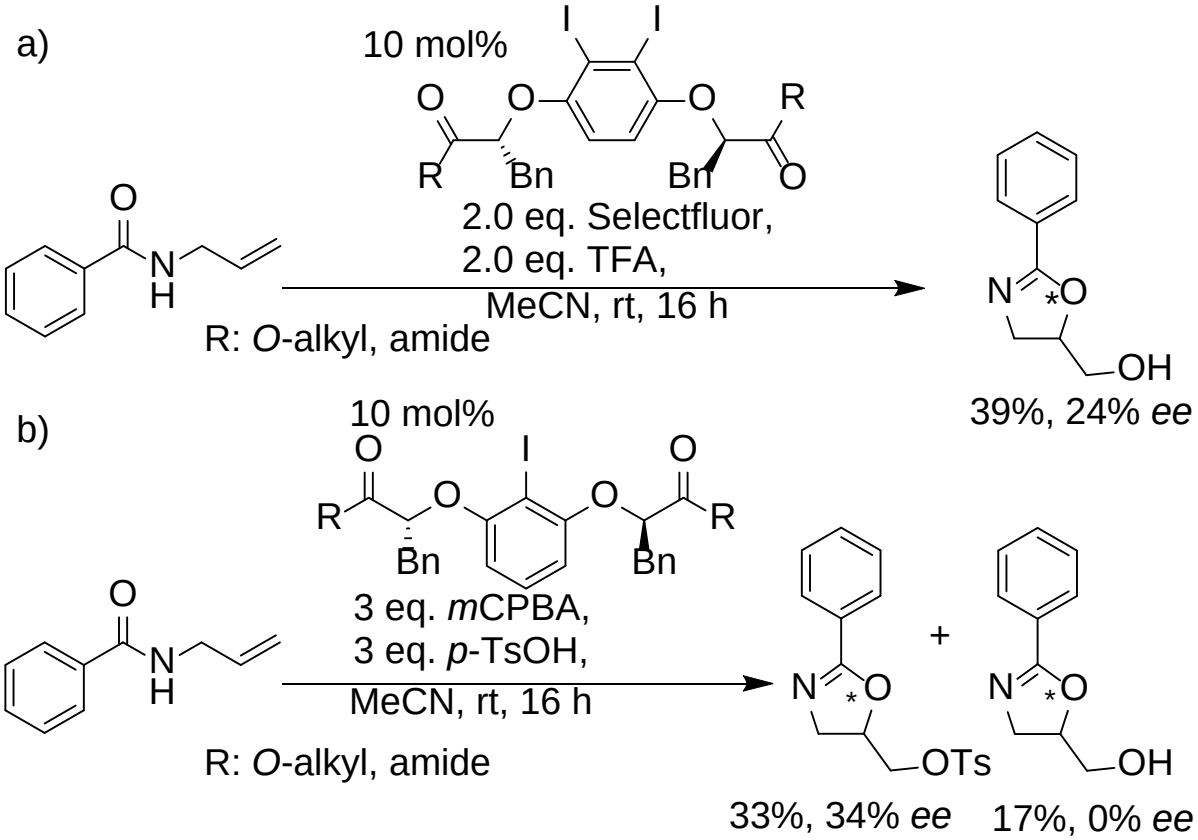
This thesis covers the design and development of a range of chiral iodoarenes and their investigation into the asymmetric cyclisation of *N*-allylbenzamide, *N*-allycarbamates and *N*-allyl-1*H*-pyrrole-2-carboxamide derivatives, or diacetoxylation of styrene.

The first part, describes the development of enantiomerically pure chiral iodo-diarylmethylamine$^{(I)}$ catalyst, oxidised to give the corresponding conformationally rigid iodine$^{(III)}$-diarylmethylamine species, evaluated in the catalytic enantioselective cyclisation of *N*-allylbenzamide (Scheme 1a) and the diacetoxylation of styrene (Scheme 1b).



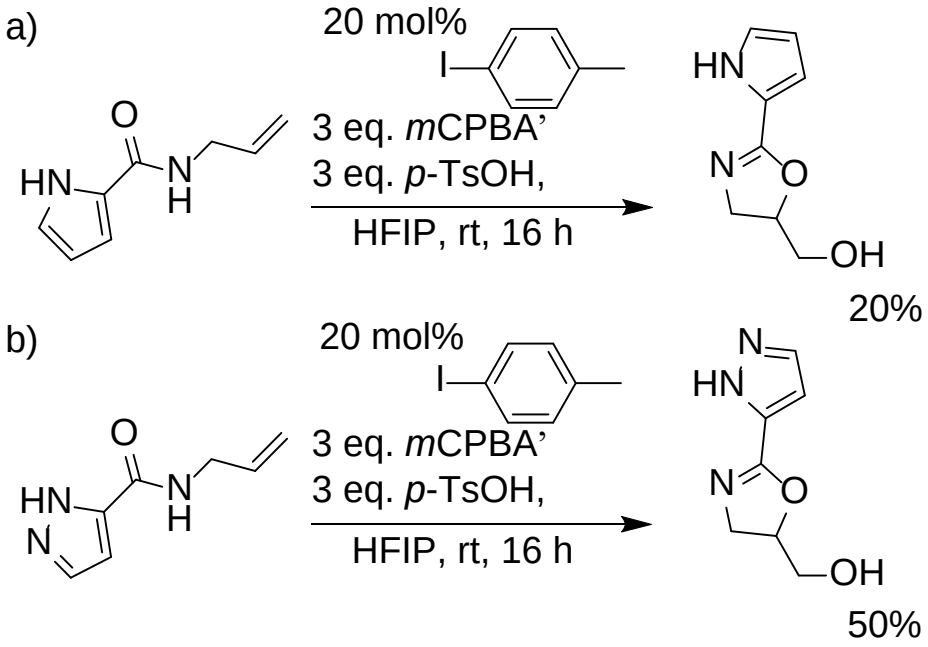
Scheme 1: Attempted Asymmetric Cyclisation of *N*-allylbenzamide and Diacetoxylation of Styrene

In the second part, illustrates the design and development of chiral monoiodo and diiodoarene lactate and lactamide precatalysts and their study into the catalytic asymmetric cyclisation of *N*-allylbenzamide using two sets of reaction conditions (Scheme 2a&b).



Scheme 2: Investigation of Chiral Iodoarene lactate and lactamide Catalysts

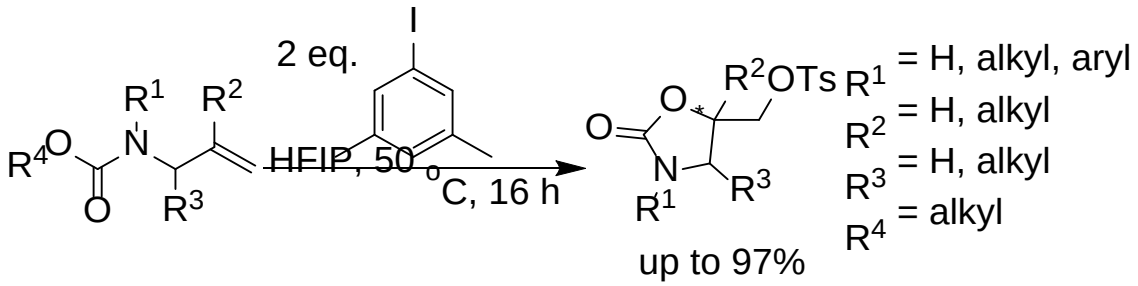
In the third part of the thesis, there is a report of attempts to cyclise *N*-allyl-1*H*-pyrrole-2-carboxamide derivatives (Scheme 3a&b) and modification of the substrate and reaction conditions to bring about cyclisation.



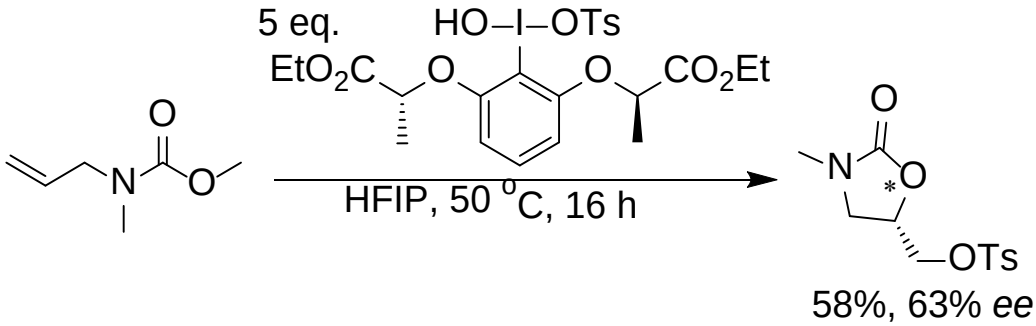
Scheme 3: Cyclisation of *N*-allyl-1*H*-pyrrole-2-carboxamide and Derivative

The final part elaborates on the comprehensive development of the cyclisation of carbamates. It depicts solvent screening, preparation and screening of a range of Koser's Reagent derivatives and carbamate substrates and cyclised product scope (Scheme 4a). The development of a one-step preparation of the novel Koser's Reagent derivative is illustrated and attempts to make the reaction catalytic or microwave-assisted are described. The development of a one-pot *in situ* generation of the hypervalent iodine(III) species followed by the cyclisation reaction is shown. It reports a chiral Koser's derivative could bring about asymmetric cyclisation with moderate enantioselectivity (Scheme 4b) and

that an oxazolidinone drug analogue could be synthesised using the reaction.



Scheme 4a: Cyclisation of *N*-allyl-carbamates

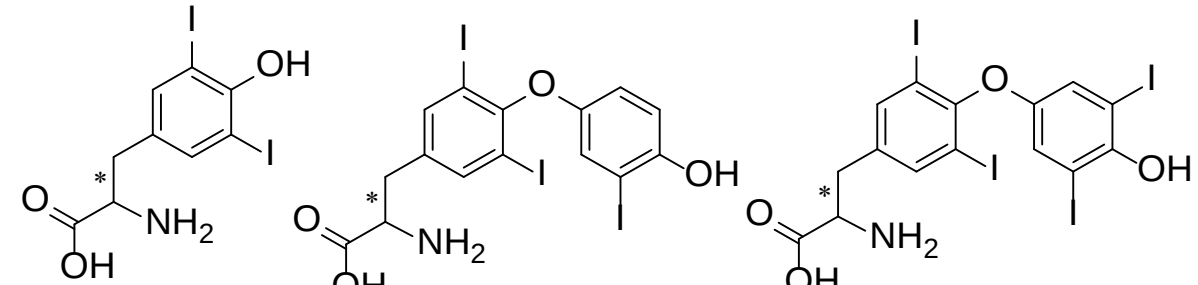


Scheme 4b: Cyclisation of *N*-methyl allyl(methyl)carbamate

1. INTRODUCTION

1.1 Iodine

The goiter-preventing effects of seaweeds containing iodine were known to the Chinese emperor Shen-Nung *circa* 3000 BC.[1] In 1811, Barnard Courtois discovered a pungent, violet vapour was generated while producing potassium nitrate from seaweed ashes.[1,2] In 1813, Joseph Louis Gay-Lussac named the substance iodine, his research showed that the novel material was an element similar to chlorine. Its name is derived from the Greek word iodes, meaning violet, from crystalline iodine's deep purple appearance.[1,2] Iodine is a nutrient fundamental to life and is crucial to human health. Iodine is required to make thyroid hormones such as diiodotyrosine **1**, triiodothyronine **1.1**, thyroxine **1.2**, needed for many bodily processes including growth, metabolism regulation, and vital for brain development in the early stages of pregnancy (Figure 1).[1,3,4] Iodine is present in a variety of foods, high concentrations are found in fish and dairy products, seaweed is a concentrated source of iodine.[3] Annual production is about 30,000 tons approximately 90% of world iodine is produced in Chile (50-60%) from caliche deposits and Japan (30-40%), extracted from brines from natural gas and oil fields.[1,5]



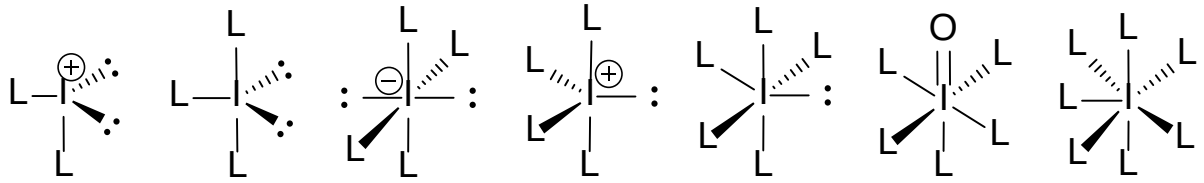
Diiodotyrosine **1** Triiodothyronine **1.1** Thyroxine **1.2**

Figure 1: Iodine Compounds Synthesised in the Human Body[4]

1.2 Iodine Chemistry

Iodine, I, is a bluish-black solid and has a glittering crystalline lustre. It slowly sublimes to a deep violet vapour and melts at 113.7 ˚C and turns dark brown. Iodine has an atomic mass of 129.9044, atomic number 53, is a non-metallic, non-radioactive element of the group 17 halogens. The electronic configuration of iodine is $4d^{10}5s^{2}5p^{5}$, with only one stable isotope that has a relative atomic mass of 127. Belonging to the main p-block group of elements, its properties, structural features, bonding, and reactivity differ from the lighter p-block elements.[1]

Iodine in organic or inorganic compounds can be found in a range of oxidation states such as -1, 0, +1, +3, +5, +7; organic compounds of trivalent and pentavalent iodine are referred to as hypervalent iodine compounds in modern literature. Polyvalent hypervalent iodine compounds **1.3**-**1.9**, can be categorised using the Martin–Arduengo *N-X-L* nomenclature, where *N* is the number of valence electrons on the central atom, *X*, either as unshared electron pairs or electrons pairs in sigma bonds attached ligands, where *L,* is the number of ligands (Figure 2).[2]



	10-I-3	*12-I-4*	*10-I-4*	*12-I-5*	*14-I-6*	*14-I-7*
1.3	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**

Figure 2: Typical Geometry of polyvalent iodine compounds[1,2]

1.3 Hypervalent Iodine Bonding

Hypervalent refers to elements in groups 15-18 that form molecules in any of their valences except in their lowest stable chemical valence of 3,2,1, and 0 respectively.[6] These elements exceed the number of valence shell electrons allowed by the Lewis-Langmuir theory, to impart stability.[7] These elements "expand" their valence shell by inserting, co-linearly, two ligands, along the axis of a pair of p electrons. These two p electrons provide the binding for the two ligands in the bond, this type of bond is called a hypervalent, three-centre-four-electron (3c-4e$^-$) bond,[6,2] It is different from covalent bonds because only one donor orbital forms two bonds. Hypervalent bonding occurs in iodine due to an overlap of the non hybridised 5p orbital with suitable orbitals on the two ligands (L) creating a linear L–I–L bond. The electronic configuration of polyvalent iodine can be described by the hypervalent bonding model (Figure 3).[2]

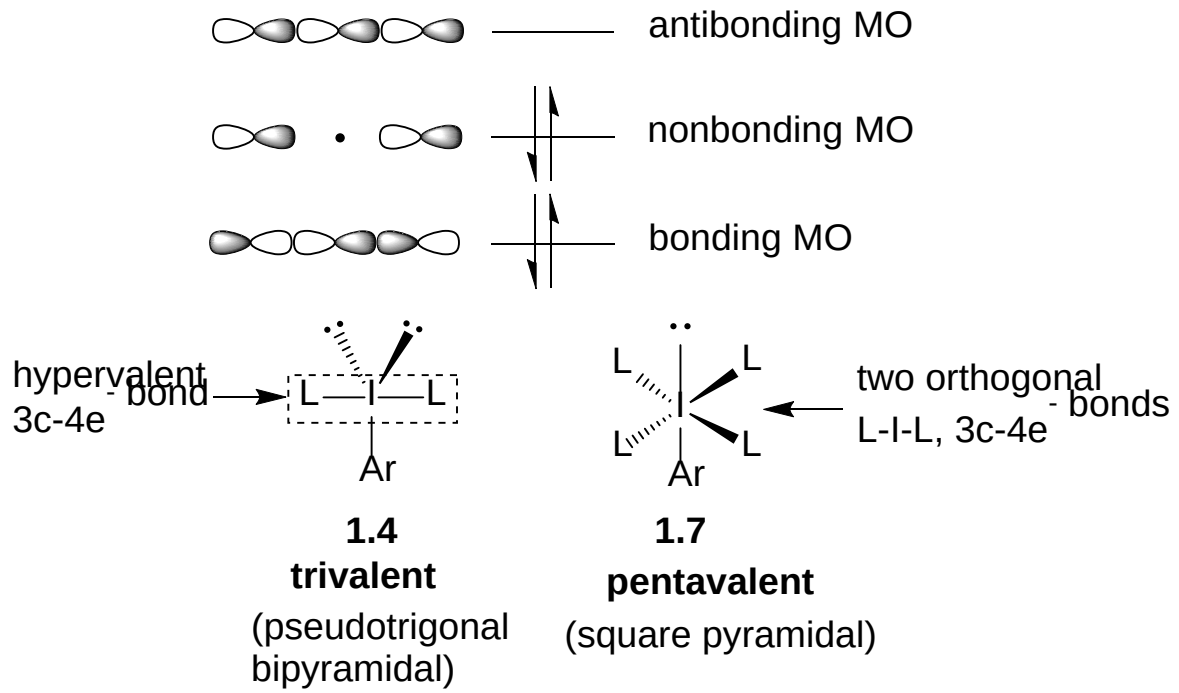
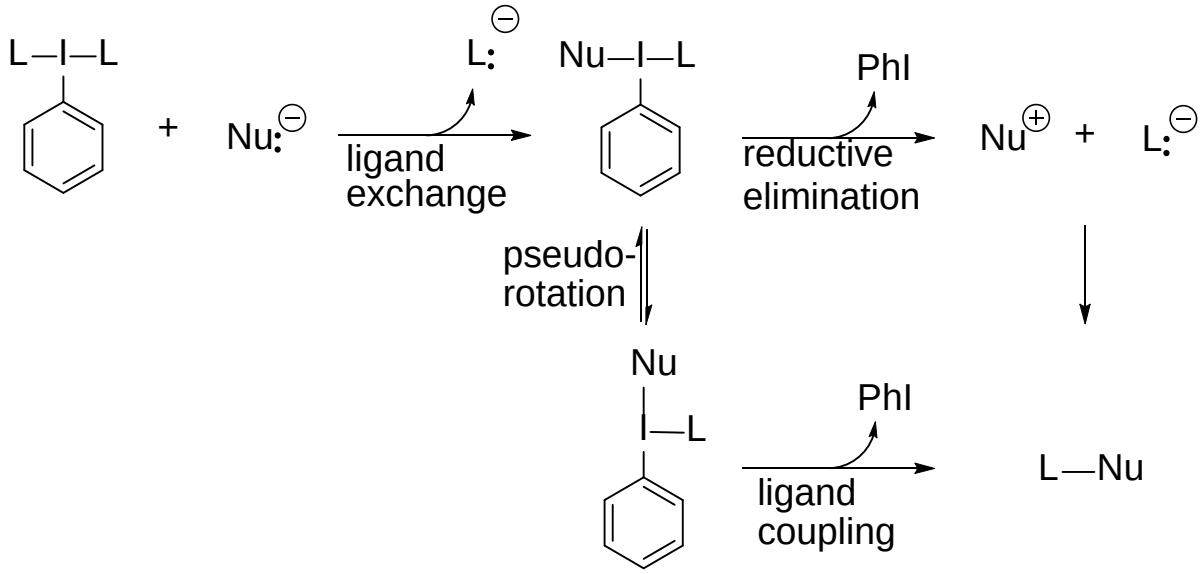


Figure 3: MO Description of 3c-4e$^-$ bonds in λ^3 and λ^5 Iodanes[2]

1.4 Hypervalent Iodine Reactivity

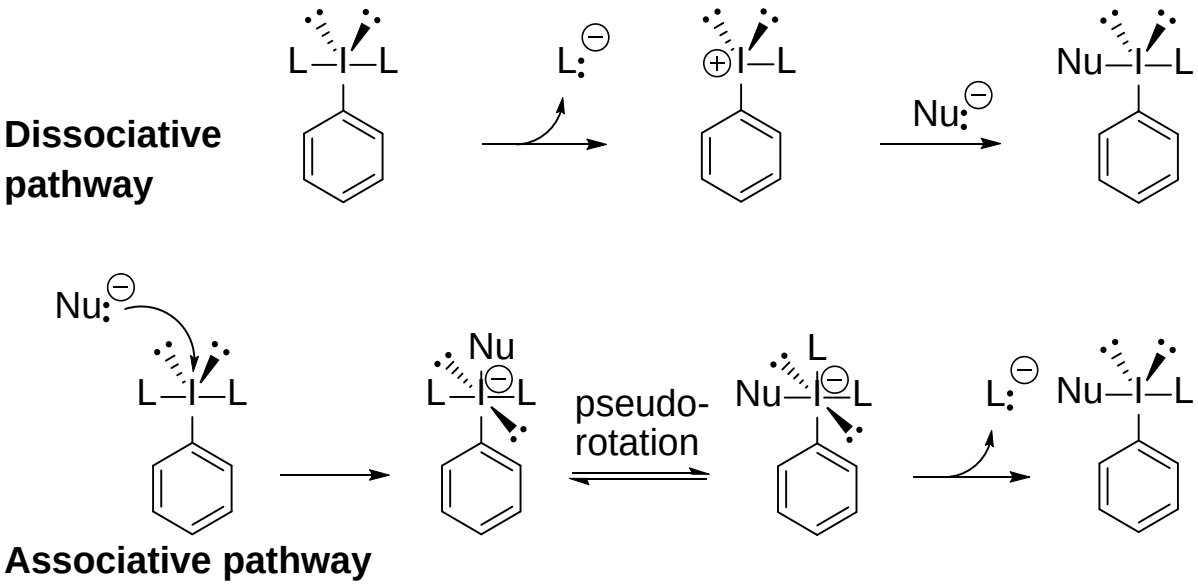
Hypervalent bonds are highly polarised and longer and weaker than common covalent bonds and confer unique structural features and reactivity. Hypervalent iodine reactivity pattern is like that of transition metals and lends itself to be used in similar ways such as catalysis. Reactions with hypervalent iodine reagents can be described in terms of oxidative addition, ligand exchange, pseudorotation is also known as positional isomerisation, reductive elimination and ligand coupling, which are characteristic of transition metal chemistry (Scheme 5).[2]



Scheme 5: Simplified Reactions of Iodine(III) Iodanes with Nucleophiles[2]

1.5 Reaction Mechanics

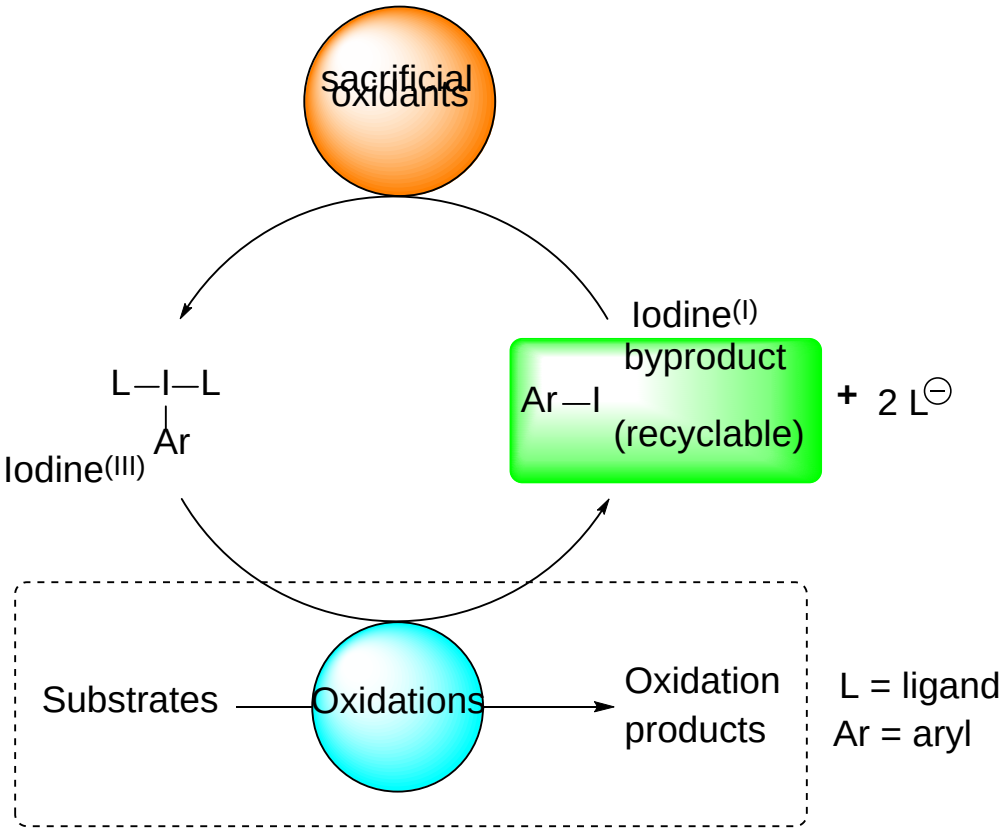
Typically hypervalent iodine(III) reactions start with ligand exchange with a nucleophile, thereafter reductive elimination of iodobenzene or a concerted ligand coupling process occurs. The ligand exchange process can be further subdivided into two possible pathways, associative and dissociative (Scheme 6).[2]



Scheme 6: Ligand Exchange Pathways for iodine(III) Iodanes[2]

1.6 Hypervalent Iodine Catalysis

The unique reactivity pattern of hypervalent iodine compounds is typically seen with transition metal chemistry.[5] Iodine compounds are stable, have low toxicity, easy to handle, are environmentally benign, recyclable, and are relatively inexpensive in contrast to heavy metals such as chromium, lead, platinum, and mercury.[8] Bulk iodine prices for the last 10 years has been in the range of $20–100 per kg.[2] Hypervalent iodine compounds have attracted significant interest due to the discovery of various catalytic oxidative transformations, forming C—O, C—N, and C—C, C—X bonds in organic molecules (X = halogen).[5,9] These catalytic oxidations are alike to transition metal catalysed reactions, but are under mild reaction conditions and are environmentally sustainable (Scheme 7).[8]

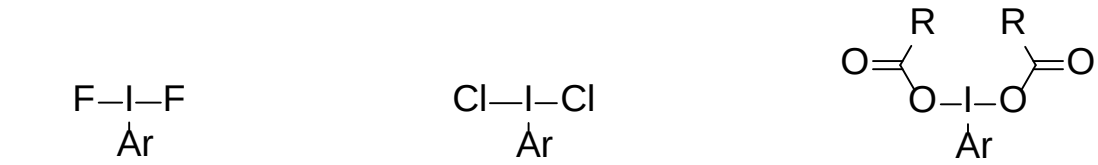


Scheme 7: General iodine(III) Iodane Catalytic Oxidation Reaction[2]

1.7 Hypervalent Iodine Reagents

Generally, hypervalent iodine reagents belong to two main groups:

- Trivalent Iodine(III) species known as λ^3 iodanes featuring a pseudo-trigonal-bipyramidal geometry (Figure 4).[2]
- Pentavalent Iodine(V) species called λ^5 iodanes featuring a square pyramidal geometry (Figure 5).[2]



(difluoroiodo)arenes **1.10**

(dichloroiodo)arenes **1.11**

[bis(acyloxy)iodo]arenes
R = CH_3 **1.12a**, CF_3 **1.12b**

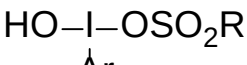
$(ArIO)_n$

iodosylarenes

1.13

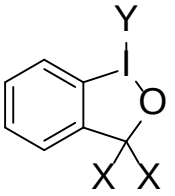
[hydroxy(tosyloxy) iodo]arenes, (HTIB)

1.14



aryliodine(III) organosulfonates
R = CH_3, CF_3, C_2H_5, C_6H_5, ClC_6H_4, $C_{10}H_{15}O$, $NO_2C_6H_4$

1.15



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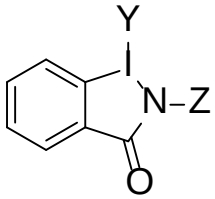
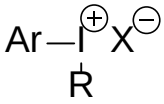


1.17

or 2X = O,
X = Me, CF_3
Y = OH, OAc, N_3, CN, etc.
Z = H, Ac, etc.



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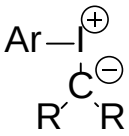

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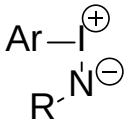
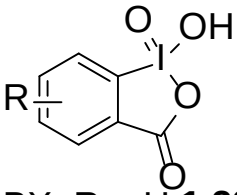


1.20

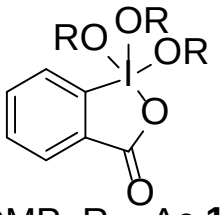
Figure 4: Common Classes of λ^3 Iodanes[2]

$ArIO_2$

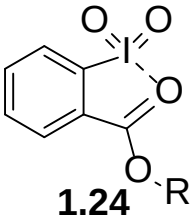
1.21



IBX, R = H **1.22**



DMP, R = Ac **1.23**



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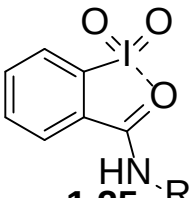

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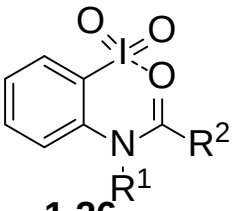

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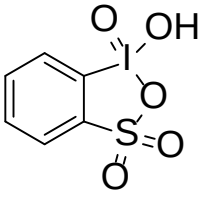
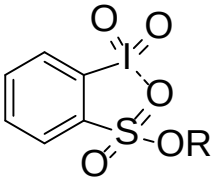


IBS **1.27**



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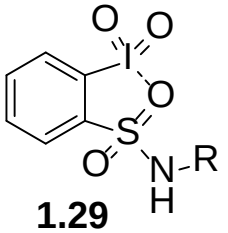
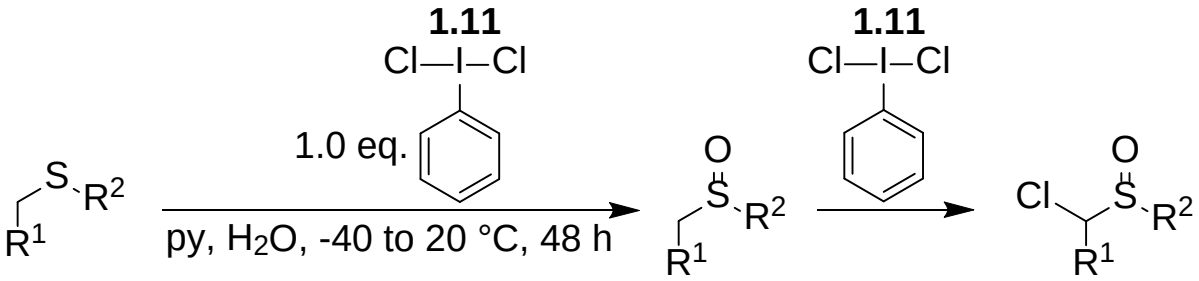


1.29

Figure 5: Common Classes of λ^5 Iodanes[2]

1.8 Historical Hypervalent Iodine(III) Applications

(Dichloroiodo)benzene ($PhICl_2$) **1.11** was the first organic polyvalent iodine compound synthesised by C. Willgerodt, in 1885.[10] Approximately 50 years later it found use as a chlorinating agent for rubber, by Bloomfield.[11] The oxidation of sulfides and selenides by Barbieri and coworkers in 1968 is one of the first examples of (dichloroiodo)benzene ($PhICl_2$) **1.11** being used in an oxidative transformation (Scheme 8).[11,12] Excess hypervalent iodine(III) reagent and longer exposure time to the reaction conditions also caused chlorination.[11,12]



Scheme 8: Oxidation of Sulfides with (Dichloroiodo)benzene[11,12]

1.9 Evolution of Chiral Hypervalent Iodine(III) Transformations

In 1906, the German chemist Richard Pribram prepared the first chiral hypervalent iodine reagent **1.30**, by reacting diphenyliodonium hydroxide solution with *L*-tartrate salts, titrated from wine liquor.[13] He did not elaborate on the structure of the product, however, later Wirth in 1997, thought it to be diphenyliodonium *L*-tartrate **1.31** but Parra in 2013 suggested alternative structures **1.32** (Figure 6).[14,15]

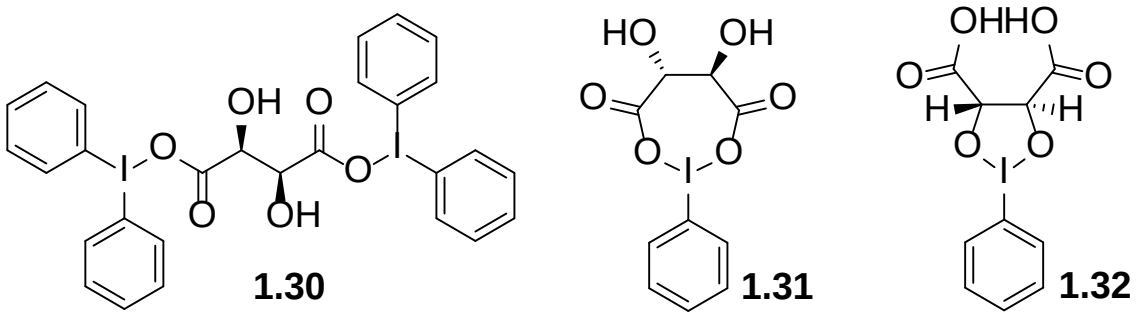
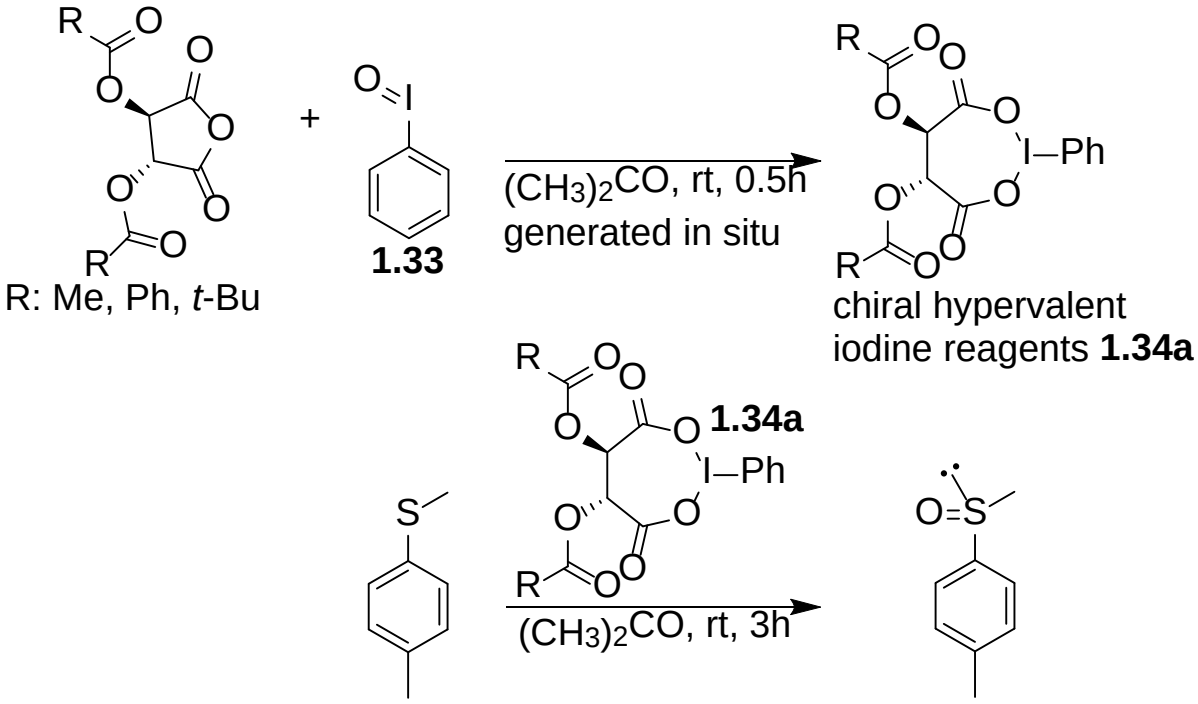


Figure 6: Postulated Structures of Pribram's Chiral Molecule[13,14,15]

1.9.1 New Class of Chiral Iodine(III) Reagents

However, it wasn't until 1986 when Imamoto and Koto described a new class of chiral trivalent iodine reagents, which they used to bring about asymmetric oxidation of sulfides into sulfoxides. These chiral reagents were generated *in situ* by reacting iodosylbenzene **1.33** with derivatives of *L*-tartaric acid anhydrides (Scheme 9). Imamoto and Koto measured the specific rotation of the isolated products to calculate the optical yields. They tried to produce analogues of their new reagent **1.34a** using iodosylbenzene **1.33** and acetyl-*L*-lactic acid, despite the reagent facilitating the desired sulfoxide in 91% yield, the optical yield crashed to 1%. They cited C_2-symmetry in the chiral molecule as crucial to controlling enantioselectivity.[16]



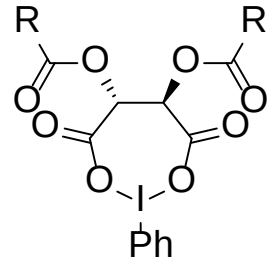
entry	chiral reagent, R	Product Yield, %	*ee*, %
1	Me	95	30 (S)
2	Ph	73	36 (S)
3	*t*-Bu	80	40 (S)

Scheme 9: Asymmetric Oxidation of Sulfides[16]

1.9.2 Chiral Koser's Derivatives

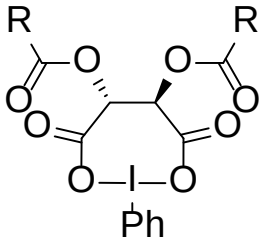
Four years later, Koser and Ray prepared both enantiomers of [menthyloxy(tosyloxy)iodo]benzene (MnTIB) **1.35**, a chiral Koser's derivative. Through ligand exchange with [methoxy(tosyloxy)iodo]benzene (MTIB) **1.36**, and equimolar of *R* or *S* menthol in dichloromethane they achieved nearly quantitative yields of the chiral Koser's derivative **1.35**. Using these chiral reagents in the oxidation of sulfides to chiral sulfoxides they managed to achieve 88% yield and up to 99% *ee*.[17] 1992, Koser and Ray revisited the work of Imamoto and Koto and conducted structural studies of their chiral reagent.[18] Koser and coworkers were the first to report the structure **1.34b** possessed T-shaped

geometry about the iodine. They proposed that the structure had a high energy configuration, and that the I-O bond was highly strained. Koser and Day repeated Imamoto and Koto's chiral reagent reaction and characterised the structure, they discovered it formed iodine(III) tartrate polymer **1.34c** (Figure 7).[16,18] Using the iodine(III) tartrate polymer **1.34c** in Imamoto and Koto's asymmetric oxidation of *para*-tolyl methyl sulfide they obtained the same optical yield of 36%. Significantly, in contradiction to Imamoto and Koto's assertion that C_2-symmetry is crucial to enantioselectivity, these iodine(III) tartrate polymers did not possess such C_2-symmetry.



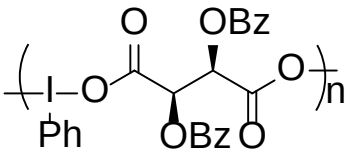
Imamoto and Koto's proposition

1.34a



Koser's and Ray's T shaped proposition

1.34b



iodine(III) tartarate polymer

1.34c

Figure 7: Koser's Structural Elucidation[16,18]

1.10 Strategies to Control Stereoselectivity

Asymmetric reactions can be achieved by using chiral hypervalent iodine(III) reagents or by using achiral hypervalent iodine(III) compounds in combination with chiral ligands. Hypervalent iodine compounds can be employed in stoichiometric, catalytic, or even excess quantities.[8] Chiral reagents or precatalysts can be designed and developed using similar strategies employed with transition metal asymmetric catalysis to maximise their enantioselectivity properties. Known chiral organoiodine(I) precatalysts or reagents which are precursors to their hypervalent

iodine(III) species display C_1 or C_2 symmetry with central, axial, or planar chirality.[9]

Essentially two classes of hypervalent iodine(III) structures can be identified:

- **Class I reagents:** A carbon substituent and two heteroatom ligands are attached to the central iodine atom to make up the hypervalent iodine(III) structure. The ligands are located in apical positions with a pseudotrigonal bipyramidal arrangement, they are effective for oxidation reactions (Figure 8a).[19]
- **Class II reagents:** Two carbon substituents and a single heteroatom ligand is attached to the central iodine atom to form the hypervalent iodine(III) species, they are effective for carbon substituent transfer and poor at oxidation reactions (Figure 8b).[19]

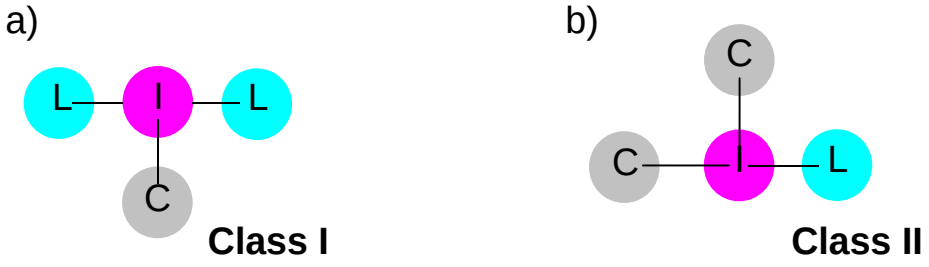


Figure 8: General Reactivity Pattern

Stereocontrol strategies could be categorised into four types depending on the kind of chirality installed:

Type I: chiral iodoarenes utilising central chirality i.e. containing one or more stereogenic centre in the carbon fragment, oxidised *in situ* to generate the corresponding chiral hypervalent iodine(III) compound. Chiral features are installed using chiral alcohols, amino alcohols, amines, and amino acids, esters, ethers, etc.; chiral groups can form co-ordinate bonds aiding intramolecular stability (Figure 9). To date, limited chiral

induction has been achieved, however, there are some asymmetric reactions with high enantiomeric excess.[19]

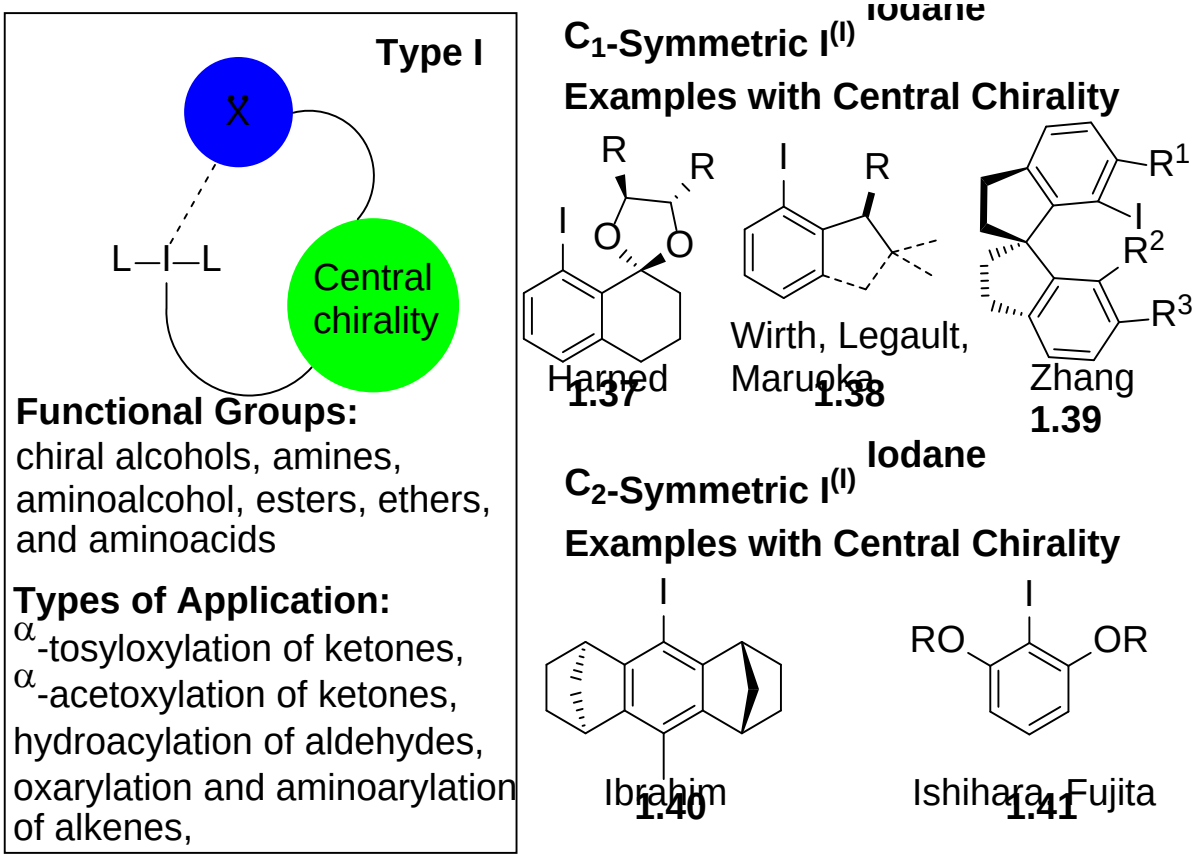


Figure 9: C_1 and C_2-Symmetric Iodoanes with Central Chirality[8,9,19,20,21,22]

Type II: chiral iodoarenes incorporates axial chirality using chiral biphenyls and binaphthyls to induce high stereoselectivity. Masson's C_2-symmetrical catalyst **1.42** gave an impressive 94% *ee* in the hydroxylative dearomatisation of phenols, and Ochiai's catalyst **1.43** achieved 53% *ee* in the α-arylation of β-ketoesters (Figure 10).[19]

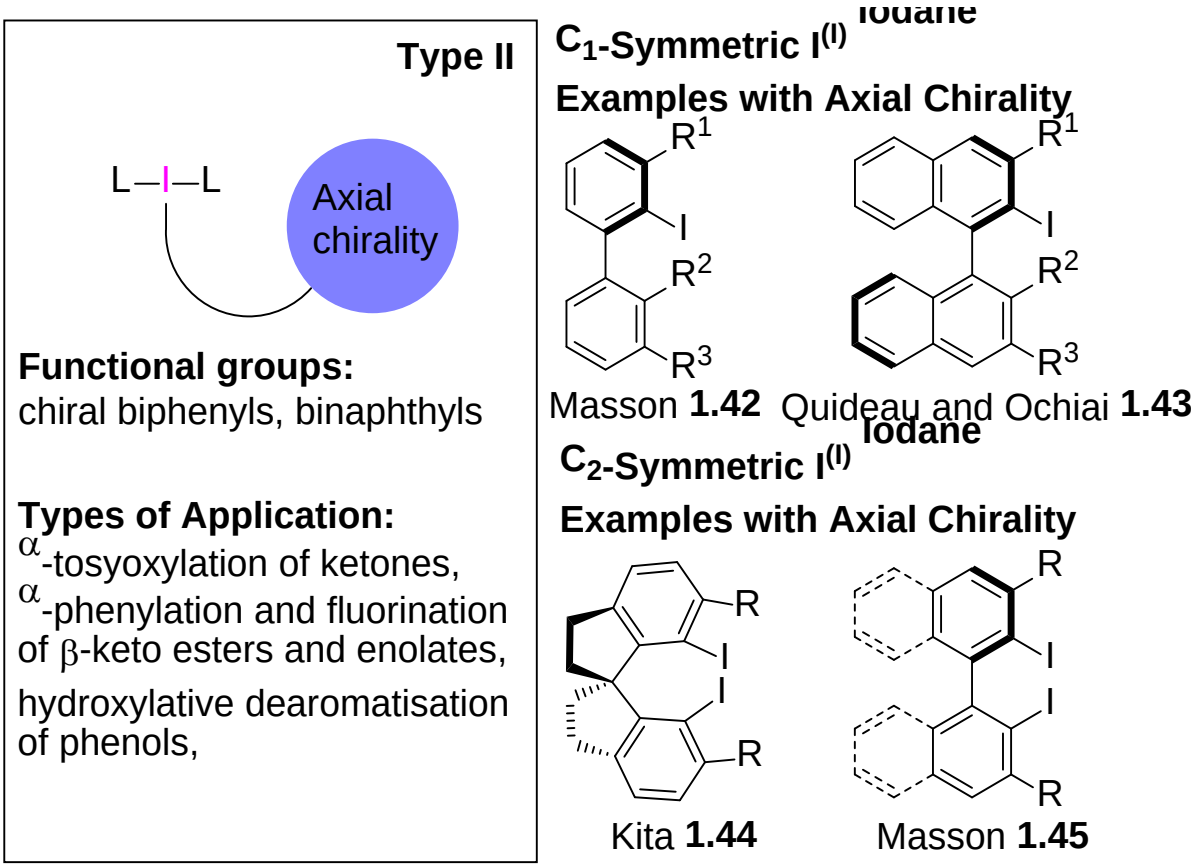


Figure 10: C_1 and C_2-Symmetric Iodoarenes with Axial Chirality[9,19,20]

Type III: chiral iodoarenes typically incorporate flat or planar chirality to induce selectivity. Wirth's catalyst **1.46** only gave racemic products in asymmetric α-oxytosylation of ketones. Zheng's planar catalyst **1.47** was employed at 15 mol% loadings in the enantioselective dearomative lactonisation of naphthols and achieved up to 72% *ee*. However, when Zheng and coworkers employed it in the fluorination of β-ketoesters they attained 92% *ee* (Figure 11).[9,19,20]

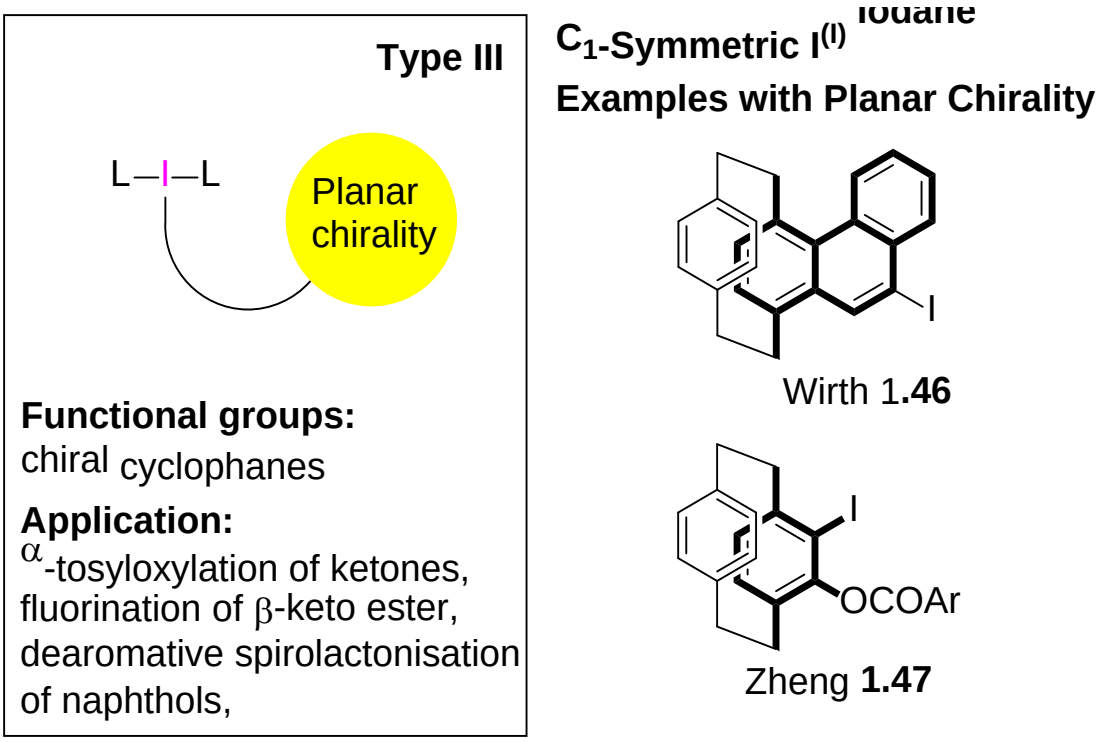


Figure 11: C_1-Symmetric Iodoarenes with Planar Chirality[9,19,20,23,24,25]

Type IV: chiral iodoarenes bearing helical chirally from lactate or lactamide appendages. These types of catalysts have surfaced as the leading strategy in hypervalent iodine asymmetric catalysis. Fujita and Ishihara developed this approach in 2010, and have enjoyed excellent enantioselectivity for many different reactions. Kita oxidative dearomatisation of naphthols using Wirth's catalyst **1.50** giving 99% *ee*, Legault's catalyst **1.48** in α-oxytosylation of enolacetates gave 90% *ee*, and Fujita's catalyst **1.49** gave 89% *ee* in diacetoxylation of alkenes (Figure 12).[9,21,22]

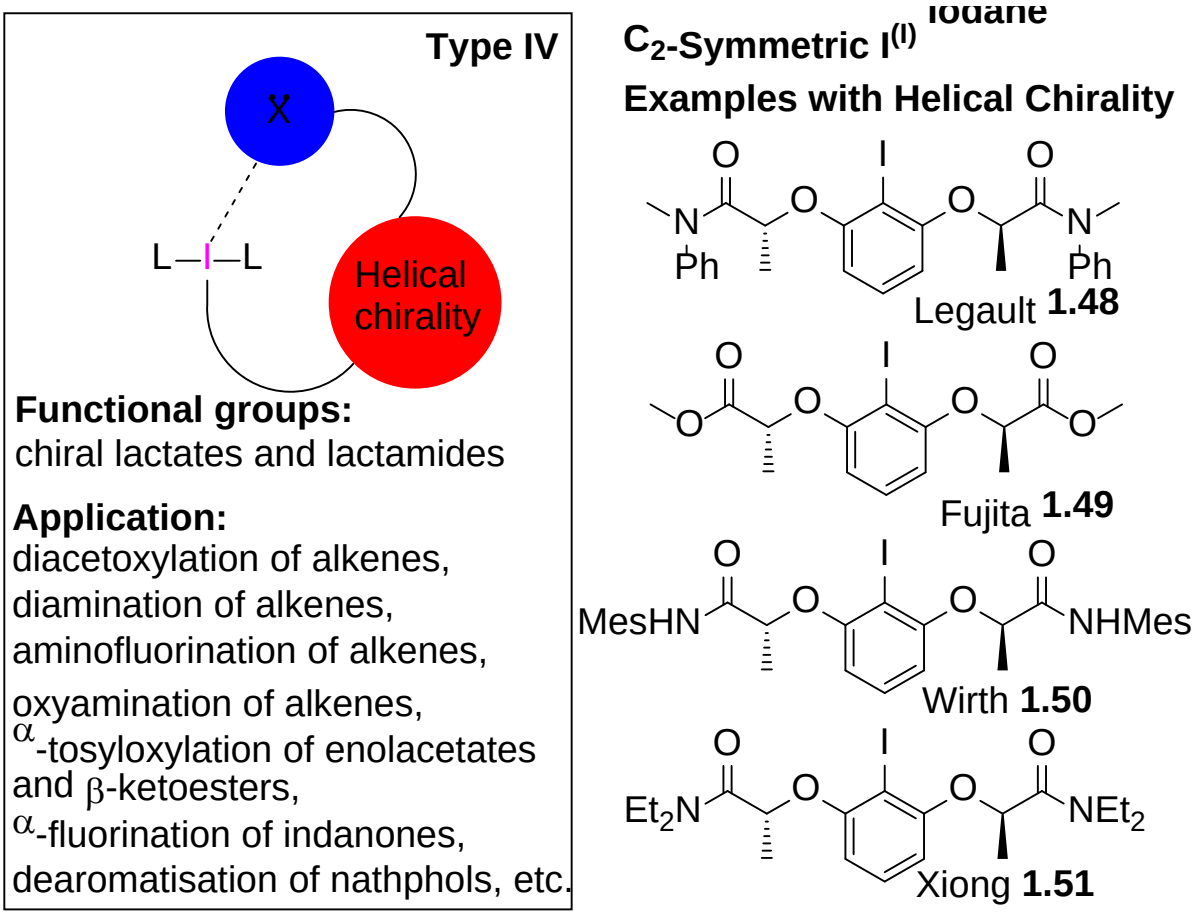
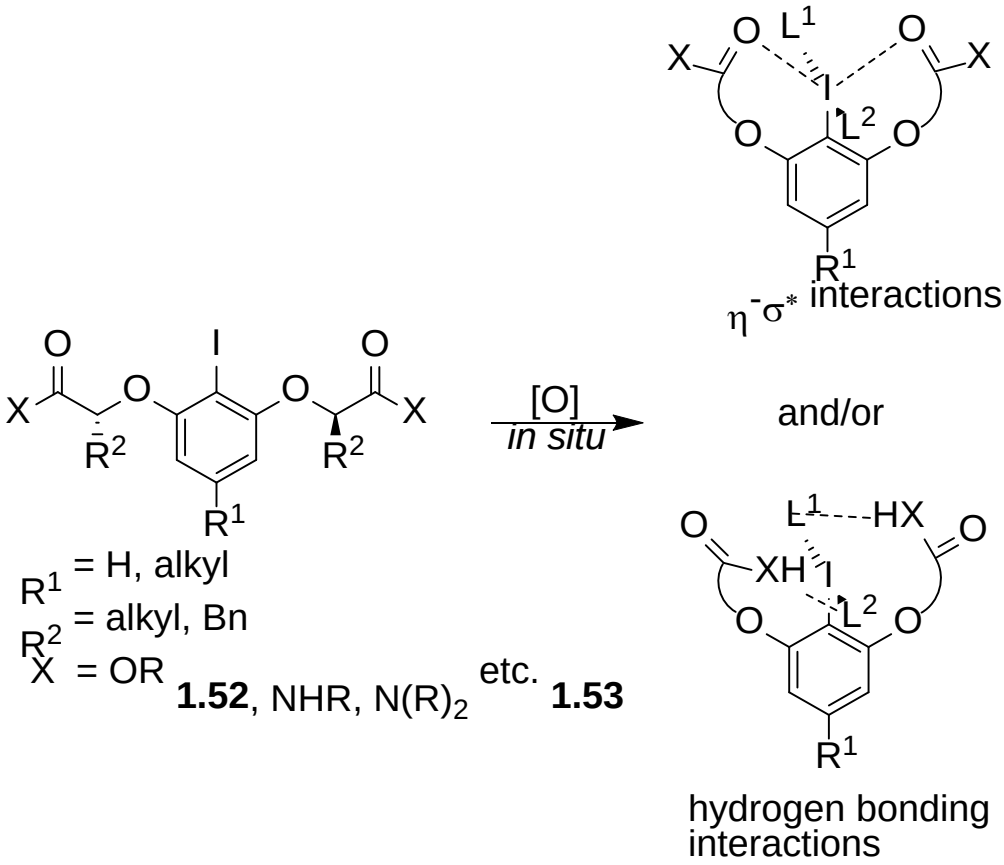


Figure 12: C_2-Symmetric Iodoarenes with Helical Chirality[20,9,19]

1.10.1 Helical Chirality

These C_2-symmetrical chiral iodoarene catalysts derived from a resorcinol centre and conformationally flexible chiral lactate ester **1.52** or lactamide **1.53** appendages rely on helical chirality. This helical chirality is thought to arise from the capability for secondary n–σ* and/or hydrogen bonding interactions between the carbonyl moiety and the generated iodine(III) species (Scheme 10).[9,19,20]



Scheme 10: Hypothetical Helical Structural Arrangements[20,9,19]

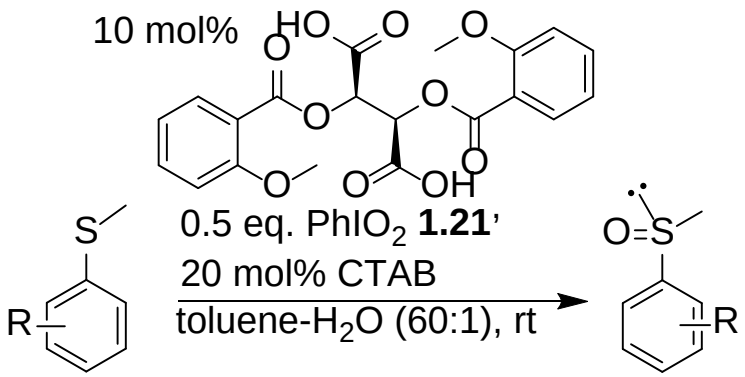
1.11 Main Types of Enantioselective Transformations

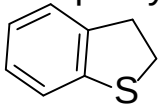
1.11.1 Oxidation of Sulfides

Many biologically and chemically active molecules are constructed from sulfoxides and sulfones. Oxidation of sulfides is an essential reaction to access sulfoxides and sulfones. Reagents such as peracids are employed in the oxidation of sulfides. Some of these reactions often result in the formation of various environmentally unfriendly byproducts and suffer from low oxygen atom efficiency. The development of environmentally friendly catalysts and oxidants is of great importance in the pursuit of greener chemistry.[26]

Asymmetric Sulfoxidation

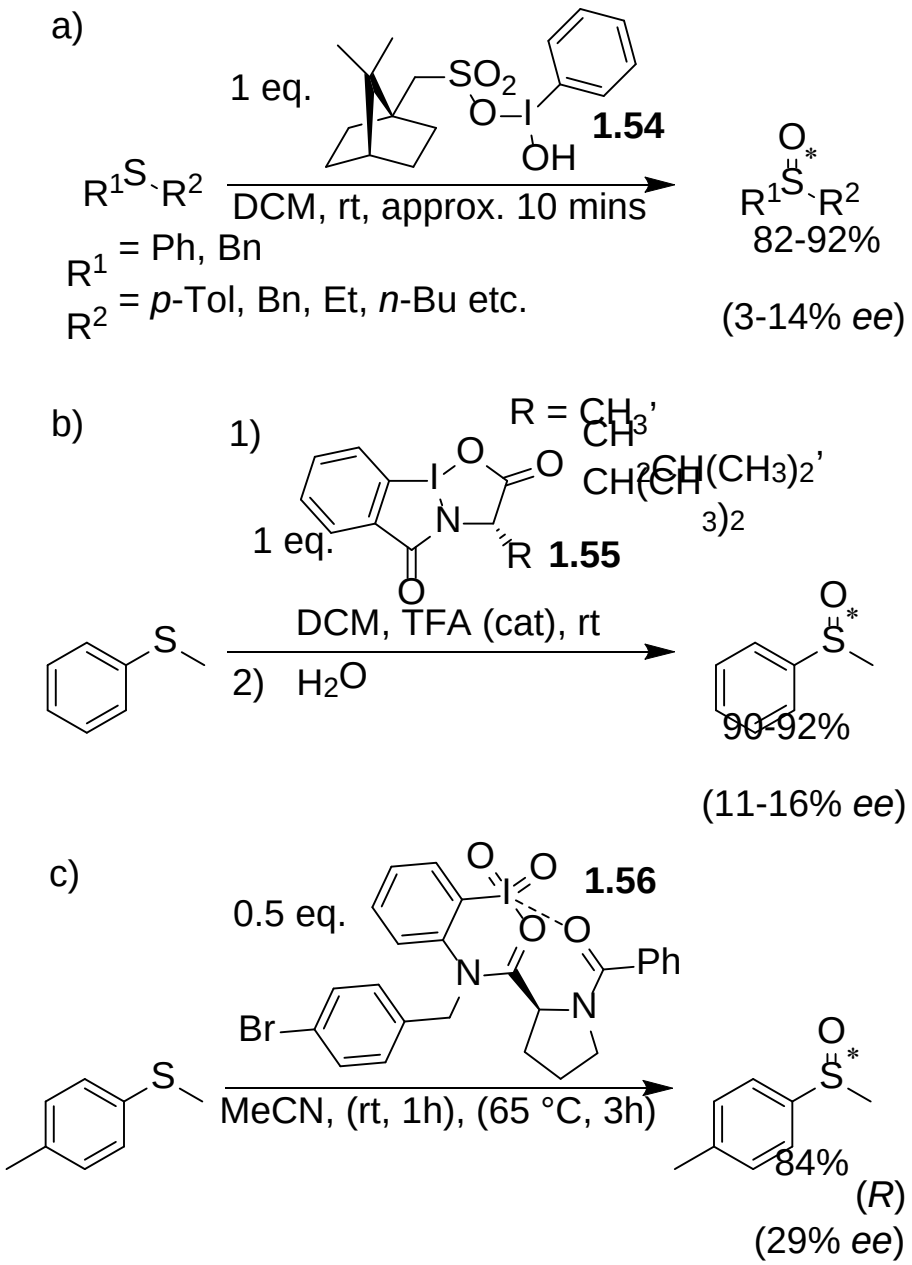
Before Kita and coworker's paper in 1999, chiral hypervalent iodine reagents generally required at least stoichiometric quantities in asymmetric oxidations. Kita and colleagues reported the first catalytic asymmetric oxidation of sulfides to sulfoxides using a novel chiral iodine(V) reagent generated *in situ*. They activated iodoxybenzene ($PhIO_2$) **1.21** by adding catalytic quantities of both cetyltrimethylammonium bromide (CTAB) and di(2-methoxy)benzoyl-*L*-tartaric acid in toluene and water to create a reverse microemulsion system. They achieved excellent yields and up to 72% *ee* (Scheme 11).[27]



entry	Substrate reagent, R	Time, h	Product Yield, %	*ee*, %
1	4-Me	2	quant	53 (*S*)
2	4-NO_2	24	91	72 (*S*)
3	3-NO_2	42	94	64 (*S*)
4	4-CN	12	quant	65 (*S*)
5	4-Br	12	quant	58 (*S*)
6	4-MeO	42	quant	46 (*S*)
7	2-naphthyl	48	90	51 (*S*)
8		48	88	38 (*S*)

Scheme 11: Catalytic Asymmetric Oxidation of Sulfides[27]

Chen and Xia in 1997, reported the oxidation of sulfides to prepare sulfoxides using Koser's reagent **1.14**. They then tried a known chiral Koser's derivative **1.54**, [hydroxy(((1*R*)(+)-10-camphorosulfonyl)oxy)iodo]benzene as the oxidiser, but only managed to achieve 14% *ee* (Scheme 12a).[28,15] The prolific hypervalent iodine chemist Zhdankin and coworkers in 2000, synthesised novel hypervalent iodine(V) benziodazole oxides **1.55**. These novel reagents had similar oxidising properties to Dess-Martin periodinane (DMP) **1.23** but were non-explosive and soluble in common, non-polar solvents such as dichloromethane. 2-iodobenzamides were oxidised with potassium bromate in sulfuric acid, at 55 ˚C for 24 hours to access the benziodazole oxides. They used them in the selective oxidation of non-symmetrical sulfides, however, enantioselectivity was poor, only achieving up to 16% *ee* (Scheme 12b).[29] Zhdankin and coworkers tried again in 2006, to improve the enantioselecivity of the oxidation of sulfides. This time they prepared chiral *N*-(2-iodyl-phenyl)-acylamide (NIPA) **1.56** from (*S*)-proline using a four-step procedure. They managed to improve on their previously reported enantioselectivity, achieving 84% yield and 29% *ee* of the (*R*)-sulfoxide (Scheme 12c).[30]



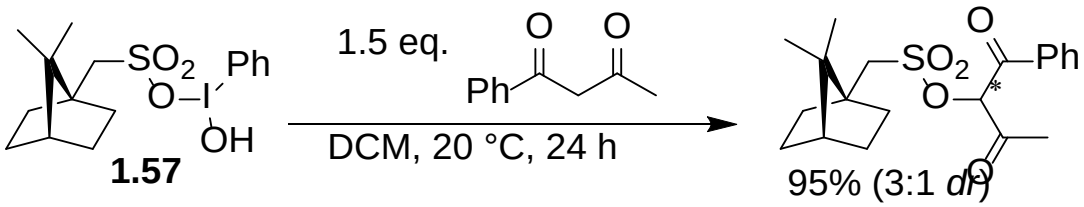
Scheme 12: Oxidation of Sulfides with Novel Chiral Iodine Reagents[28,15,29,30]

1.11.2 α-Functionalisation of carbonyl compounds

Carbonyl functionalisation at the α-position represents an important class of reaction due to their huge potential to access numerous α-substituted ketone derivatives. Koser’s and coworkers in 1982, used his namesake reagent **1.14** stoichiometrically to bring about the first α-oxytosylation of ketones.[31]

1.11.2.1 Asymmetric α-Oxytosylation of Ketones

Varvoglis and coworkers in 1990 assessed the effectiveness of their novel, chiral, Koser's derivative [hydroxy(((1*R*)(+)-10-camphorosulfonyl)oxy)iodo]benzene **1.57** on the asymmetric α-oxytosylation of ketones.[31,32] They created their novel chiral reagent by ligand exchange from (diacetoxyiodo)benzene and (1*R*)(+)-camphorsulfonic acid. Varvoglis and coworkers discovered improved regioselectivity in non-symmetrical ketones. However, the reaction generally suffered from poor stereoselectivity and only one product showed any significant stereoselectivity (3:1 *dr*) (Scheme 13).[32]



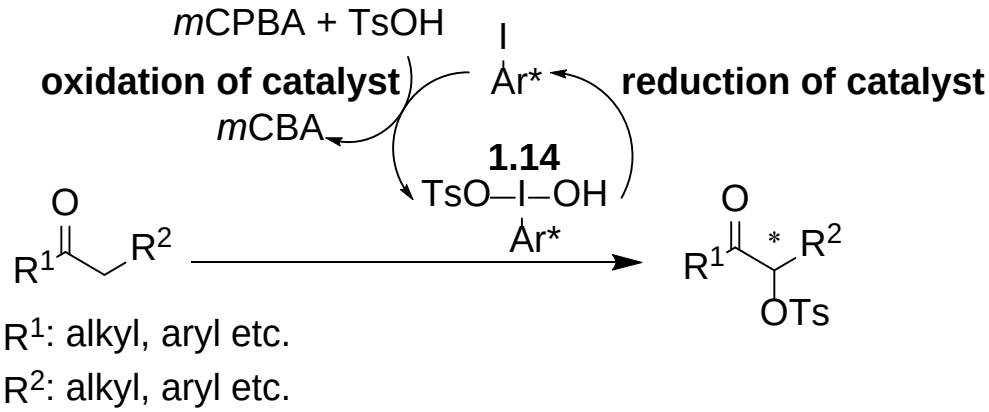
1.57

95% (3:1 *dr*)

Scheme 13: Varvoglis' α-Oxytosylation of Ketones[32]

1.11.2.2 Wirth's Search for Enantioselectivity

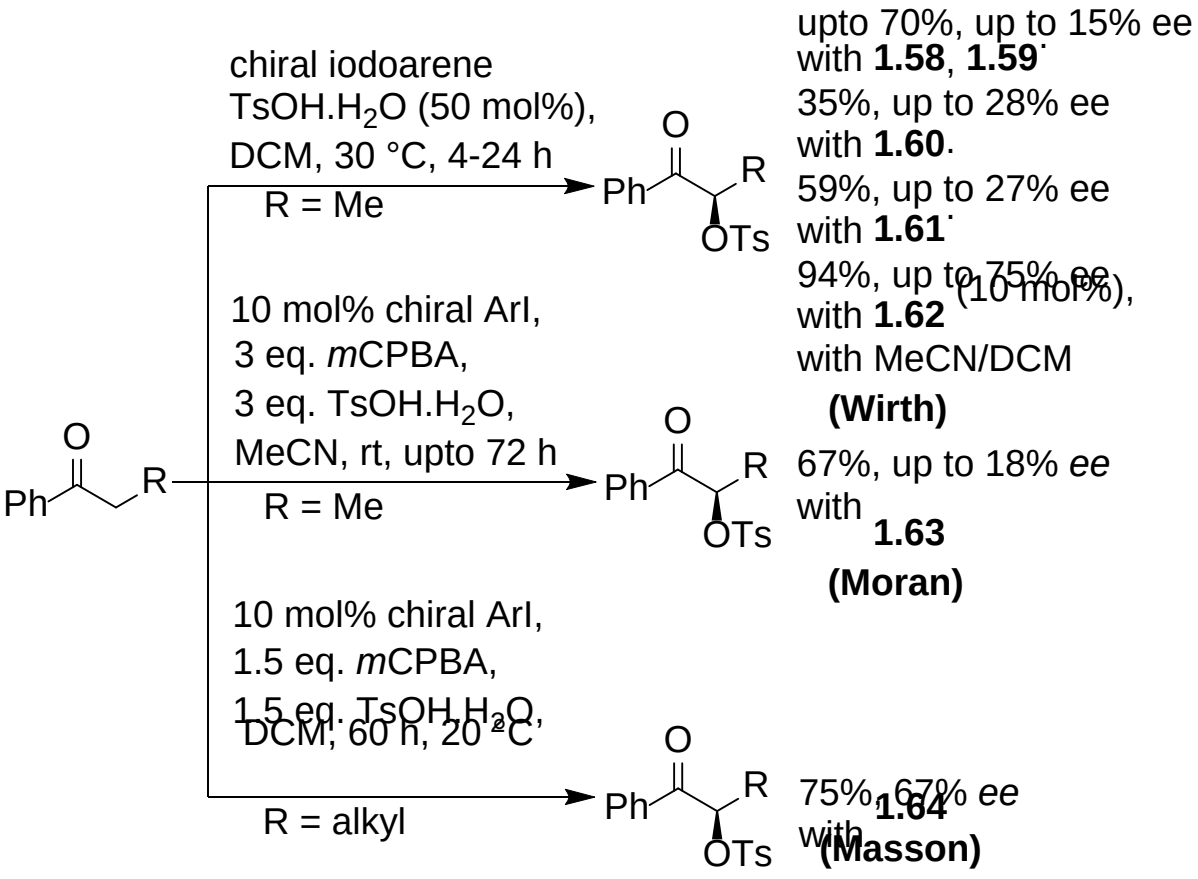
Wirth and coworkers in 1997, had worked on asymmetric α-oxytosylation of ketones with limited success.[14] They were inspired by the work of Togo and Yamamoto, discovering that iodoarene catalysed α-oxytosylation of acetophenone was possible with stoichiometric quantities of *meta*-chloroperbenzoic acid (*m*CPBA) oxidant (Scheme 14).[14,33,34]



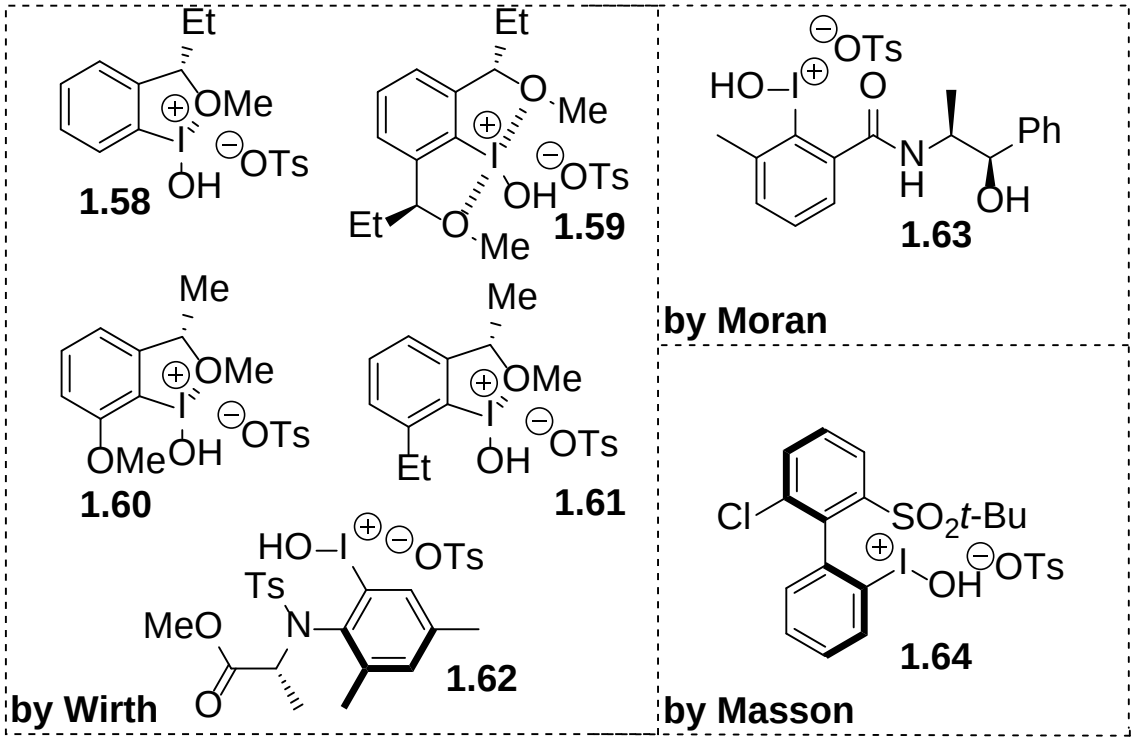
Scheme 14: Proposed Catalytic Enantioselective iodine(III)-mediated α-Oxytosylation of Ketones Mechanism[34]

Wirth and coworkers in 2007, reported the extensive screening of enantiopure hypervalent iodine(III) reagents to find efficient iodoarene catalysts in their asymmetric α-oxytosylation of ketones. Wirth's team prepared ethers, esters, binaphthyl iodoarene derivatives, and even naphthalene-based precatalysts.[35] (*S*)-1-ethyl-2-iodo-3-(1-methoxyethyl)benzene **1.58** precatalyst afforded the best enantioselectivity in the first asymmetric catalytic α-oxytosylation of ketones, albeit with moderate selectivity.[14] The following year Wirth and coworkers reported on the catalytic asymmetric α-oxytosylation of ketones using enantiopure iodoarenes with ester appendages, improving enantioselectivity by another 11%.[35,36,37] Moran and Rodríguez in 2012, reasoned that lactic acid derivatives of iodoarenes had also been effective catalysts and reagents in reactions.[38] They postulated amides and ethers may offer superior, effective asymmetric catalysis, and synthesised a range of iodoarenes by amidation or esterification. They had limited success, achieving 67% yield and 18% *ee* for the asymmetric catalytic α-oxytosylation of propiophenone, using Wirth's reaction conditions, with their novel norephedrine derivative iodoarene catalyst **1.63**. Others have persisted to improve on Wirth's asymmetric catalytic α-oxytosylation of

propiophenone such as Masson and coworkers trying in 2017. Their novel axially chiral iodoarene bearing a sulfone substituent **1.64**, achieved 67% *ee*[39]. In 2021, Wirth inspired by Masson and coworkers, had finally achieved some significant enantioselectivity with up to 94% yield and 75% *ee* using a novel C-N axially chiral iodoarene **1.62** (Scheme 15).[40]



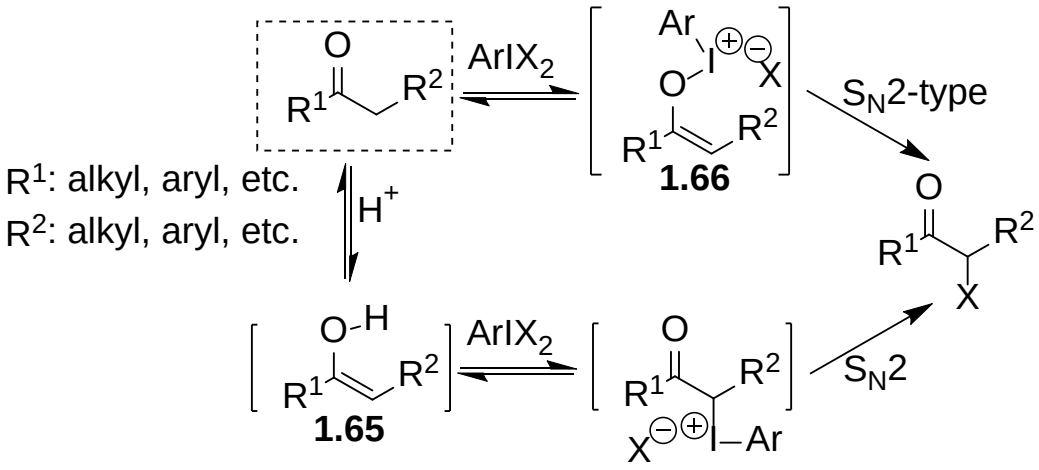
Chiral Iodoarenes Catalysts



Scheme 15: Asymmetric α-Oxytosylation of Ketones[14,35,36,37,38,39,40,41]

1.11.2.3 Iodine$^{(III)}$-Mediated α-Oxidation Mechanism

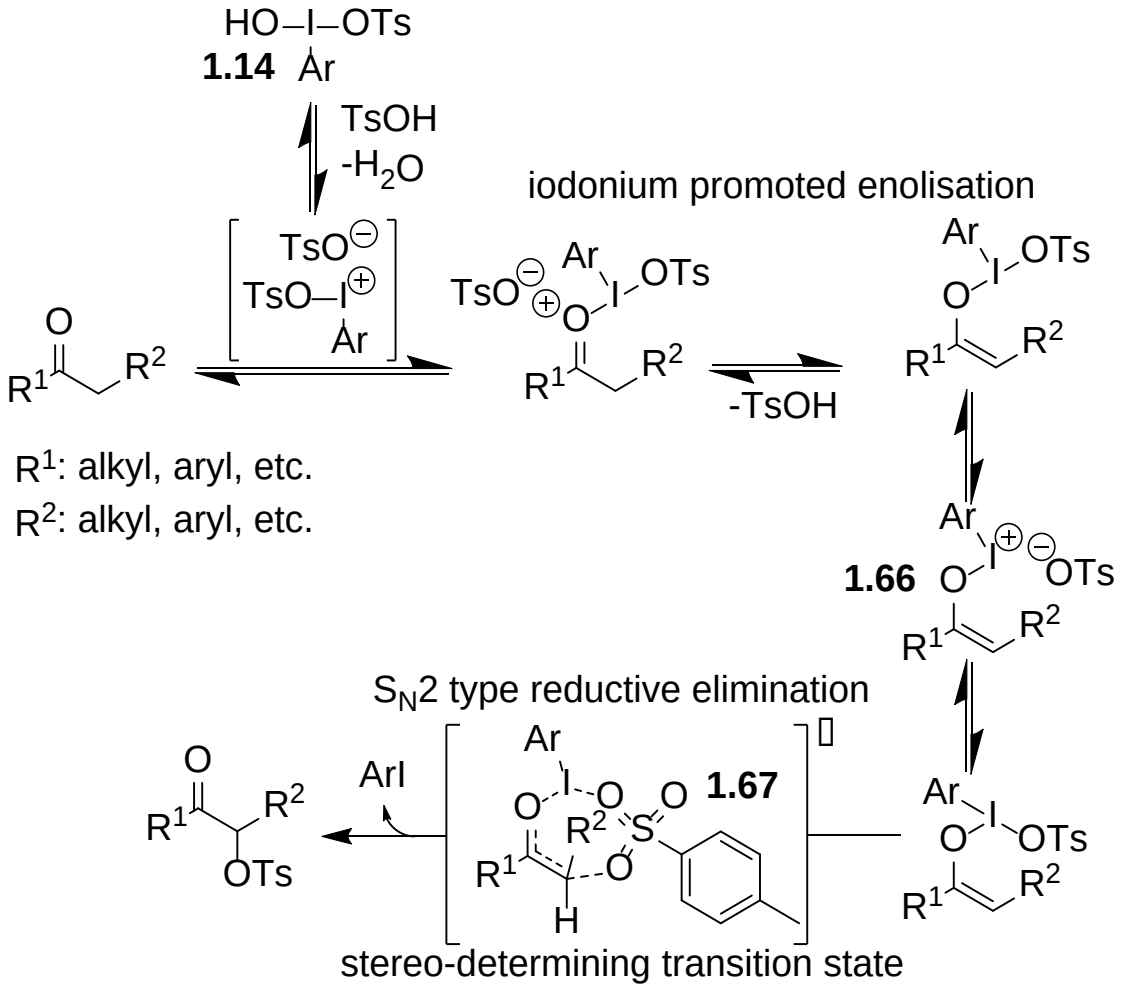
The iodine(III) mediated α-oxidation of carbonyls is a very well-examined transformation, however, the mechanism remains ambiguous. Typical, α-functionalisation of ketones proceeds via the creation of an enol or enolate intermediate followed by electrophilic substitution S_E1, under basic conditions.[34] However, iodine(III) mediated α-oxidation of carbonyls is understood to be facilitated under oxidative and acidic conditions. The reaction has two possible pathways. Firstly, creating an enol intermediate **1.65**, and then the alkene is oxidised by the iodine(III) reagent, followed by S_N2 displacement or an iodonium enolate **1.66** is created, followed by S_N2 type reductive elimination (Scheme 16).[34,42]



Scheme 16: Iodine(III)-Mediated α-Oxidation Pathways[34,42]

1.11.2.4 Computational Investigation of α-Oxytosylation of Ketones

Legault and coworkers conducted extensive computational studies in 2015, to fully elucidate the mechanism of α-oxytosylation of ketones. They proposed a new iodonium-promoted enolisation mechanism and identified the stereo-determining transition state **1.67** (Scheme 17).[34]

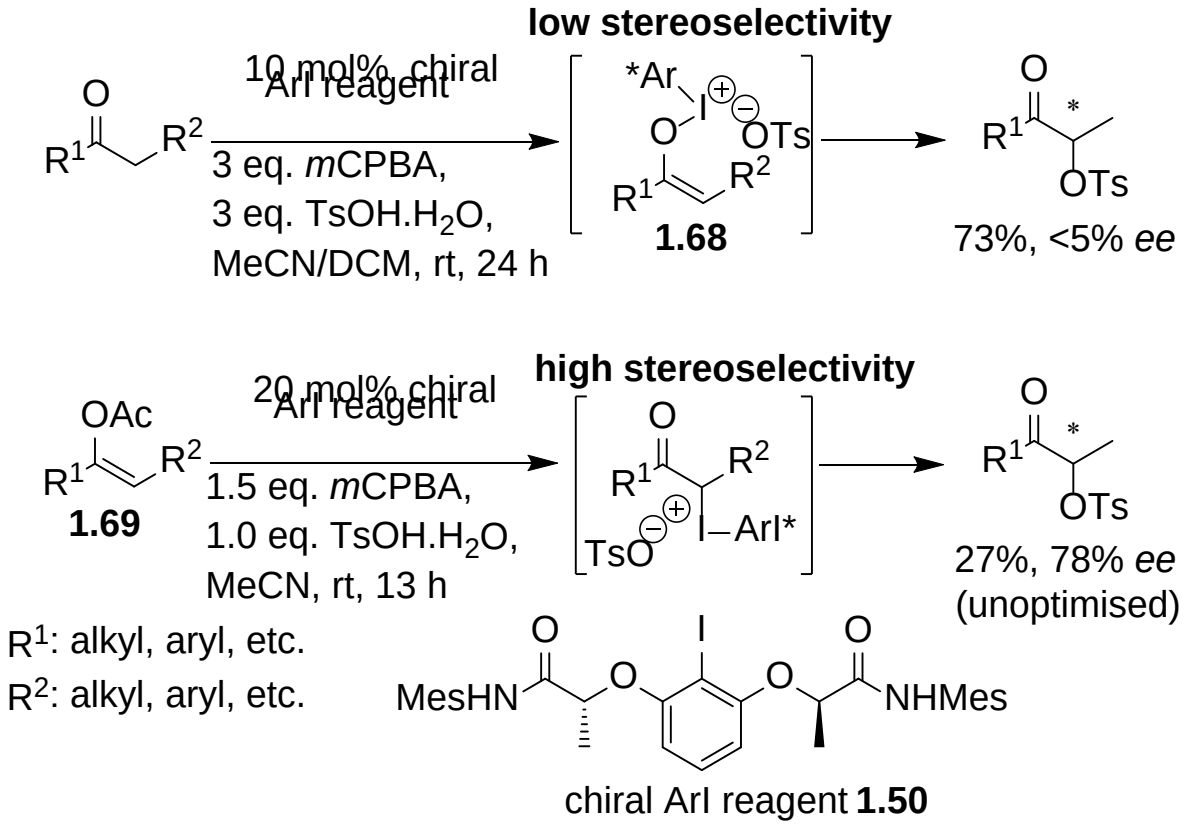


Scheme 17: New Iodonium Promoted α-Oxytosylation Mechanism[34]

1.11.2.5 Legault's Pathway Blocking Enantiocontrol Strategy

Legault and coworkers later on in 2015, reported an alternative strategy, armed with the knowledge from their computational and experimental work. They postulated that there is a distinction in the mechanism pathways between the α-oxytosylation of ketones and the corresponding enol ester. They theorised that iodonium promoted enolisation is the favoured pathway, however, if that pathway was blocked, then the disfavoured pathway would result in enantiocontrol of the product. They achieved up to 70% optimised yields and up to 90% *ee* using C_2-symmetrical iodoarene derivatives with an enol acetate substrate but

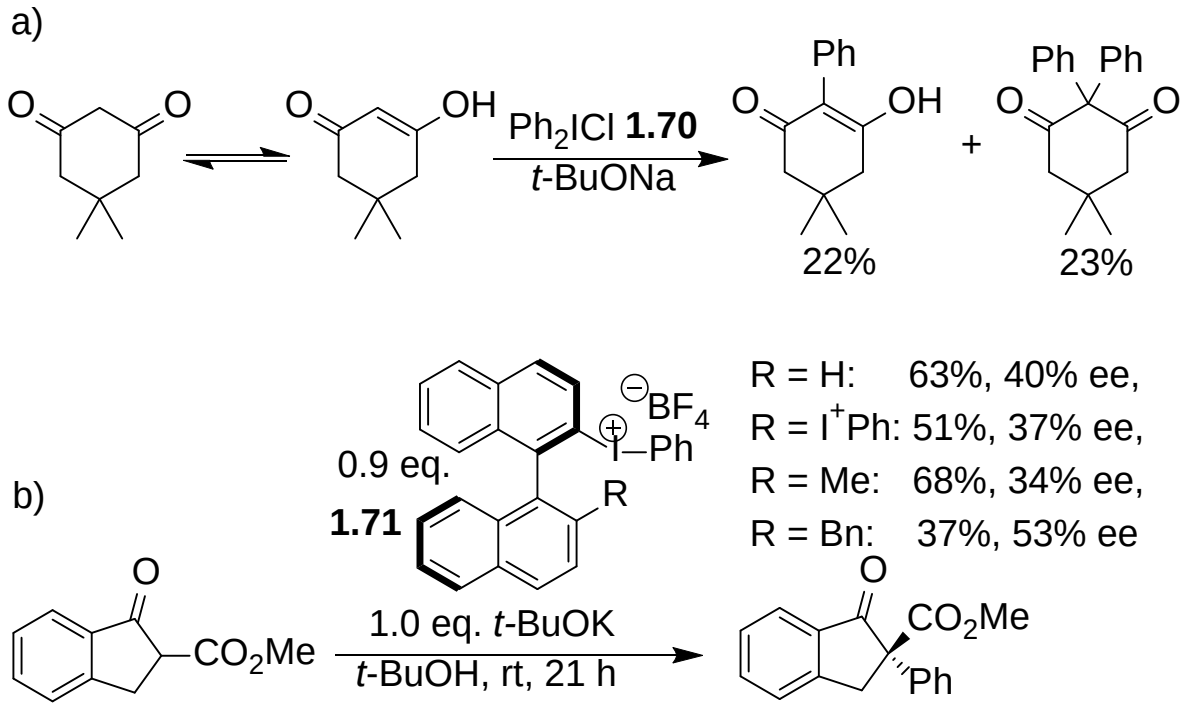
found poor enantiocontrol with the corresponding ketone. They proved that an S_N2 type reductive elimination of an *O*-enolate intermediate **1.68** occurs in the former instance, providing low stereoselectivity and in the latter case, high enantiocontrol is achieved through S_N2 type substitution of a *C*-enolate **1.69** (Scheme 18).[43]



Scheme 18: Legault's New α-Oxytosylation Strategy[43]

1.11.2.6 α-Arylation of Carbonyls

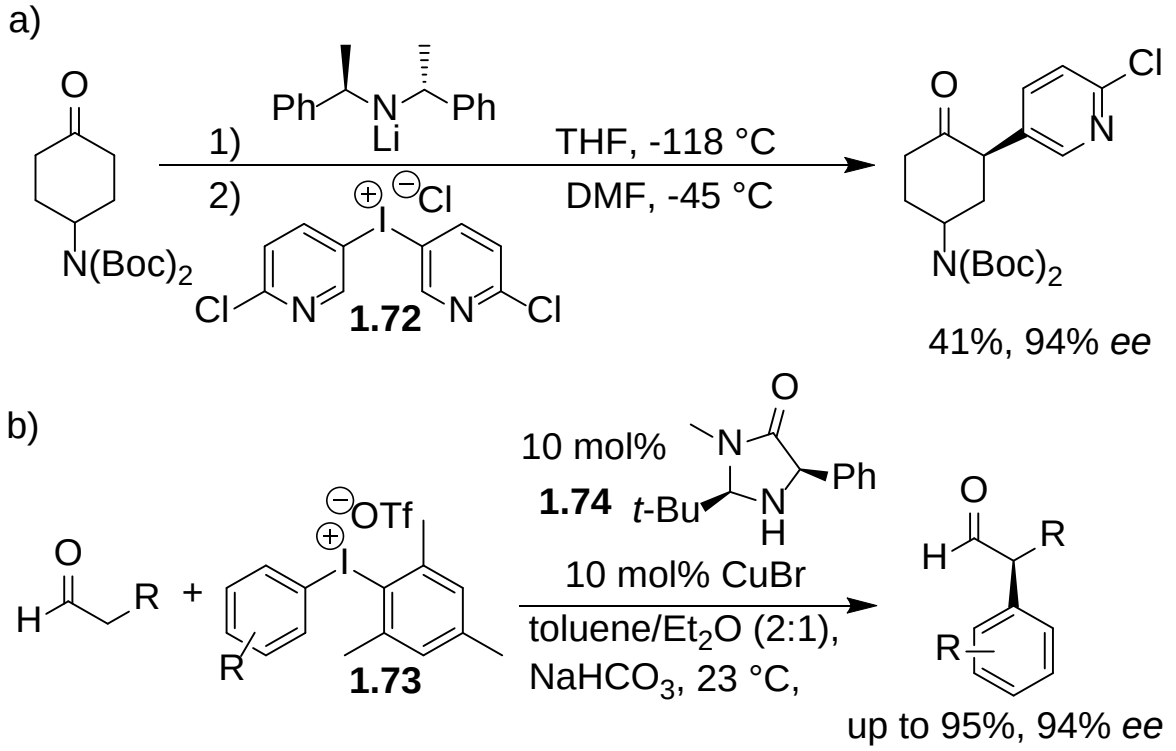
Beringer and co-workers in 1960 showed that hypervalent iodine(III) reagents **1.70** can be used for the α-arylation of carbonyl compounds (Scheme 19a).[44,41] Ochiai and coworkers were developing chiral diaryliodonium reagents, in 1999, they reported the first asymmetric α-arylation of β-ketoesters with iodonium tetrafluoroborate salts **1.71** (Scheme 19b).[45]



Scheme 19: First Racemic and Asymmetric α-Arylation of Carbonyls[44,41,45]

1.11.2.7 Chiral Base Asymmetric α-Arylation Strategy

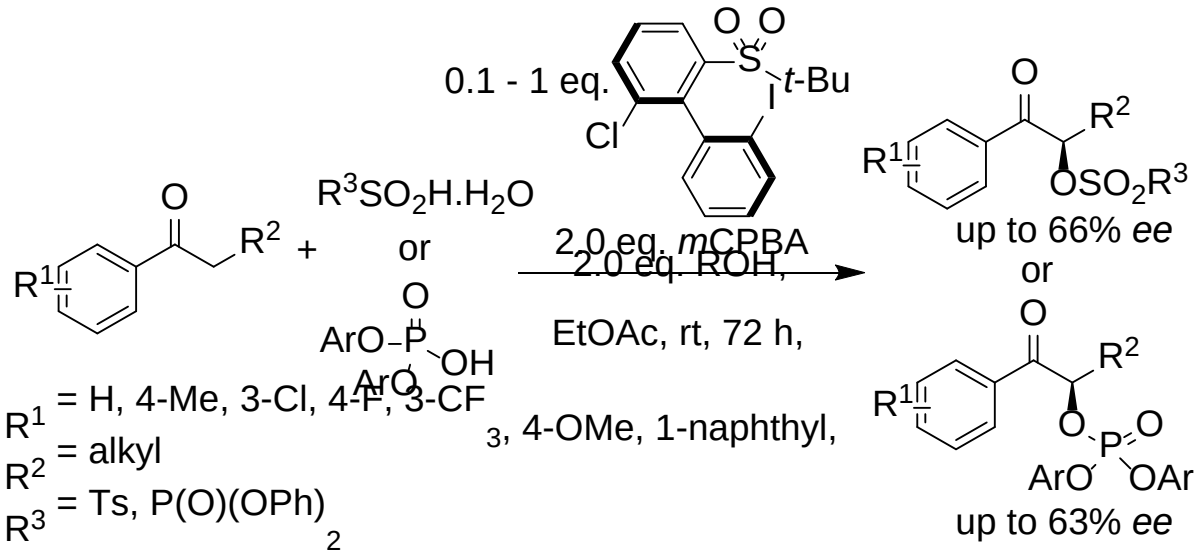
Aggarwal and Olofsson in 2005 discovered an alternative strategy. Using a chiral base to desymmetrise the substrate, then treating the substrate with an achiral diaryliodonium salt **1.72**, high enantioselectivity was obtained[46]. However, the scope was very limited to certain prochiral, cyclic ketone substrates (Scheme 20a).[44,46] Allen and MacMillan achieved highly enantioselective α-arylation of aldehydes using diaryliodonium salts **1.73** with copper bromide and an amine catalyst **1.74** in 2011 (Scheme 20b).[47]



Scheme 20: Asymmetric α-Arylations[44,46,47]

1.11.2.8 α-Oxysulfonylation and α-Oxyphosphorylation

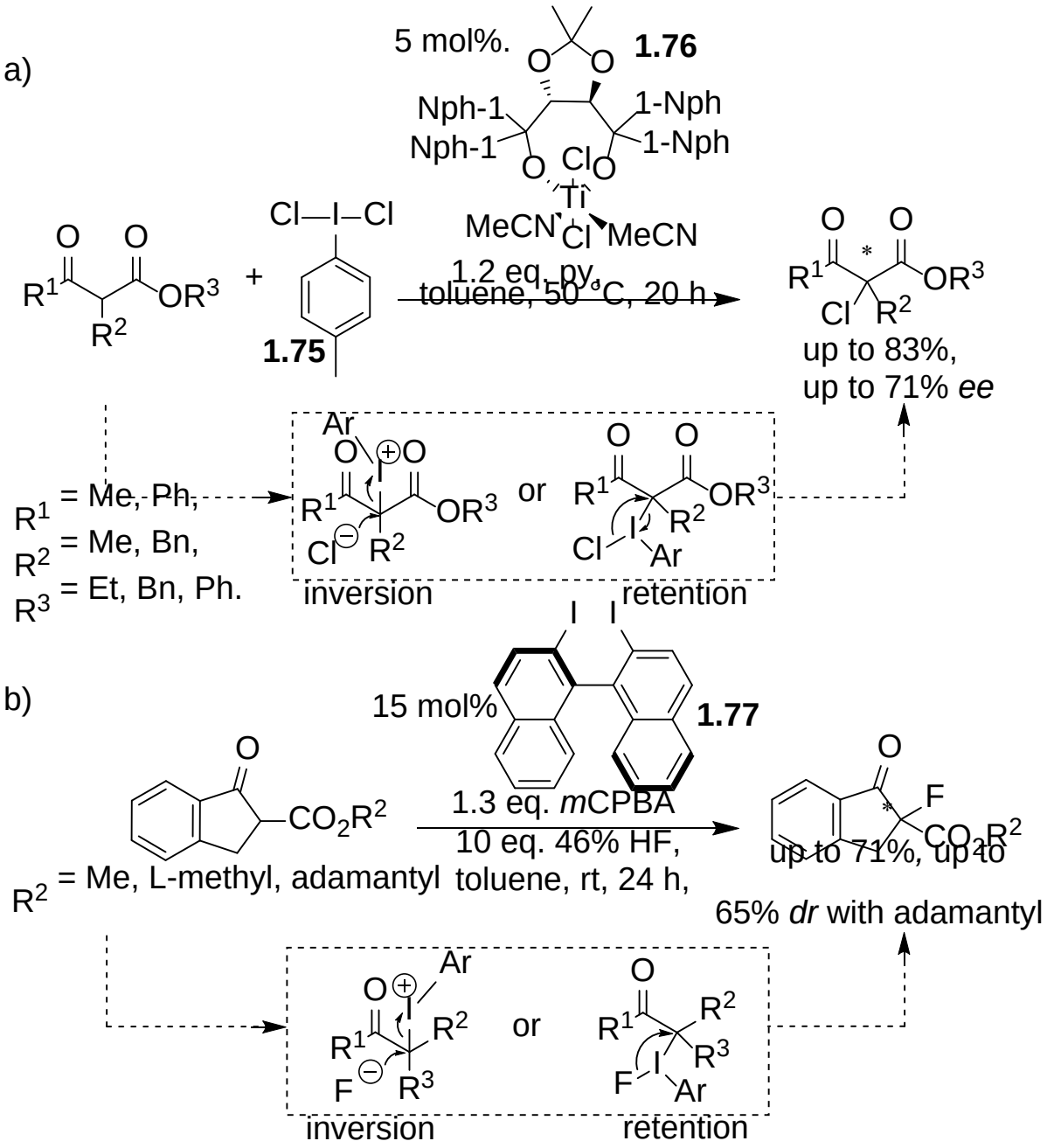
Masson and coworkers in 2017 demonstrated α-sulfonyl and α-phosphoryl oxylation, as well as α-oxytosylation of ketones, was possible. These reactions proceed via the same α-oxytosylation mechanism that was previously described (Scheme 21).[39]



Scheme 21: Asymmetric α-Sulfonyl and α-Phosphoryl Oxylation[39]

1.11.2.9 Asymmetric α-Halogenations of Ketones

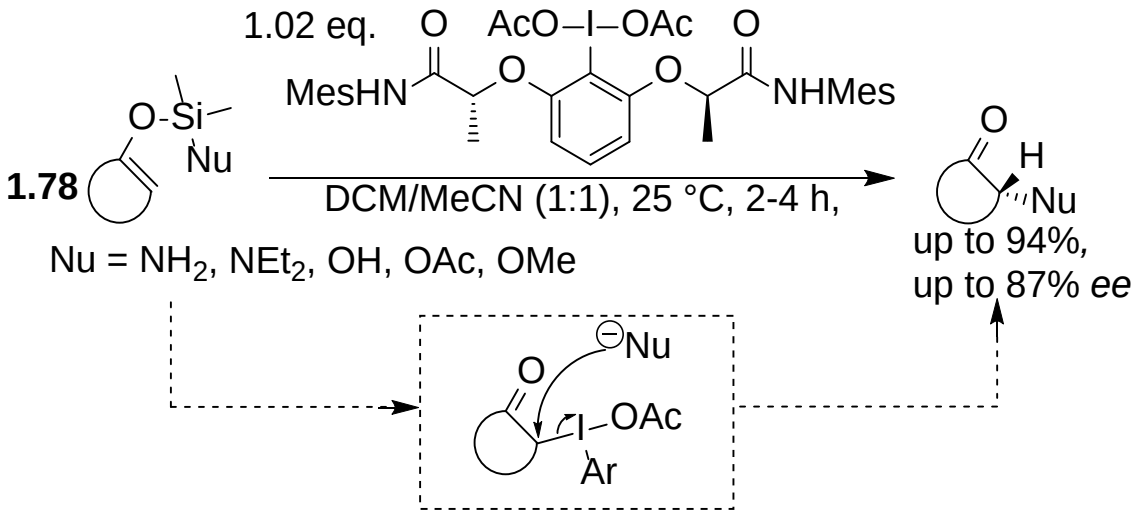
In 2004, Togni and coworkers discovered the catalytic asymmetric chlorination of β-ketoesters using titanium complex catalyst **1.76** with (dichloroiodo)toluene **1.75** (Scheme 22a).[48,49] In 2014, Kita and Shibata developed a catalytic, enantioselective, fluorination of β-ketoesters, using chiral 1,1′-binaphthyl diiodides **1.77** with hydrogen fluoride (HF) and *meta*-chloroperoxybenzoic acid (*m*CPBA) oxidant to generate *in situ* iodine(III) reagent, Ar-IF_2, achieving moderate enantioselectivity.[50] Using sterically hindered β-ketoesters gave good enantioselectivity, however, no further improvements in selectivity could be obtained, despite increasing catalyst **1.77** loading to 50 mol % (Scheme 22b).[41]



Scheme 22: Asymmetric α-Halogenations[41]

1.11.2.10 α-Functionalisation of Carbonyls Using Silyl Tethered Enol Ethers

Wirth and coworkers in 2014, developed asymmetric α-oxygenation and α-amination of carbonyls using a polarity inversion strategy for N- or O-nucleophile transfer to α-functionalise carbonyls using silyl tethered enol ethers **1.78** and they achieved high enantioselectivity (Scheme 23).[41,51]



Scheme 23: Asymmetric α-Oxygenation and α-Amination[41,51]

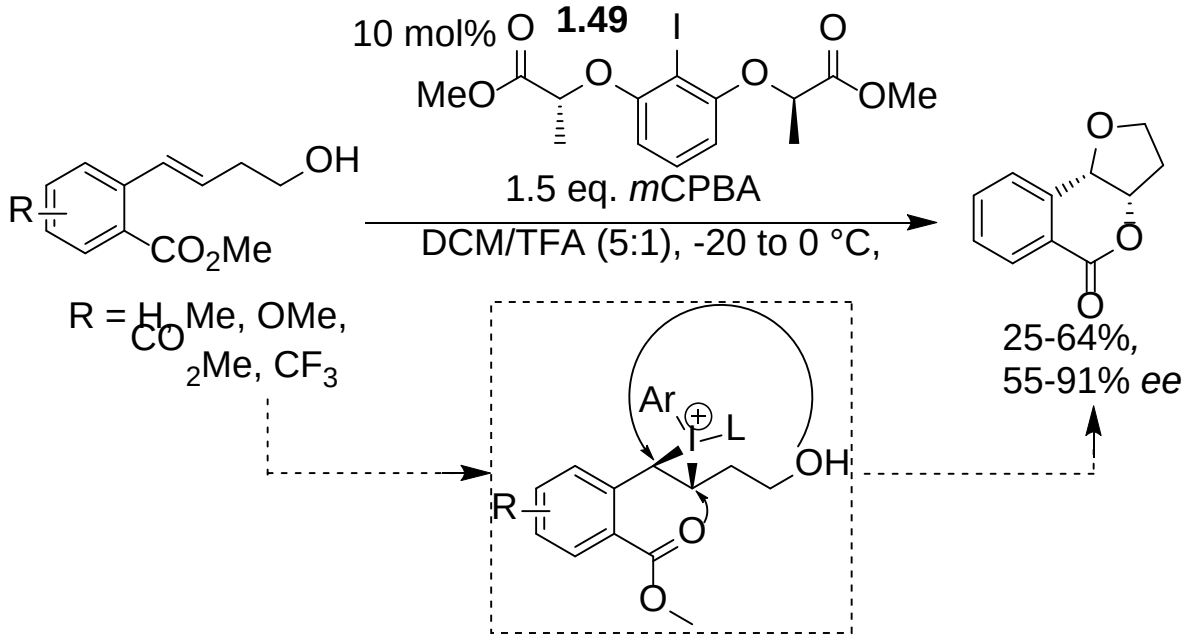
1.11.3 Alkene functionalisation

Alkene and alkyne substrates can be functionalised oxidatively by chiral hypervalent iodine reagents to facilitate a wide range of stereoselective transformations dependant on the reaction conditions. Asymmetric difunctionalisation of alkenes can be employed to form polysubstituted products, making one or two vicinal stereogenic centres from two identical or dissimilar nucleophiles. There have been numerous reports within scientific literature of asymmetric lactonisation, diamination, dioxygenation, iodocarboxylation, tetrahydrofuranylation, aziridination, aminofluorination, dihalogenations of alkenes.[9,15]

1.11.3.1 Asymmetric Lactonisation of Alkenes

The first asymmetric catalytic difunctionalisation of alkenes was reported by Fujita and coworkers in 2012, involving the oxidative double cyclisation of 2-(4-hydroxybut-1-enyl)benzoates using a C_2-symmetrical iodoarene bearing bis methyl lactate appendages **1.49** (Scheme 24).[9,15, 52] The mechanism follows with the oxidation of the iodoarene$^{(I)}$ by *meta*-chloroperoxybenzoic acid (*m*CPBA) and activated by trifluoroacetic acid

(TFA) to a chiral iodine(III) species. Diastereofacial attack across the internal alkene occurs by the chiral iodine(III) reagent to create the iodonium intermediate. Which then proceeds via S_N2 substitutions of the hydroxy and carboxymethyl groups, resulting in the inversion of the stereochemistry. The reaction suffers from low yields due to oxidation of the alkene substrate directly by the oxidant.[15,52]

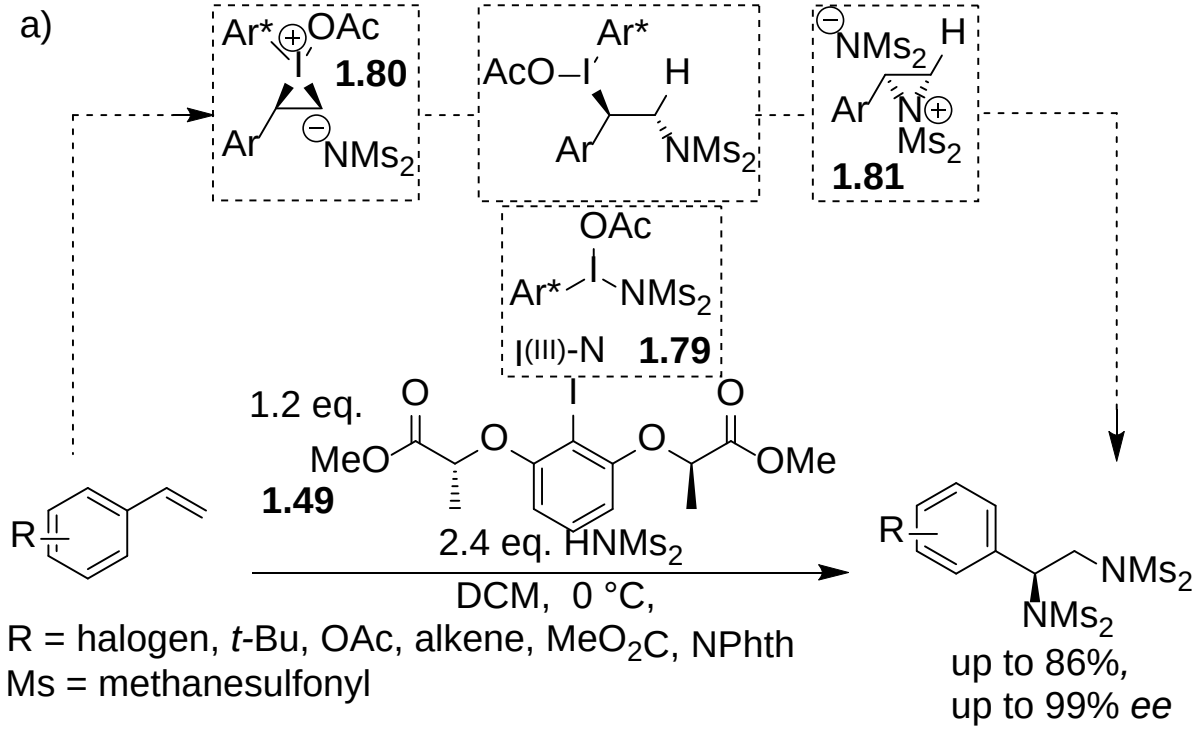


Scheme 24: Fujita's Catalytic Enantioselective Oxylactonisation[52]

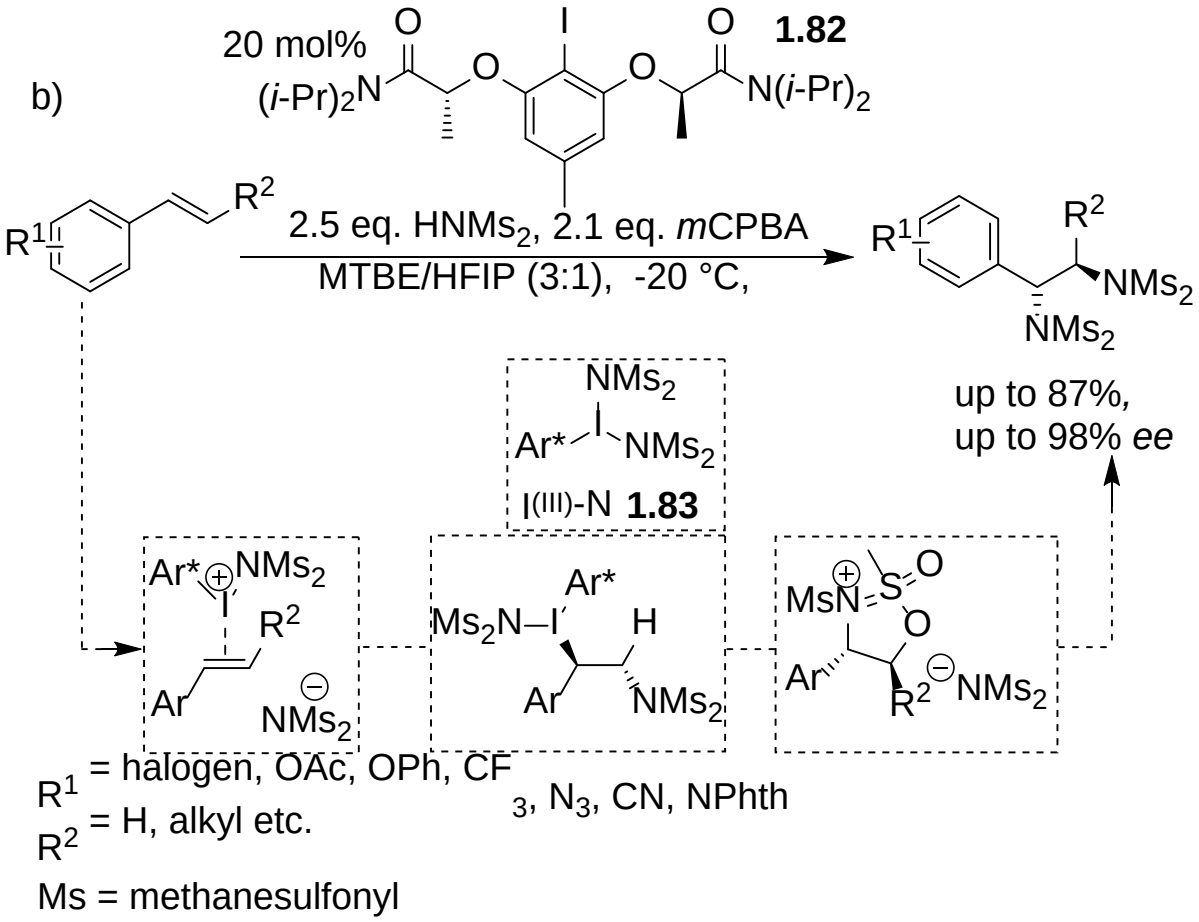
1.11.3.2 Enantioselective Diamination of Alkenes

Vicinal diamines represent one of the most vital functional moieties in organic chemistry due to their presence in a wide variety of biological and pharmaceutical molecules.[48] In 2011 Muñiz and coworkers reported, the first asymmetric intermolecular diamination of styrenes using the privileged C_2-symmetrical iodoarene bislactate methyl diester **1.49**.[53] The mechanism follows with the generation of the iodine(III) species **1.79** acting as a Lewis acid, which adds across with the alkene, forming an iodonium intermediate **1.80**, proceeding with nucleophilic attack from NMs_2 anion. Protonation of the acetate ejects acetic acid from the

iodonium intermediate and it is postulated a charged aziridinium ring **1.81** is formed. Ring opening of the aziridinium occurs with nucleophilic attack by a second NMs_2 anion to give the final product (Scheme 25a). In 2017, Muñiz and coworkers made their asymmetric diamination reaction catalytic, using a chiral C_2-symmetrical iodarene bislactamide **1.82**. Conversely, the catalytic mechanism and conditions differed from the stoichiometric diamination, instead using *meta*-chloroperoxybenzoic acid (*m*CPBA) oxidant and dimesylamine to generate/regenerate the iodine(III) catalyst **1.83** (Scheme 25b).[54]



Scheme 25a: Stoichiometric and Catalytic Asymmetric Diamination[53,54]

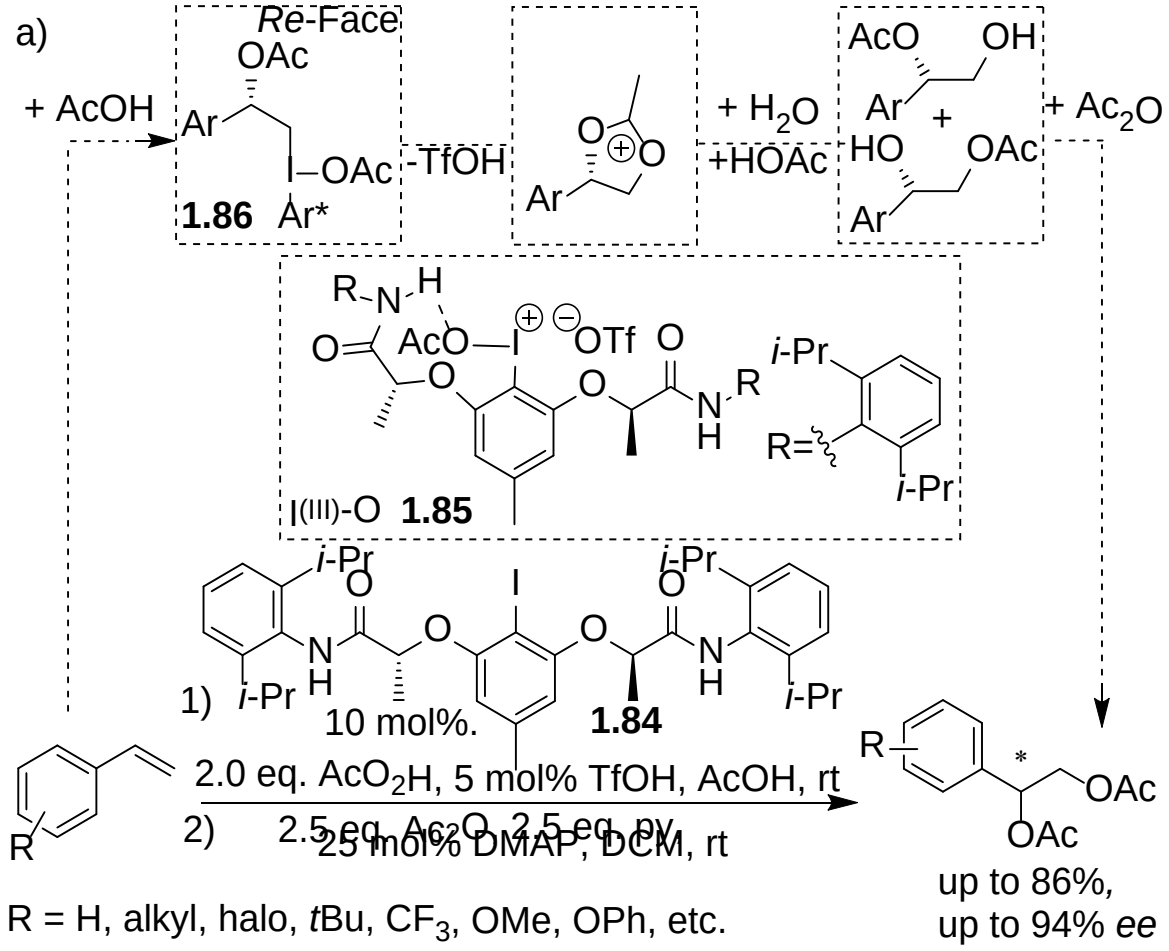


Scheme 25b: Stoichiometric and Catalytic Asymmetric Diamination[53,54]

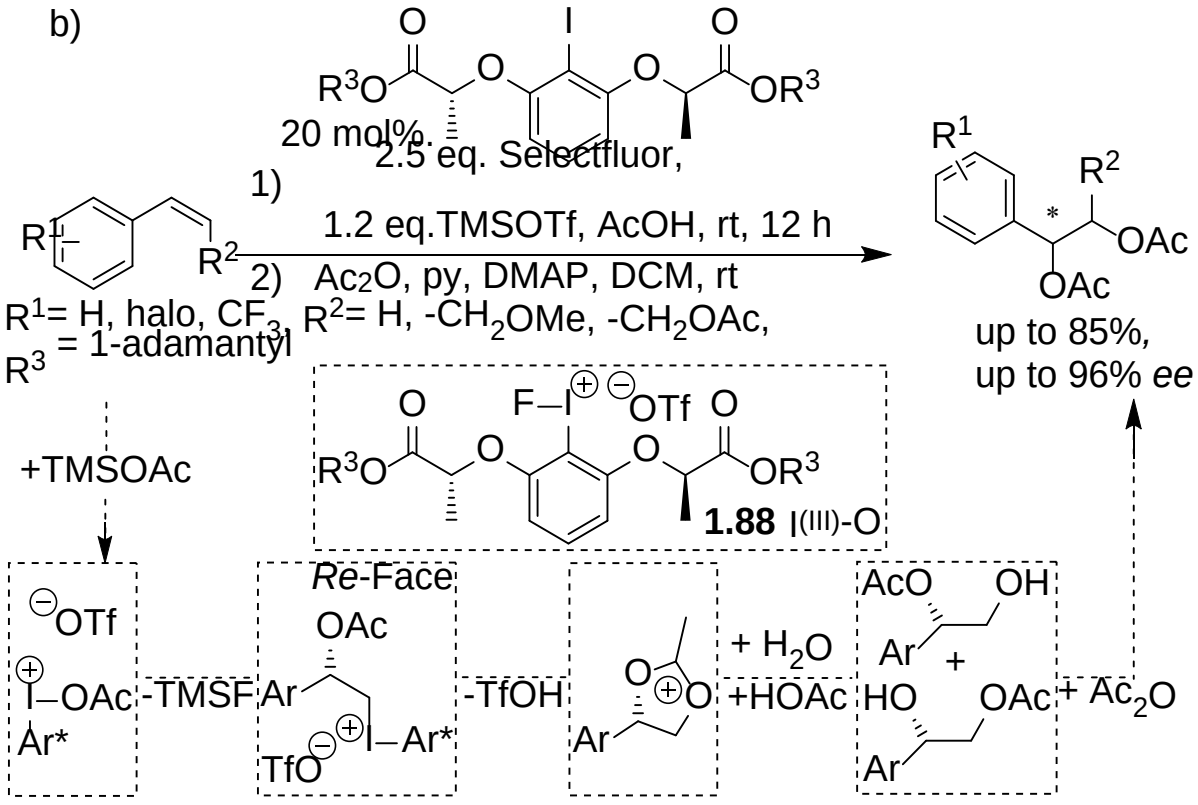
1.11.3.3 Dioxygenation of Styrenes

Muñiz and colleagues reported another first, in 2015, the first catalytic enantioselective diacetoxylation of internal and external alkenes using a C_2-symmetrical iodoarene bislactamide **1.84** (Scheme 26a).[9,55] It was postulated triflic acid activation through protonolysis of the iodine(III) species was essential to drive diacetoxylation and that one of the acetate ligands would disassociate and the other acetate ligand would perform in hydrogen bonding with the amide **1.85**. The iodine(III) catalyst then co-ordinates with the alkene forming an iodonium intermediate **1.86**, followed by nucleophilic attack from the disassociated acetate anion to the *re*-face. Nucleophilic addition of the acetate regenerates I(I) catalyst and gives a dioxolane ring intermediate **1.87**. Ring opening is via Prévost mechanism

of a nucleophilic attack by an acetate ion or by Woodward pathway through water addition to form a hydroxyacetate, two regioisomers are created. The regioisomers upon reaction with acetic anhydride, affords the vicinal *(S)*-diacetoxylated product in high enantiomer excess[9]. They remedied the flaw of peroxy oxidants competitively epoxidating the alkene substrate, by changing to Selectfluor.[56] An extra step is created where the trimethylsilyl triflate (TMSOTf) reacts with the acetic acid solvent to create triflic acid and trimethylsilyl acetate. Then ligand exchange occurs with the F ligand to generate the iodine(III) species **1.88** which then catalyses diacetoxylation of the substrate (Scheme 26b).[56]



Scheme 26a: Asymmetric Catalytic Diacetoxylation of Styrenes[9,55,56]



Scheme 26b: Asymmetric Catalytic Diacetoxylation of Styrenes[9,55,56]

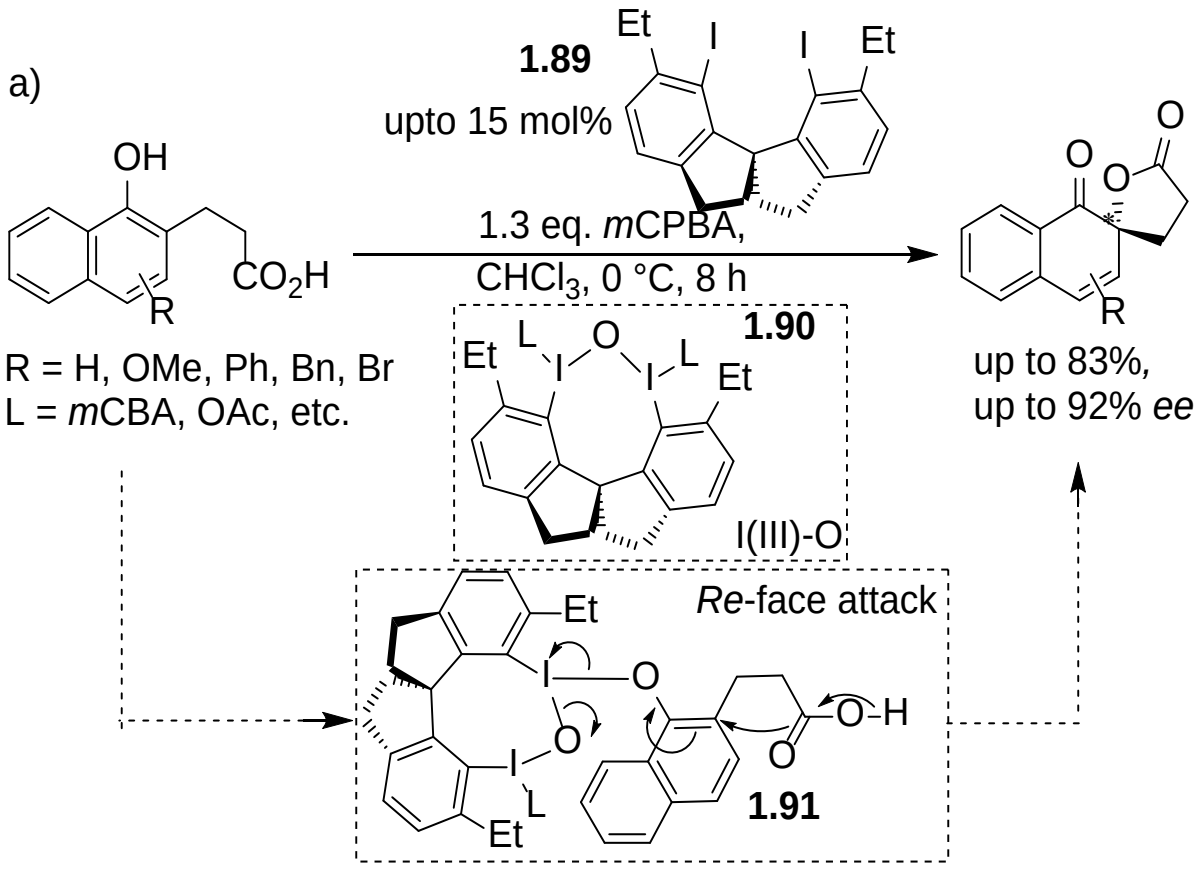
1.11.4 Phenolic oxidation

Biosynthesis of natural compounds, which control crucial biological activities, frequently relies on phenolic oxidations, development of these types of dearomatisation reactions are of great interest in natural product and total synthesis.[48]

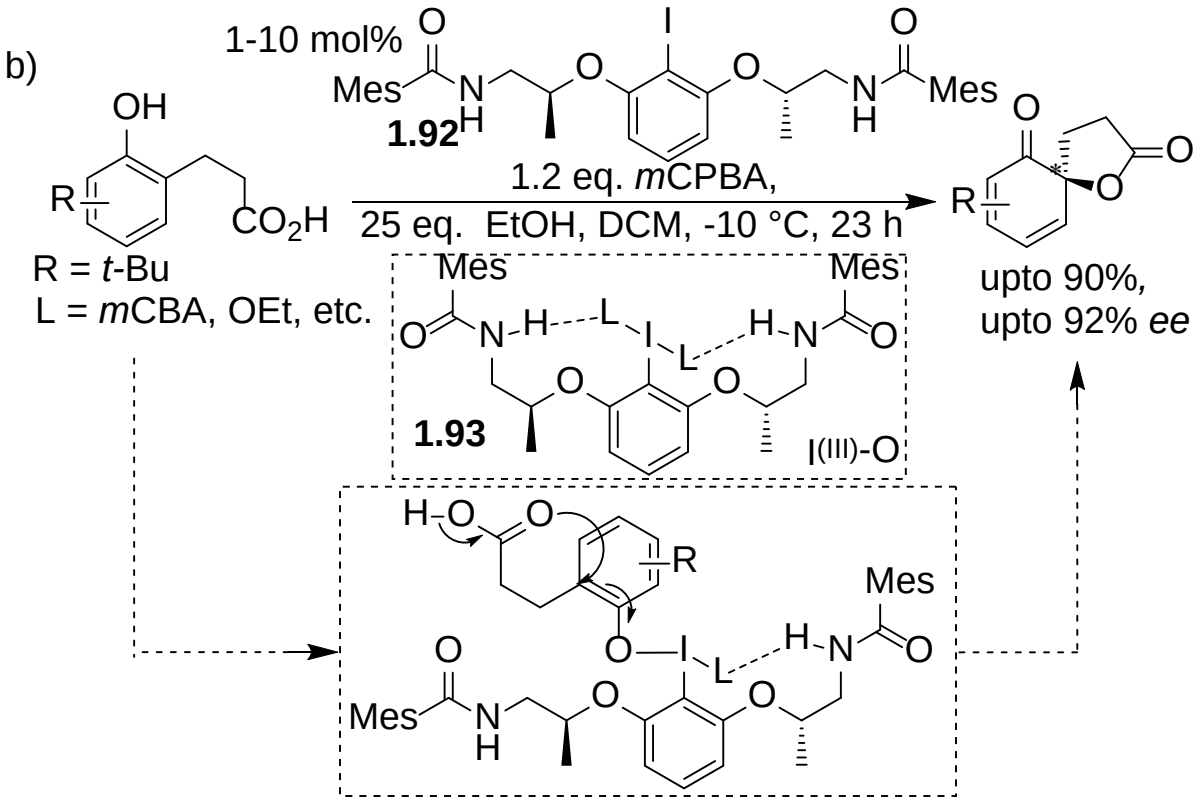
1.11.4.1 Enantioselective Dearomatising Spirolactonisation

Kita and coworkers reported hypervalent iodine(III) mediated dearomatisation of phenols as early as 1987, they reported in 2008, the intramolecular asymmetric dearomatising spirolactonisation of naphthols employing chiral spirobiindane **1.89**.[48,57,58] The mechanism followed with the oxidation of the ArI compound to generate the iodine(III) species **1.90** which contained a fragile μ-oxo bridge between the iodines, acting as a Lewis acid. The iodine(III) species would form an iodonium phenolate

intermediate **1.91**, dearomarisation occurs to eject the iodine(III) reagent. Nucleophile attack would quickly follow from the carbonyl oxygen, to facilitate cyclisation and (Scheme 27a). Ishihara and coworkers further rationally developed the catalytic asymmetric oxidative dearomatisation reaction further by utilising C_2-symmetrical iodoarene bislactamide **1.92**.[59] It was anticipated they would exhibit hydrogen bonding with the amides and ligands or interactions between the electron deficient iodine(III) centre and Lewis basic groups, to aid enantiocontrol **1.93** (Scheme 27b).[59]



Scheme 27a: Catalytic Asymmetric Dearomatising Spirolactonisation[48,57,58,59]



Scheme 27b: Catalytic Asymmetric Dearomatising Spirolactonisation[48,57,58,59]

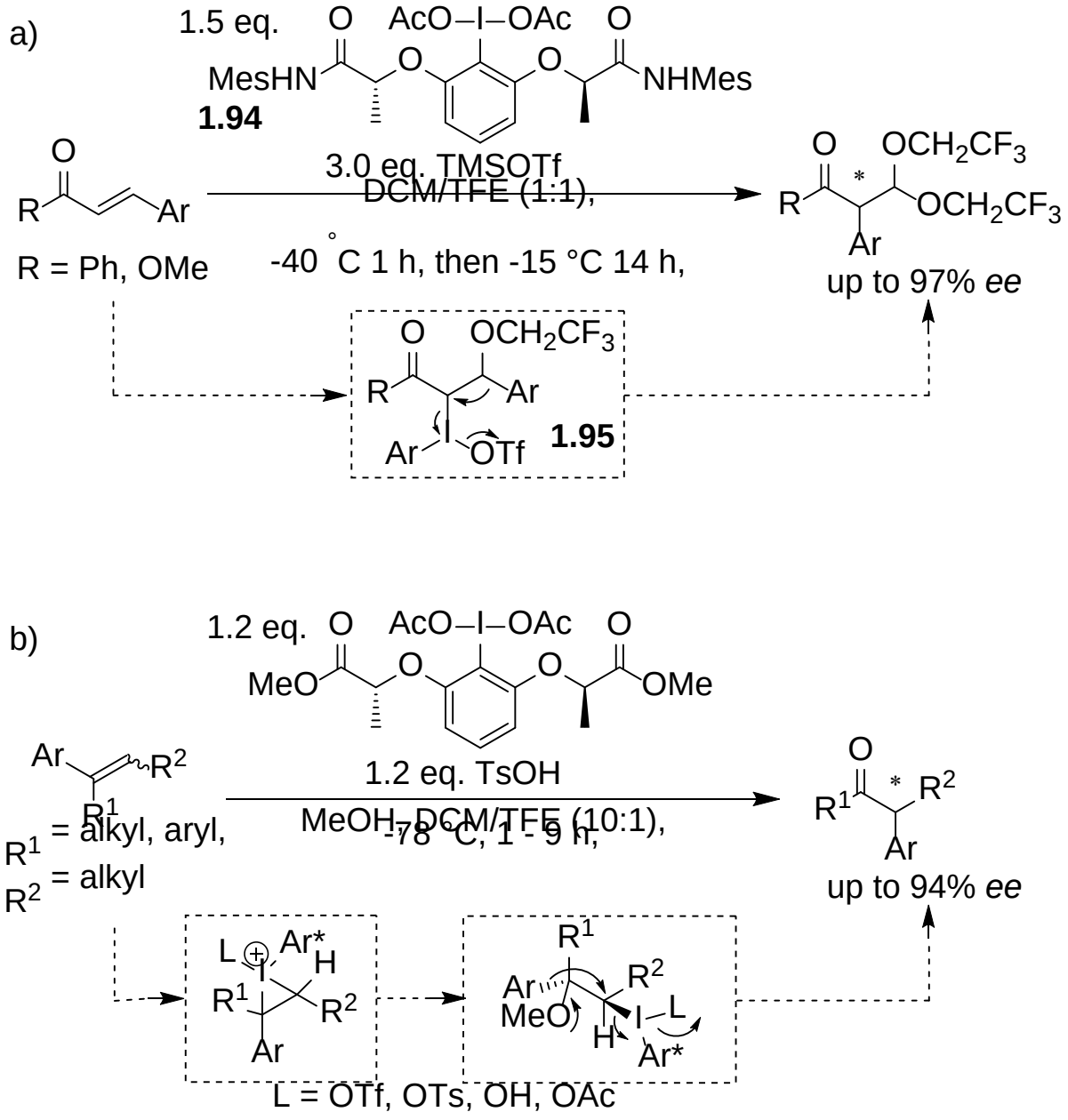
1.11.5 Rearrangement reactions

Electrophiles can readily react with hypervalent iodine(III) species and then perform as a leaving group to create cationic intermediates. These cationic intermediates can then undergo nucleophilic attack or perform intramolecular rearrangements through 1,2-migration, Hofmann rearrangement, Beckmann rearrangement, ring contraction, ring expansion, [3,3]-sigmatropic/iodonium-Claisen rearrangement, and other miscellaneous rearrangements.[48,60]

1.11.5.1 1,2-Aryl Migration

Wirth and coworkers in 2013, developed high stereoselectivity via an oxidative rearrangement, transformations of α,β-unsaturated carbonyls to α-arylated carbonyls.[61] The *in situ* generation of an iodine(III) reagent **1.94**

occurs, which reacts with the alkene substrate to form an iodonium intermediate **1.95** followed by stereoselective 1,2-aryl migration (Scheme 28a).[61] Wirth and coworkers used the 1,2-aryl migration strategy again in 2016, to report enantioselective oxidative rearrangement of disubstituted alkenes using C_2-symmetrical iodoarene reagents **1.49** (Scheme 28b).[62] It is noteworthy that neither of Wirth's transformations was catalytic.[61,62]



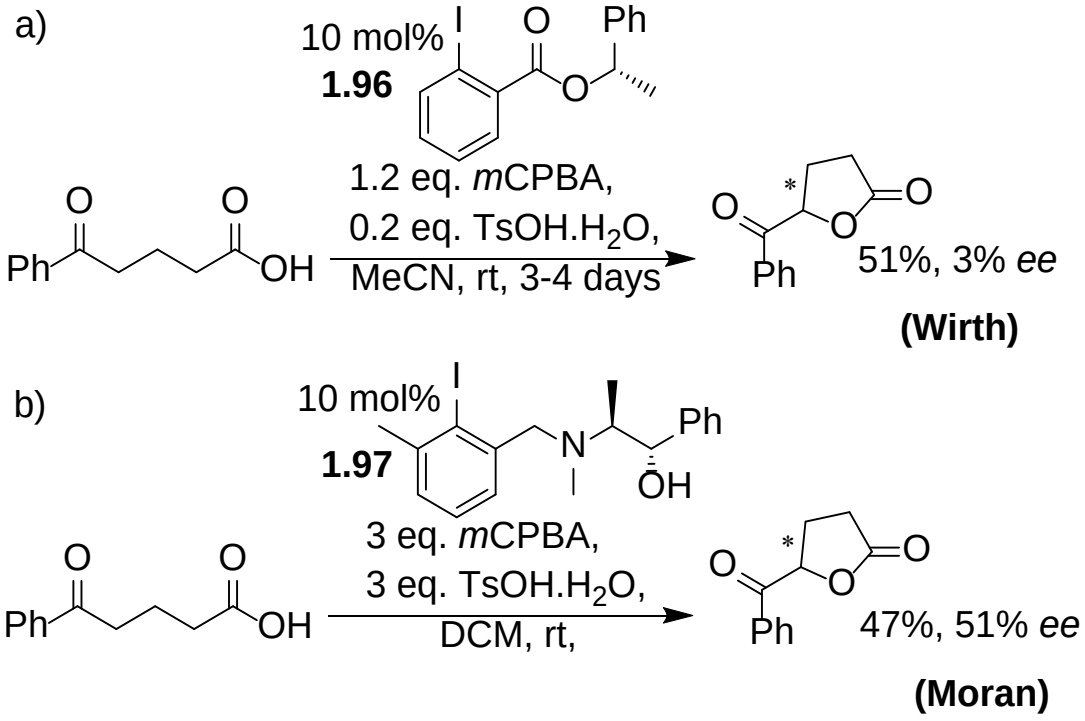
Scheme 28: Asymmetric Aryl Rearrangement[41,61,62]

1.11.6 Heterocyclisation reactions

Cyclisations, mediated by hypervalent iodine(III) reagents, are of great utility in the synthesis of heterocycles. Heterocycles are found in many natural products, biologically and pharmacologically important compounds.

1.11.6.1 Asymmetric Lactonisation of Ketones

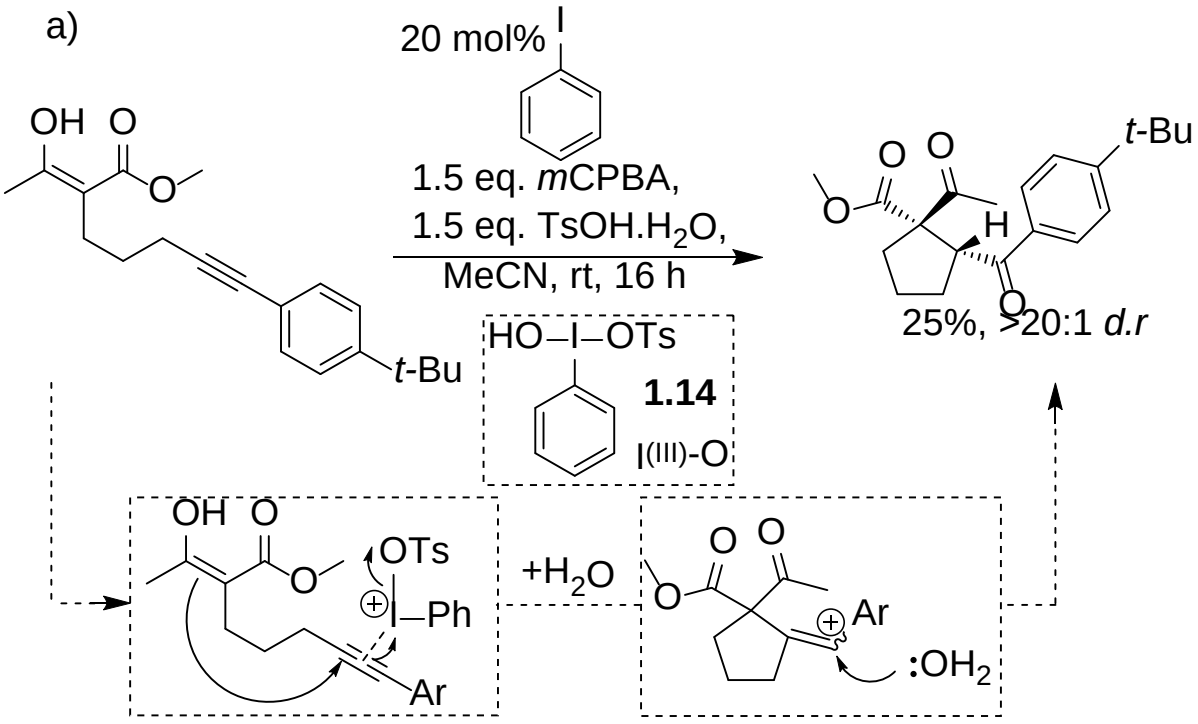
Wirth and coworkers while screening chiral hypervalent iodine(III) precatalysts for their α-oxytosylation of ketones found their conditions also facilitated enantioselective lactonisation of 5-oxo-5-phenylpentanoic acid.[37] Wirth and coworkers with their enantioselective lactonisation conditions only achieved a meager 3% *ee* with their novel iodoarene catalyst **1.96** (Scheme 29a).[37] Moran and Rodríguez's novel iodoarene catalyst **1.97** with a pseudoephedrine appendage, surpassed that with 51% *ee* albeit with 3 equivalents of both the oxidant and tosylate source (Scheme 29b).[38]



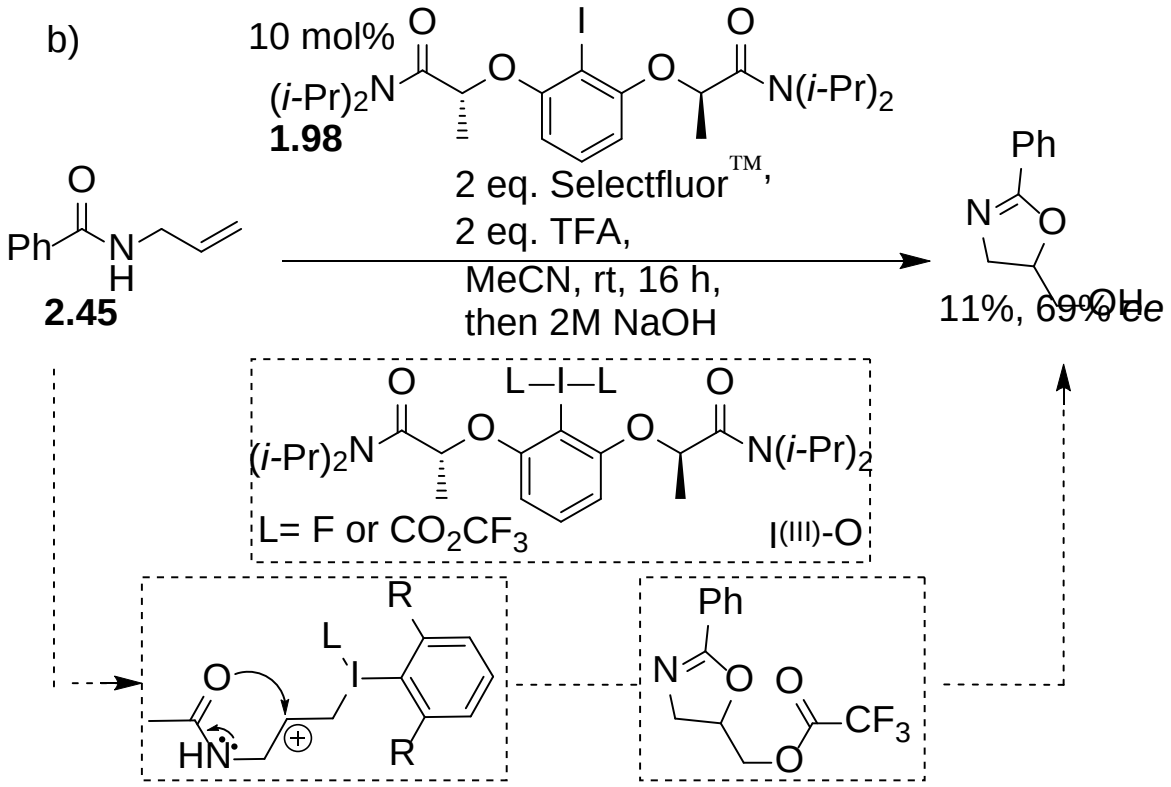
Scheme 29: Asymmetric Cyclisation of Ketones[37,38,41]

1.11.6.2 Asymmetric Cyclisations by the Moran Group

Moran and coworkers have over the past decade or so, specialised in the cyclisation of substrates mediated by hypervalent iodine(III) compounds. They have had many important achievements both in terms of catalysis and enantiomeric excess such as the 5-exo-dig cyclisation of δ-alkynyl β-ketoesters and the iodoarene-catalysed **1.98** cyclisation of unsaturated amides **2.45** (Scheme 30a&b).[63,64,65]



Scheme 30a: Asymmetric Cyclisations of Alkenes and Alkynes[63,64,65]



Scheme 30b: Asymmetric Cyclisations of Alkenes and Alkynes[63,64,65]

1.12 Oxazolidinones

Oxazolidinones are five-membered heterocyclic rings displaying potent pharmacological properties with superior antimicrobial and antibiotic activity by inhibiting protein synthesis.[66] Oxazolidinone drugs possess the vital oxazolidinone ring moiety, which is crucial for treating pathogenic gram-positive bacterial infections and other diseases. (Figure 13).[67] They can also be used as Evans' auxillaries.[66]

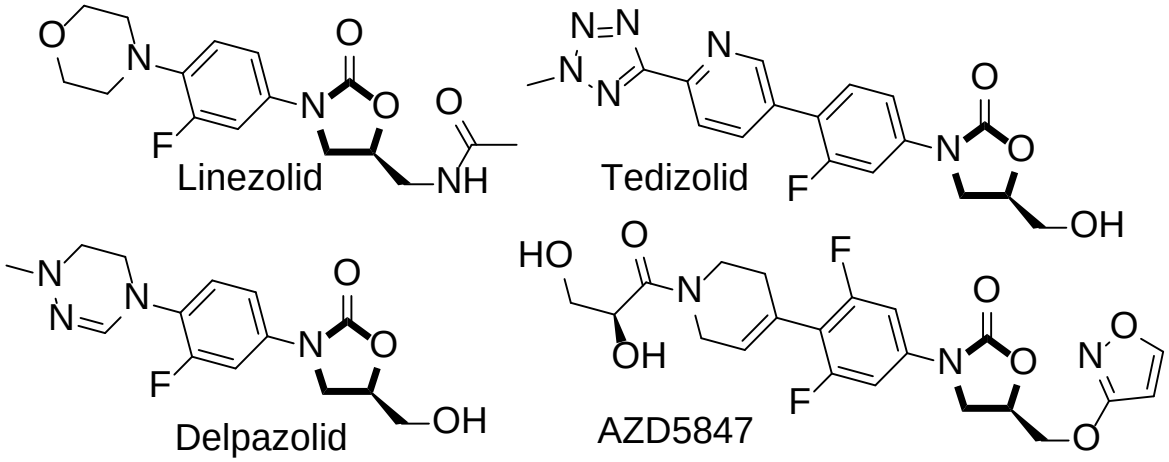
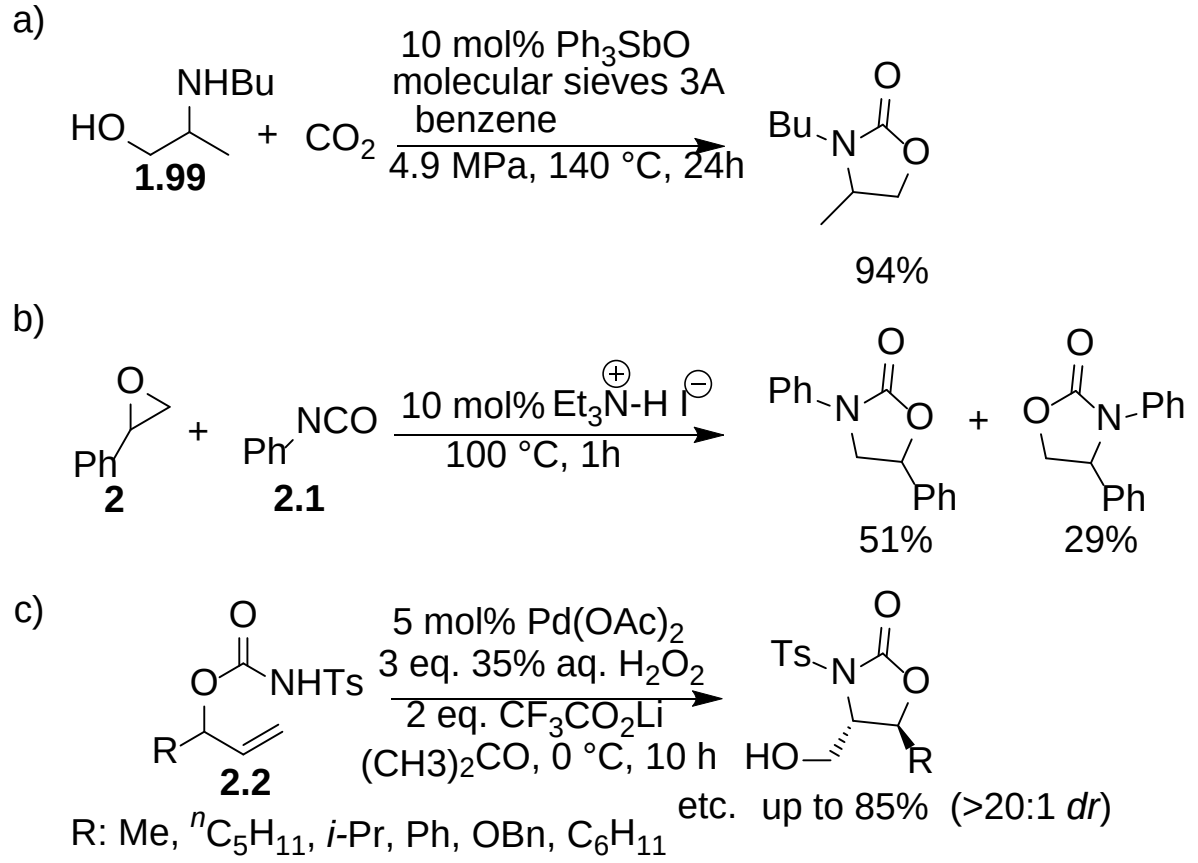


Figure 13: Examples of Pharmaceutical Oxazolidinones[67]

1.12.1 Oxazolidinone Synthesis

There are many methods used to synthesise oxazolidinone rings such as reacting aniline derivatives with an epoxide to form an aminoalcohol **1.99** followed by carbonylative ring closure (Scheme 31a).[67,68] Carbonylation of aminoalcohols to access oxazolidinone rings is a common approach with numerous examples and variations in the literature. An alternative method is the ring expansion of aziridines or epoxides into oxazolidinones catalytically using an iodide salt with solvent. However, in 2020, Nishiyori and coworkers manage to form *in situ* triethylamine hydroiodide for the catalysed coupling of an epoxide **2** with isocyanates **2.1** under solventless conditions[69]. Unfortunately, these types of reactions can suffer from poor regioselectivity (Scheme 31b).[67,69] Ubiquitous palladium catalysis can also

be employed to access oxazolidinones. Indeed, Zhu and coworkers devised a procedure for the aminohydroxylation of alkenes **2.2**, achieving up to 85% yield (Scheme 31c).[67,70]

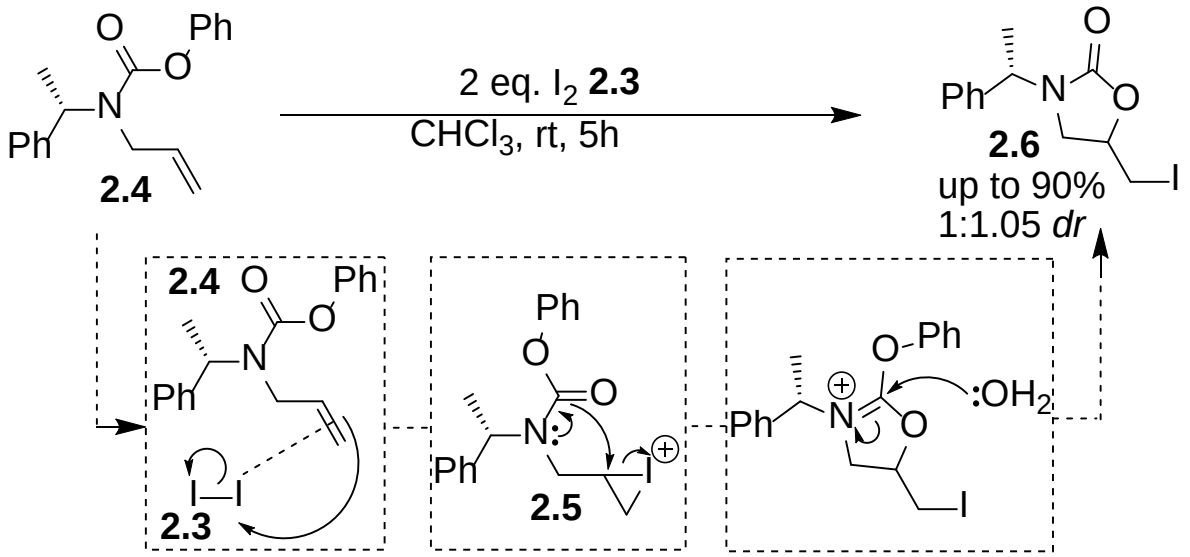


Scheme 31: Oxazolidinone Synthesis Strategies[68,69,70]

1.12.2 Iodocyclocarbamation

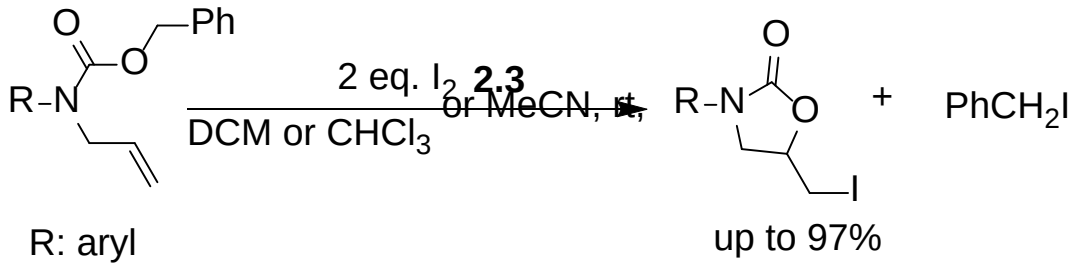
Cardillo and coworkers in 1987 had shown that molecular iodine **2.3** can bring about iodocyclocarbamation of *N*-allyl carbamate **2.4**, however, they did not manage to achieve any noteworthy diastereoselectivity, nor did they expand or develop a scope for the reaction. The reaction was initiated by the co-ordination of molecular iodine **2.3**, causing the alkene **2.4** to attack the iodine forming an iodonium cation intermediate **2.5**. Rapid intramolecular ring closure occurs by the carbonyl oxygen attacking the activated alkene and the lone pair on the nitrogen transferring to form a carbon-nitrogen double bond. The double bond is broken by the addition

of water and then forms an oxonium cation and phenol is ejected. A further water molecule deprotonates the oxonium cation to quench the charge, creating the final oxazolidinone product **2.6** (Scheme 32).[71]



Scheme 32: Iodocyclocarbamation of *N*-allyl carbamates[71]

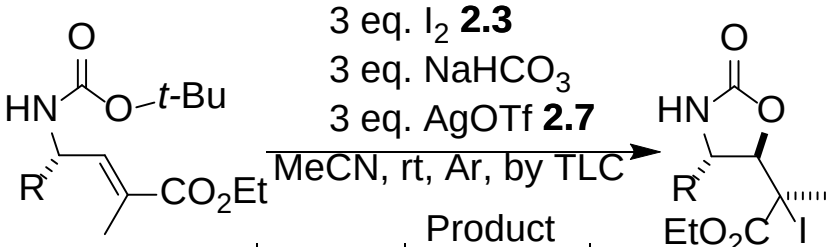
In 2020, Bell and coworkers did address the shortcomings of the work of Cardillo and his colleagues, providing a scope and elaborating on the reaction mechanism and limitations of the reaction, those limitations included a lack of enantioselectivity (Scheme 33).[71,72]



Scheme 33: Iodocyclocarbamation Scope of *N*-allyl carbamates[72]

1.12.3 Asymmetric Iodocyclocarbamation

Guindon and his team in 1995, developed reaction conditions that used molecular iodine **2.3**, sodium bicarbonate, and expensive silver triflate **2.7** to impart cyclisation of carbamates with internal alkenes. However, their oxazolidinone reactions were further employed in radical-mediated hydrogen-transfer stereocontrol reactions (Scheme 34).[73]



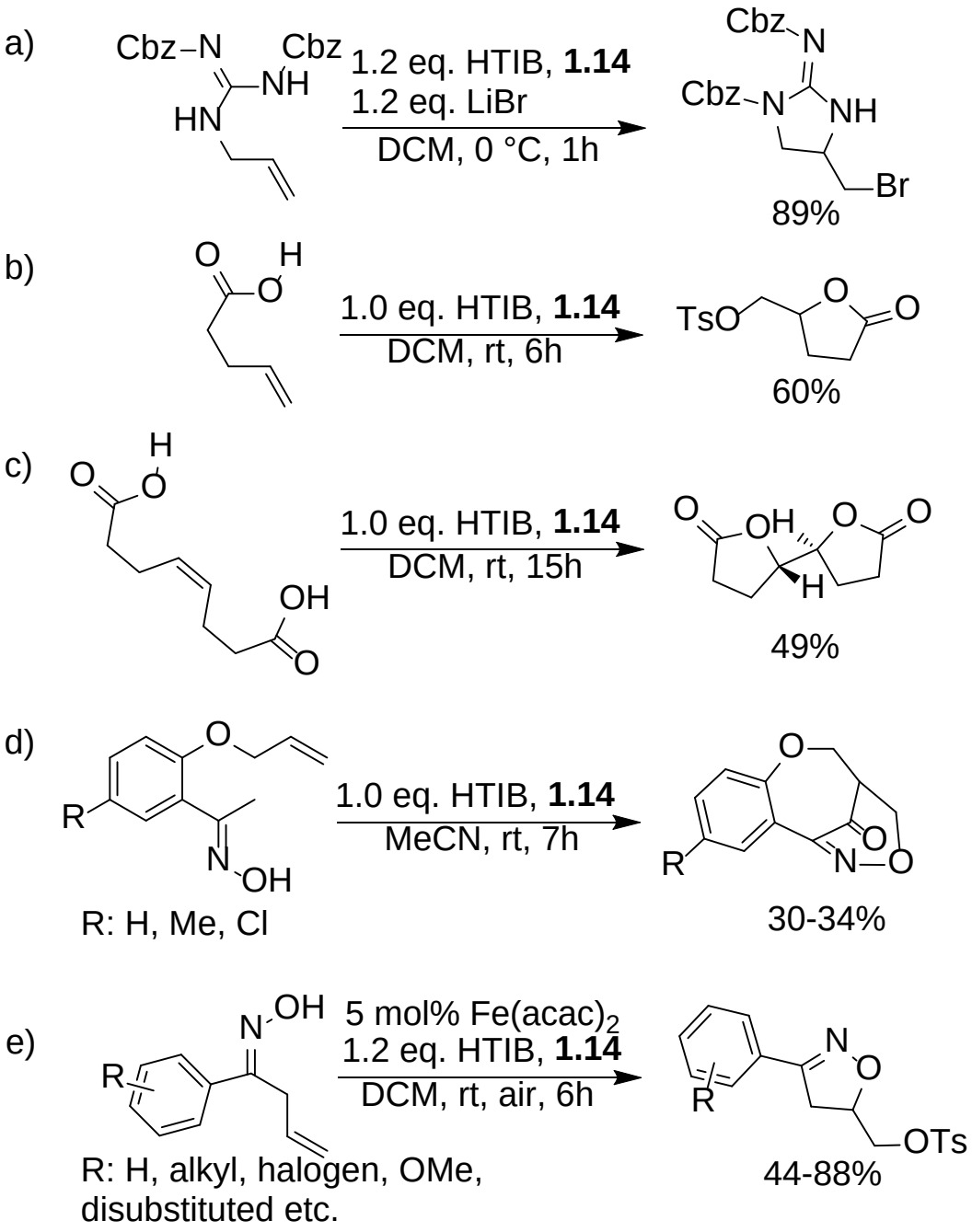
Entry	R	Product Yield (%)	*d.r.*
1	H	73	3:1
2	Me	77	9:1
3	Et	85	9:1
4	*i*-Pr	76	9:1
5	*c*-C_6H_{11}	87	8:1
6	*t*-Bu	82	12:1
7	Ph	76	11:1

Scheme 34: Cyclisation of Carbamates with Internal Alkenes

1.13 Koser's Reagent, (HTIB) 1.14, Mediated Cyclisations

Koser's reagent, [hydroxy(tosyloxy)iodo]benzene (HTIB), **1.14**, has previously been employed as a stoichiometric reagent in a variety of cyclisations. Unsaturated *N*-allylguanidines have been cyclised with Koser's reagent (HTIB), **1.14**, and lithium bromide by Cariou and coworkers (Scheme 35a).[74,75] Shah and coworkers described alkenoic and alkendioic acids reacting with Koser's reagent (HTIB), **1.14**, to give lactones and bis-lactones (Scheme 35b&c).[75] The use of Koser's reagent (HTIB), **1.14**, is reported by De and Mallik, in a [4+2] cycloaddition of

oximes of *ortho*-allyloxyacetophenones to generate nitrosoalkene derivatives (Scheme 35d).[76] Yang and coworkers described the cyclisation of unsaturated oximes with Koser's reagent (HTIB) **1.14**, and an iron(II) catalyst (Scheme 35e).[77] However, there currently are no examples of Koser's reagent (HTIB) **1.14**, or derivatives being used in the cyclisation of *N*-allyl carbamates.



Scheme 35: Koser's reagent (HTIB) Mediated Cyclisations[74,75,76,77]

1.14 Oxazolines

Oxazolines are five-membered heterocycles found in numerous ligand scaffolds, natural products, and biologically active compounds.[78] They are present in food stuffs such as coffee, cocoa, meat products and are used in flavourings for their organoleptic properties.[3] A diverse range of properties has been observed for oxazoline derivatives, their applications include polymer production, as moderators in analytical procedures, and as conformational rigid peptide mimics, natural products with pharmacological properties. Their medicinal properties have resulted in the synthesis of various therapeutic and biologically-active compounds for use as anti-diabetic, anti-bacterial, anti-fungal, anti-microbial, anti-oxidant, anti-pyretic, anti-malarial, anti-viral, anti-inflammatory, CNS stimulant activity, anti-hypertensive, anti-depressive, anti-hypercholesterolemic, anti-cancer, anti-HIV, anti-tumour and anti-Alzheimer agents (Figure 14).[78]

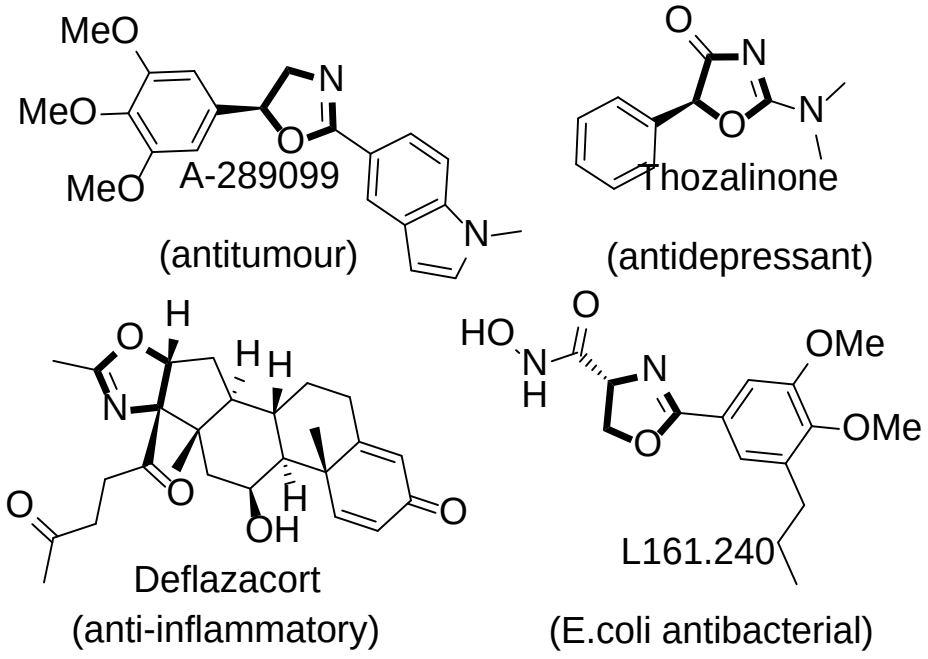
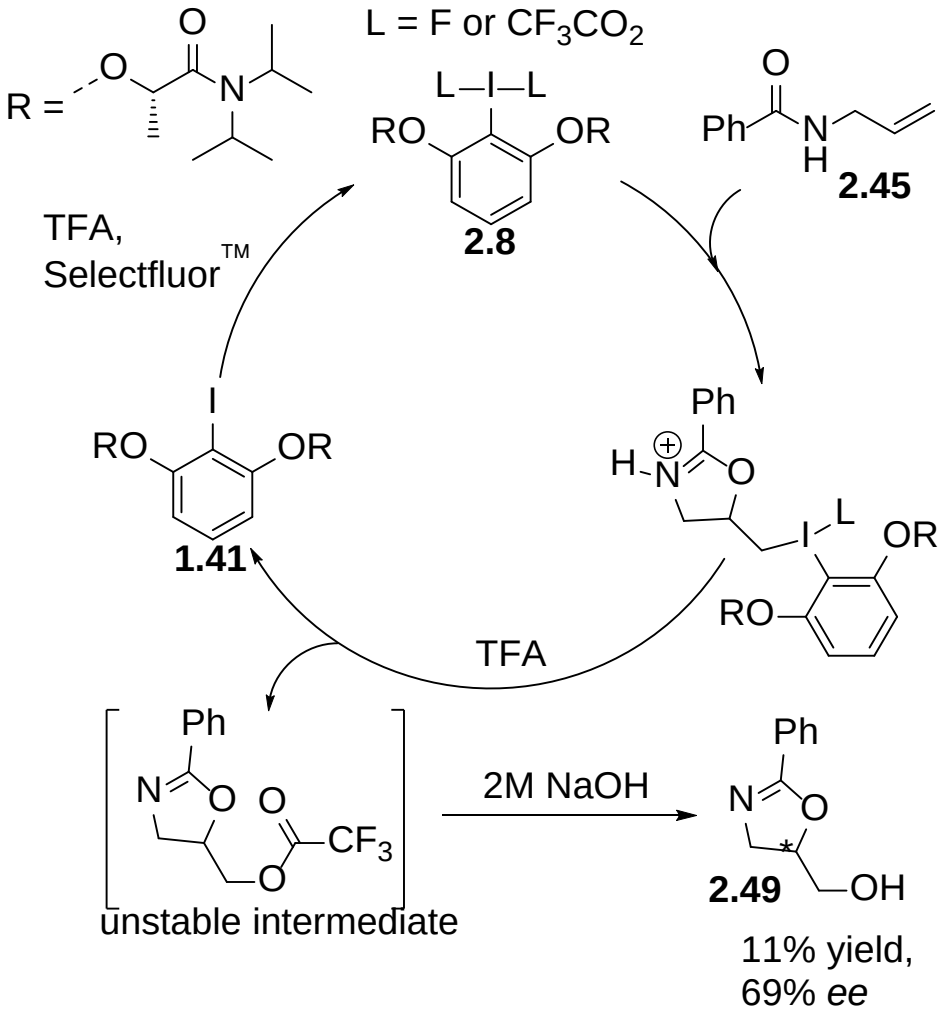


Figure 14: Oxazoline Derivatives with Pharmacologically Activity[78]

1.14.1 Hypvalent Iodine(III) Mediated Oxazoline Synthesis

Moran and coworkers in 2015 reported the catalytic cyclisation of unsaturated amides **2.45** using iodine(III) catalysts **2.8** generated *in situ*. They managed to achieve moderate to good enantiomeric excess albeit with a very low yield, using a chiral Fujita-Ishihara type catalyst **1.41** (Scheme 36).[64] It was envisaged substantial improvement was possible both in terms of enantiomeric excess and forming the aromatic pyrrole derivative for the natural product synthesis of the biologically important Leupryin$_{A1}$.

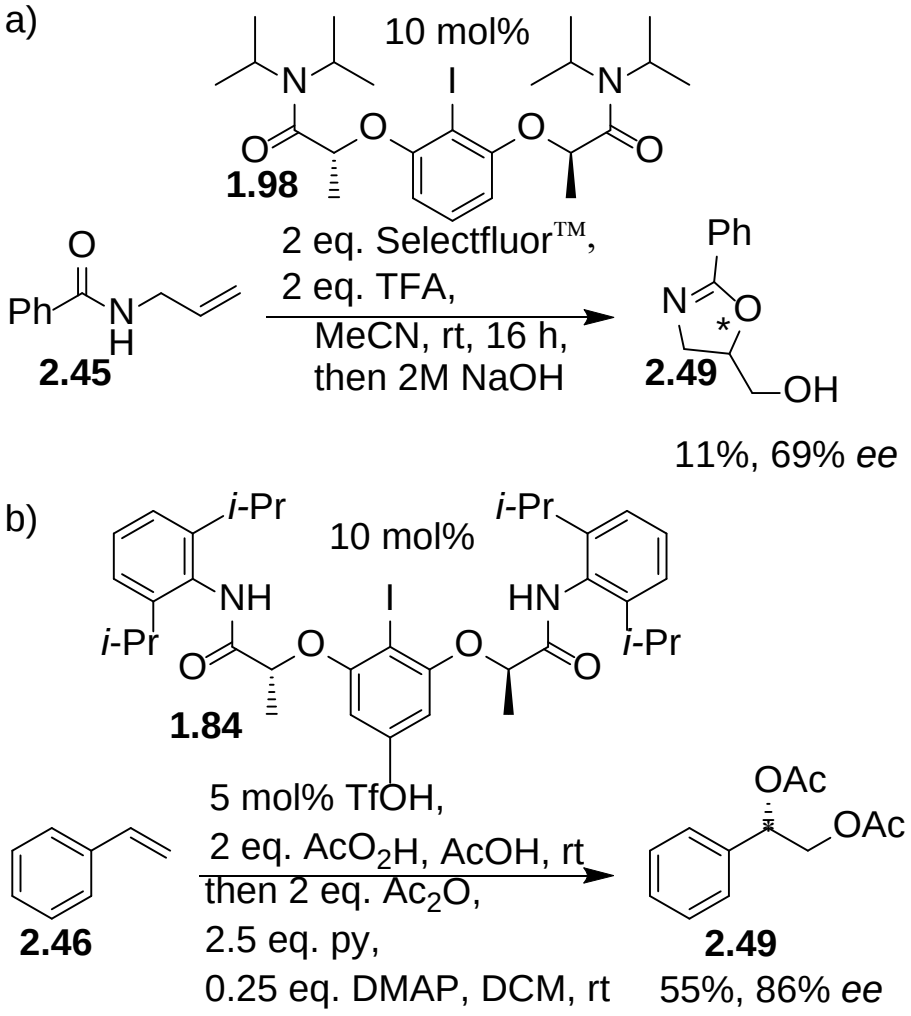


Scheme 36: Asymmetric Catalytic Cyclisation of *N*-allylbenzamide[64]

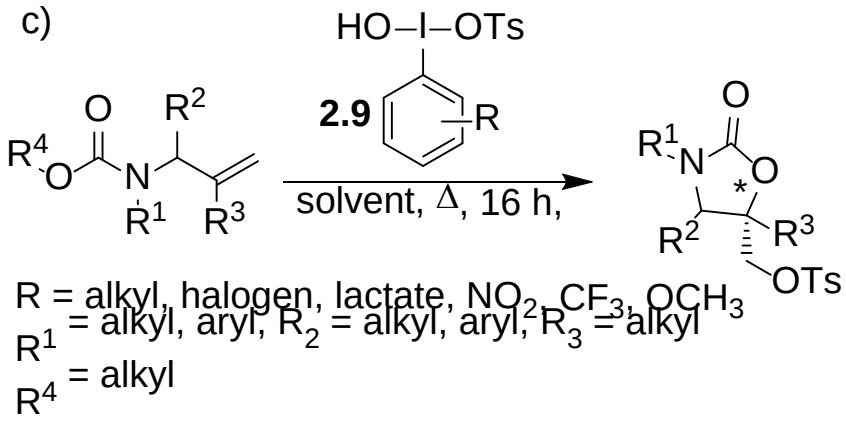
2. Aims and Objectives

2.1 Overall Aims

The aim was to design and develop highly efficient and effective chiral iodoarene catalysts and then evaluate them in a small number of selected enantioselective reactions. The cyclisation of *N*-allybenzamide **2.45** (Scheme 37a) and the diacetoxylation of styrene (Scheme 37b) were selected to investigate chiral catalysts. The aim was also to develop a hypervalent iodine(III) mediated carbamate cyclisation reaction using Koser's type reagents **2.9** and develop an accompanying chiral hypervalent iodine(III) catalyst to impart enantioselectivity (Scheme 37c).



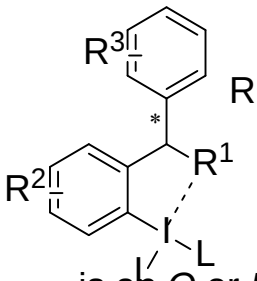
Scheme 37a&b: Selected Asymmetric Reactions for Development



Scheme 37c: Selected Asymmetric Reactions for Development

2.2 Objectives

1. Develop a conformationally rigid chiral iodine(III) precatalyst and evaluate its effectiveness in imparting enantioselectivity (Figure 15).

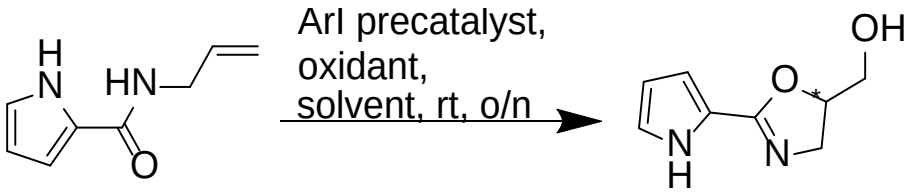


R^2 and R_3: alkyl etc.

where R^1 is an *O* or *N* moiety capable of forming co-ordinate bond with iodine

Figure 15: Basic Structure of Conformationally Rigid iodine(III) Compound

2. Develop an *in situ* hypervalent iodine(III) species, catalysed cyclisation reaction of *N*-allyl-1*H*-pyrrole-2-carboxamide to give the biologically important pyrrole substituted oxazoline fragment (Scheme 38).



Scheme 38: Cyclisation of *N*-allyl-1*H*-pyrrole-2-carboxamide

3. Synthesize a range of chiral iodoarenes and diiodoarenes, investigate their effectiveness in the asymmetric cyclisation of *N*-allylbenzamide (Figure 16).

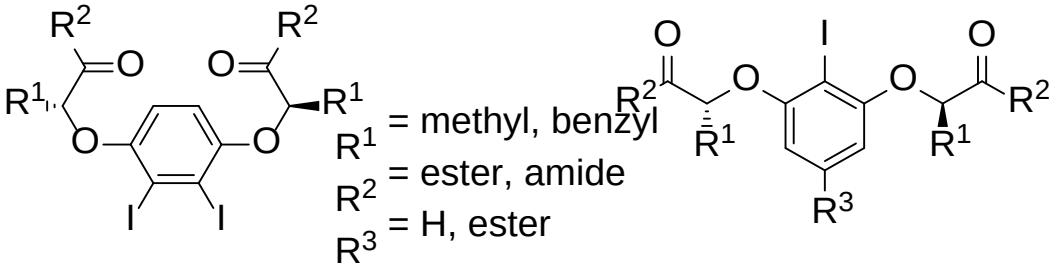
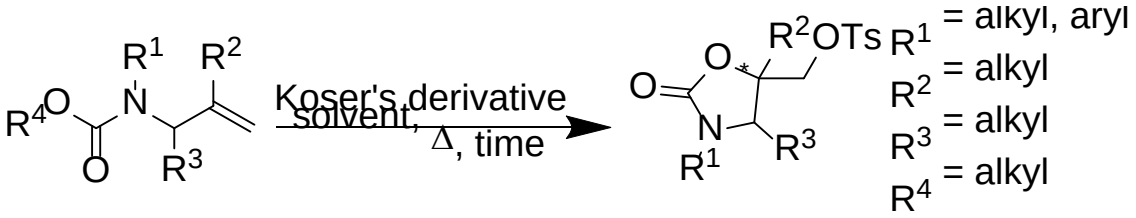


Figure 16: Structures of Monoiodo and Diiodoarenes

4. Develop a Koser's type iodine(III) mediated cyclisation reaction of *N*-allyl carbamate and its derivative (Scheme 39).

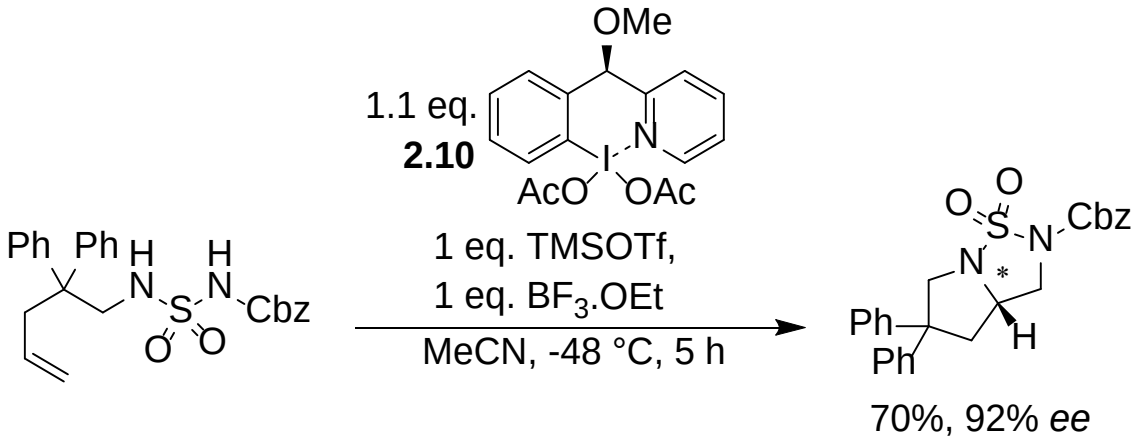


Scheme 39: Cyclisation of *N*-allyl-carbamates

3. Results and Discussion

3.1 Conformationally Rigid Chiral Bis(aryl)iodobenzene(III) Reagent

In 2014, Wirth and coworkers reported the asymmetric cyclisation of diaminosulfone derivatives, while screening various catalysts including conformationally flexible C_2-symmetrical iodoarene bislactate esters **1.52** and bislactamide **1.53** compounds bearing the effective helical chirality.[79] Disappointingly, these catalysts only produced racemic products, the authors cited weaker *n*–σ interactions between carbonyl oxygen of the lactate or lactamide moieties with the hypervalent iodine, and potential interference of the nitrogen atoms in the substrate. They observed more conformationally rigid catalysts gave better enantiomeric excess. Armed with this knowledge, they designed a chiral precatalyst with a benzylic centre attached to a pyridine moiety. It was anticipated coordination of the nitrogen in the pyridine to the iodine atom would occur, potentially acting as a ligand in the iodine(III) structure **2.10**. They hypothesised the short distance to the stereogenic centre would enable high enantiocontrol to be achieved. Using the novel catalyst **2.10** in their cyclisation reaction they achieved a respectable 70% yield with an impressive 92% *ee* (Scheme 40).[79] However, they could not discount secondary interactions by the oxygen of the methoxy coordinating to the iodine as well.



Scheme 40: Conformationally Rigid Iodine(III) Cyclisation

3.1.1 Conformationally Rigid Iodo-diarylmethylamine(III)

A bis(aryl)iodobenzene type catalyst using a similar strategy employed by Wirth and coworkers was prepared and investigated for enantioselectivity in asymmetric reactions. The chiral catalyst would require a Lewis base group to coordinate with the iodine(III) centre, to impart conformational rigidity. From a literature search, a suitable candidate was identified bearing a trifluoromethanesulfonylamine, Lewis base group to coordinate with the hypervalent iodine(III) atom **2.11** (Figure 17).[80]

2.11

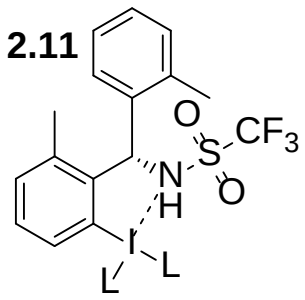
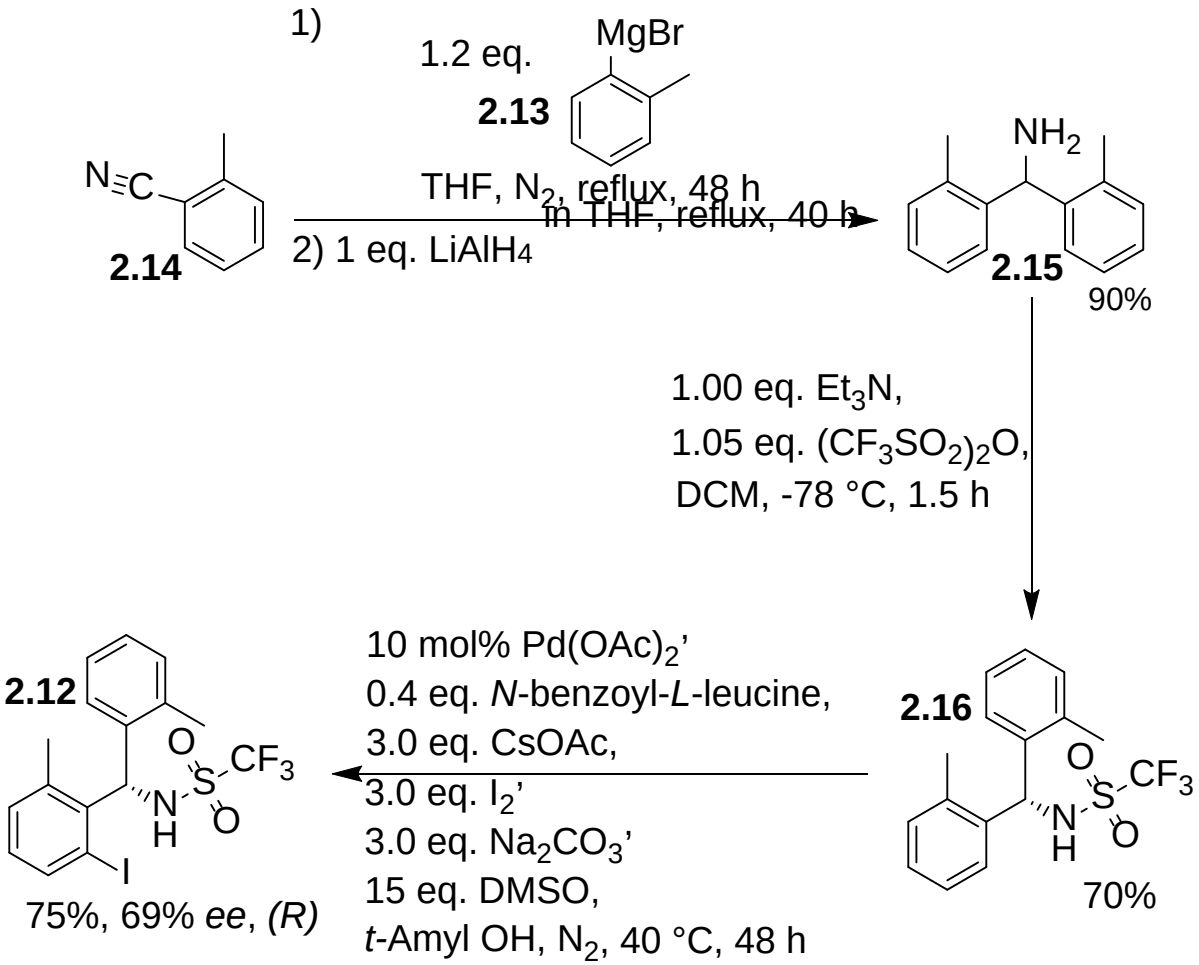


Figure 17: Chiral bis(aryl)iodobenzene$^{(III)}$ with a Triflamide Group

3.1.2 Triflamide Iodo-diarylmethylamine Catalyst Synthesis

Novel use of the known compound **2.12**, was first reported by Wang and coworkers in 2013.[80] The synthesis starts with a Grignard reaction with *o*-tolylmagnesium bromide **2.13** and *o*-tolunitrile **2.14**, creating the bis(2-methylphenyl)methanimine intermediate, which is then reduced to the requisite di-*o*-tolylmethanamine **2.15** with lithium aluminium hydride ($LiAlH_4$). The amine group is then converted to a triflamide protecting group to give the corresponding *N*-(di-*o*-tolylmethyl)-1,1,1-trifluoromethanesulfonamide **2.16**. Followed by a complicated, one-pot, enantioselective palladium catalysed C−H iodination to give the desired triflamide iodo-diarylmethylamine product **2.12**, both the racemic and *(R)*-enantiomer were synthesised for use in developing the HPLC chiral

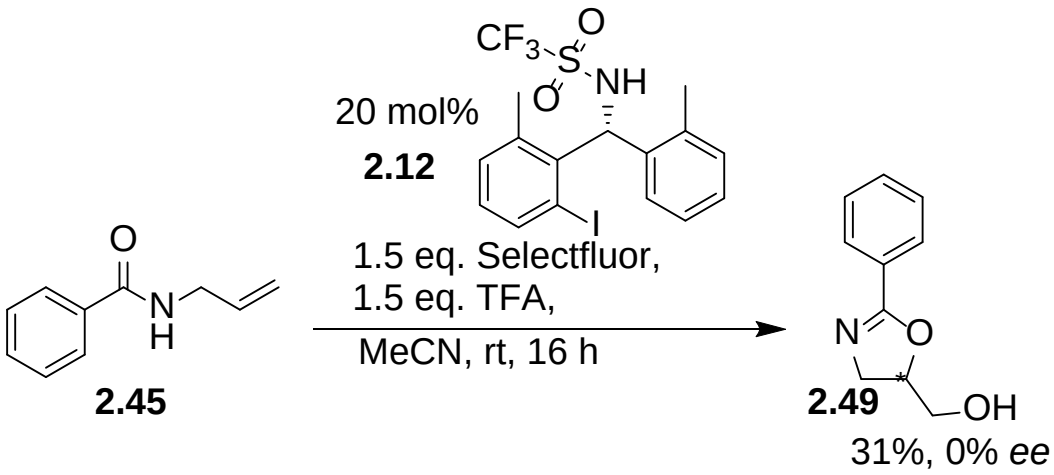
resolution conditions. The enantiomeric excess was evaluated to be slightly less at 69% compared to the reported 78% *ee* (Scheme 41).[80]



Scheme 41: Synthesis of Chiral Bis(aryl)iodobenzene Catalyst[80]

3.1.3 Catalytic Asymmetric Cyclisation of *N*-allylbenzamide

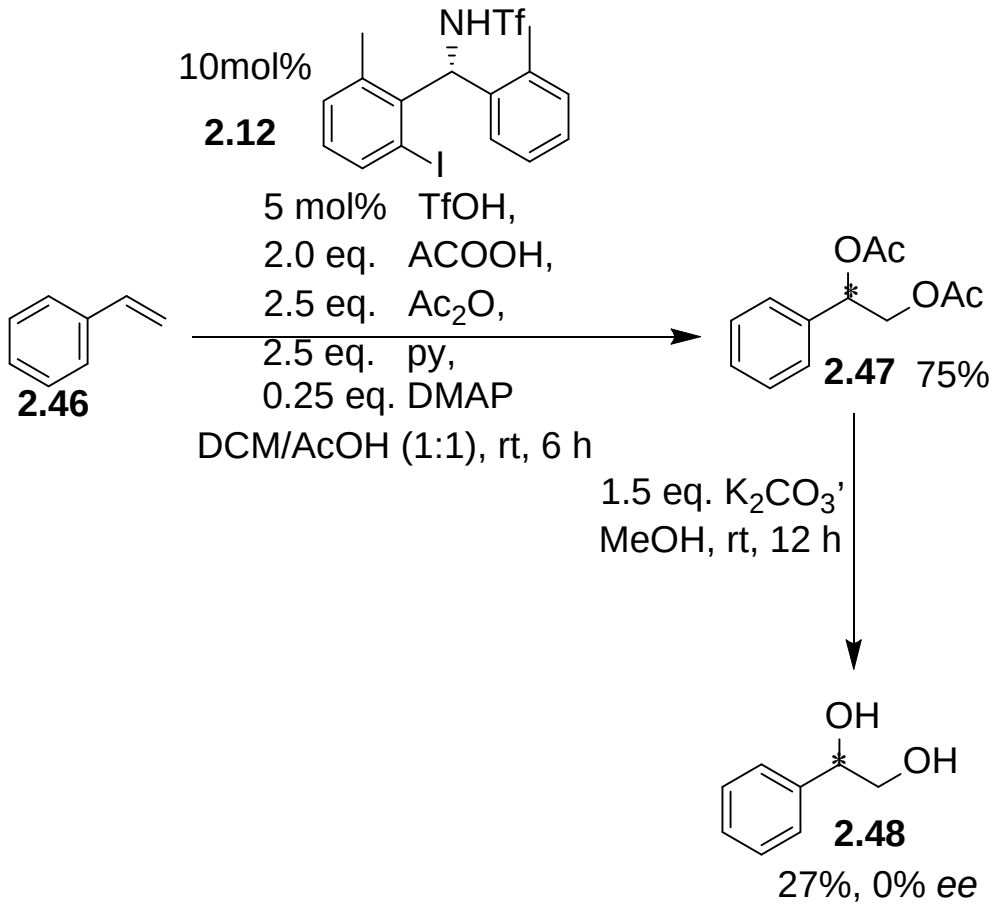
The chiral iodo-diarylmethylamine catalyst was used in the asymmetric cyclisation of *N*-allylbenzamide **2.49** at 20 mol% catalyst **2.12** loading, producing only 31% yield **2.49**. Using the chiral resolution conditions reported by Moran and coworkers both enantiomers were detected, however, the product **2.49** was found to be racemic (Scheme 42).[64]



Scheme 42: Asymmetric Cyclisation of *N*-allylbenzamide[64]

3.1.4 Vicinal Difunctionalisation of Alkenes

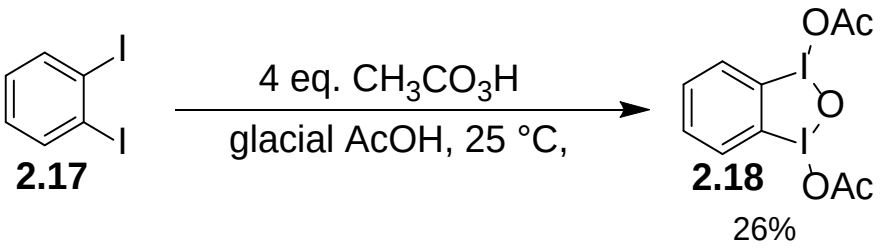
Undeterred by the disappointing result the iodo-diarylmethylamine chiral catalyst **2.12** was then evaluated in the Woodward-Prevost diacetoxylation of styrene **2.46**. The vicinal diacetate product **2.47** required conversion to the corresponding vicinal diol **2.48** before chiral resolution and analysis. The diacetate product **2.47** was produced in 75% yield, however, the corresponding vicinal diol **2.48** was found to be racemic (Scheme 43). Due to the poor results across two asymmetric reactions, it was decided to discontinue further development.



Scheme 43: Enantioselective Diacetoxylation of Styrene

3.2 1,2-Diiodoarene Catalysts

Muñiz and coworkers in 2016, inspired by the work of Kita and his 1,2-diiodoarene catalyst **2.17**, reported that Kita's oxidised 1,2-diiodoarene gave superior catalytic loading efficiency of 3 to 4% in the amination of arenes.[81,82] Muñiz and coworkers investigated the oxidation of 1,2-diiodobenzene with peracetic acid, which gave a μ-oxo-bridged bisiodine(III) acetate derivative **2.18**. X-ray analytical studies found the *in situ* generated five-membered bisiodine(III) μ-oxo-ring **2.18** was highly strained (Scheme 44). This was due to substantial distortion of linearity of the I-O-I in the five-membered arrangement, which gave rise to its high reactivity compared to single iodine(III) species. Muñiz and coworkers, unfortunately, did not synthesise chiral derivatives of their diiodo moiety and hence it could not be used in asymmetric hypervalent iodine catalysis.



Scheme 44: Oxidation of 1,2-Diiodobenzene with Peracetic acid[82]

3.2.1 Chiral 1,2-Diiodoarene

Inspired by Muñiz and coworker's limited use of their diiodo catalyst **2.17**, there was an opportunity to design and develop a superior chiral catalyst with the diiodo moiety.[82] As previously mentioned, helical chirality is the most successful enantiocontrol strategy with regards to hypervalent iodine(III) catalysis. Therefore, combining a Fujita-Ishihara type catalyst with a diiodo moiety could create a powerful new class of superior chiral iodoarene catalysts.[22] Given the above parameters, a rudimentary catalyst design was envisaged **2.19** (Figure 18).

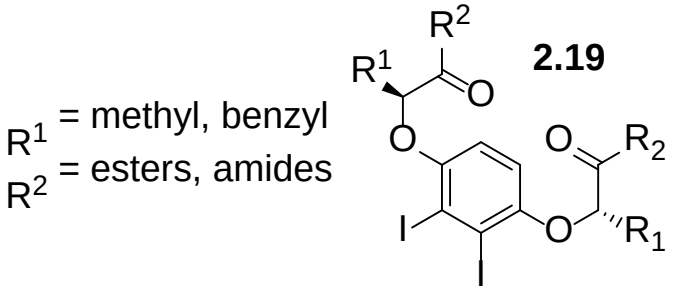
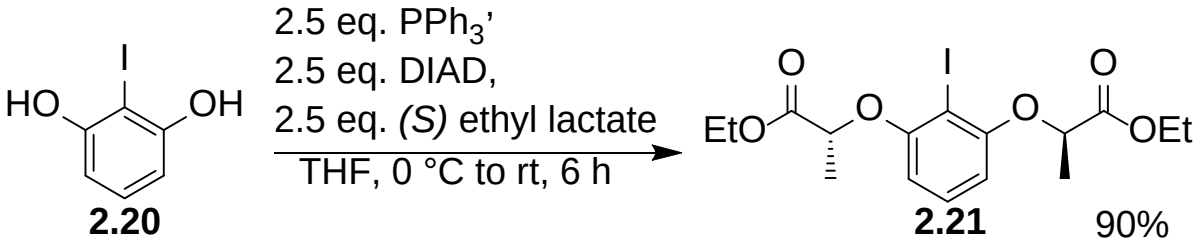


Figure 18: Diiodo Fujita-Ishihara Type Chiral Catalyst Design

3.2.2 Helical Iodoarene Catalyst Synthesis Strategy

It was anticipated that the well-established Fujita-Ishihara synthetic procedure would be employed to access the desired chiral diiodo derivatives. Ishihara's procedure started with resorcinol **2.20** or derivatives and subjected them to a Mitsunobu coupling reaction to install

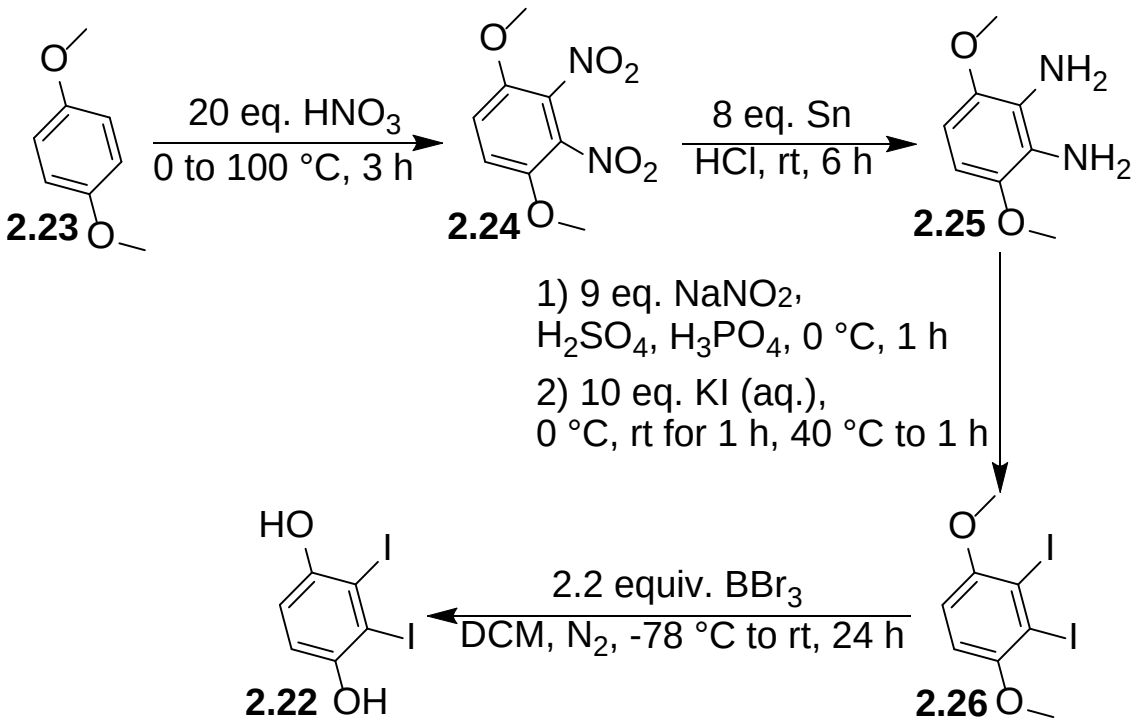
the *(S)* lactate ethyl ester appendages **2.21** (Scheme 45).[22] Then conversion to the corresponding carboxylic acid, then acyl chloride intermediate, which can then be used to access a range of bislactate esters **1.52** and bislactamides **1.53.**[22]



Scheme 45: Ishihara's Mitsunobu Reaction

3.2.3 2,3-Diiodohydroquinone Synthesis Strategy

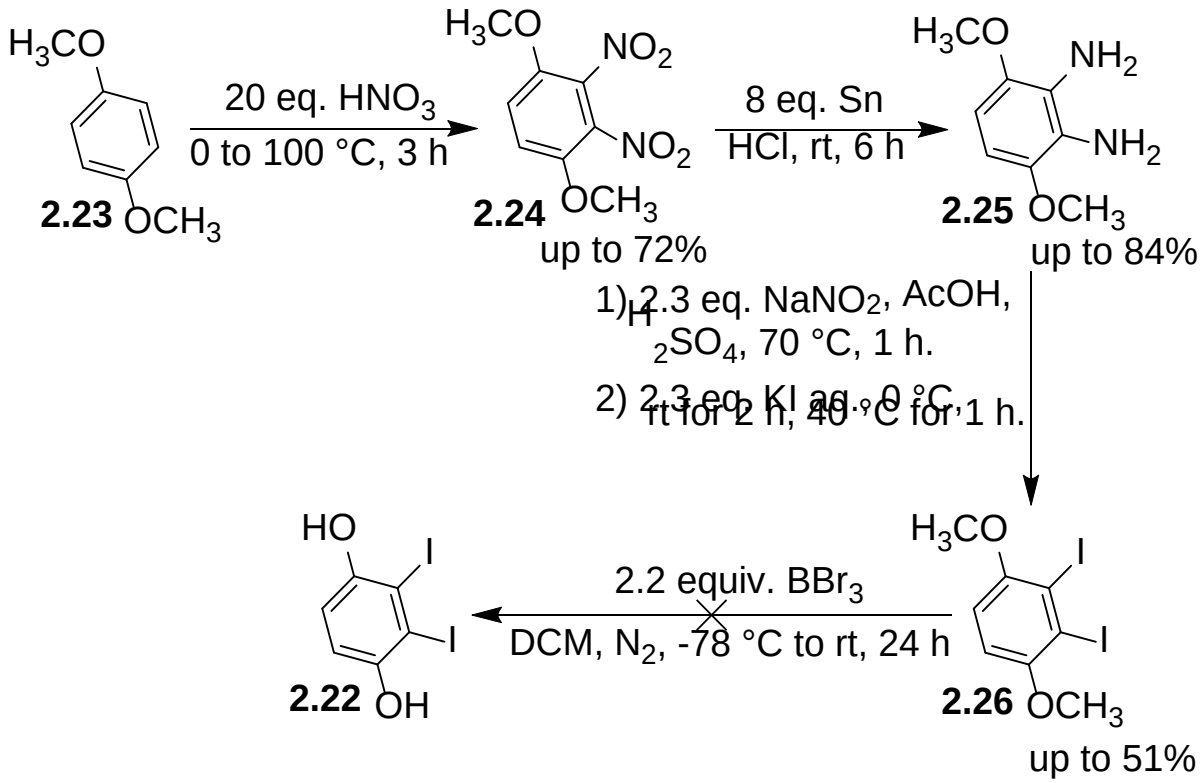
However, the new procedure required 2,3-diiodohydroquinone substrate **2.22**, which was not commercially available, a procedure by Hammershøj and coworkers was found to synthesise the substrate **2.22** (Scheme 46).[83] It involved starting with relatively cheap, 1,4 dimethoxybenzene **2.23** and di-nitrating at the ortho and meta positions on the phenyl ring, giving the dinitro intermediate **2.24**. Followed by a simple and quick reduction to the corresponding diamine **2.25**. Once the diamine **2.25** was formed a challenging double diazotisation reaction could be conducted to afford the 1,4-dimethoxy-2,3-diiodobenzene **2.26**. Which could then be demethylated using a literature procedure by Ricks-Laskoski and coworkers, to the 2,3-diiodohydroquinone substrate **2.22**, before the Mitsunobu reaction can be conducted.[84]



Scheme 46: 2,3-Diiodohydroquinone Synthesis Strategy[83]

3.2.4 Development of 2,3-Diiodohydroquinone Preparation

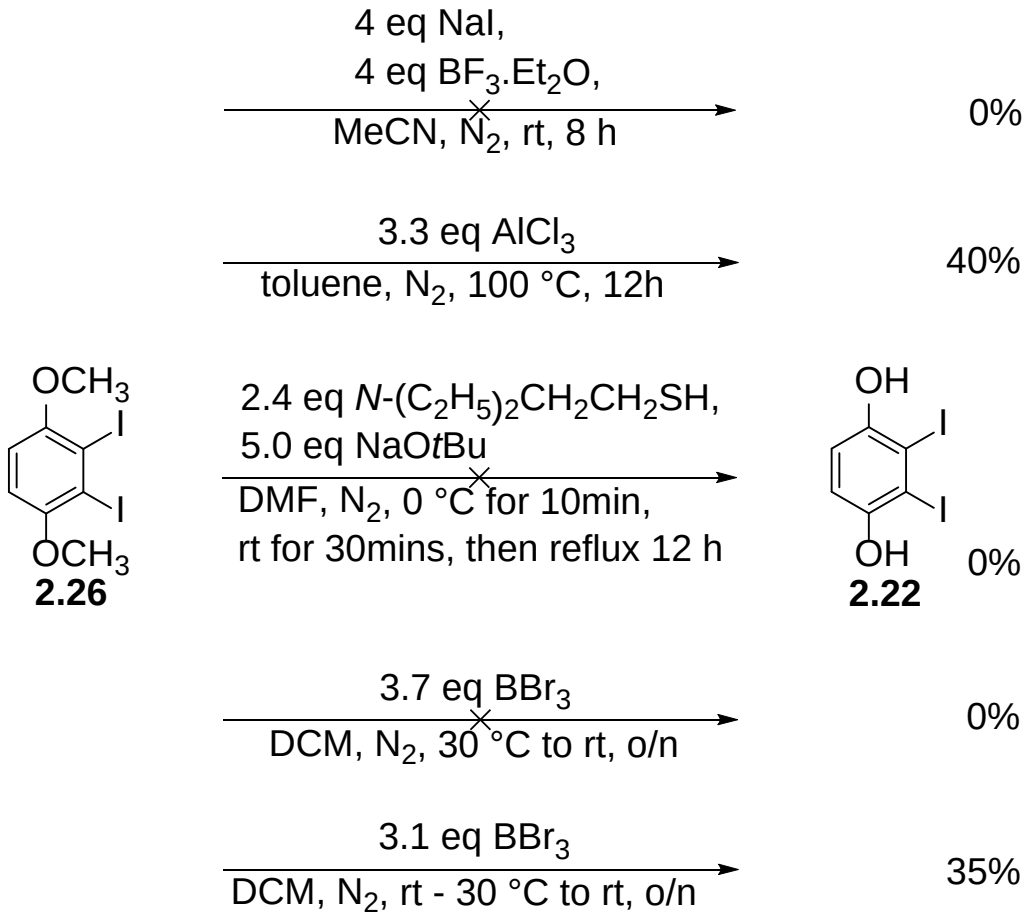
Dinitration of the 1,4-dimethoxybenzene **2.23** proceeded with an acceptable yield of up to 72% **2.24**, however, the reaction suffered from regioselectivity issues and did also produce the 2,5-dinitro byproduct. Reduction of the nitro groups to the corresponding diamine **2.25** occurred without any issues and achieved a yield of up to 84%. Double vicinal iodination was difficult and involved producing a double diazonium salt followed by displacement of the azo group with a halide i.e. iodide. The yields were low probably due to the steric hindrance of trying to iodinate two adjacent phenyl positions, in literature yields of over 60% were reported. Unfortunately, lower yields of up to 51 % **2.26** were observed, which heavily impacted the continued synthesis. The final ether cleavage or demethylation step was problematic, the selected generic literature procedure employed did not bring about the desired transformation (Scheme 47).[83]



Scheme 47: 2,3-Diiodohydroquinone Preparation[83]

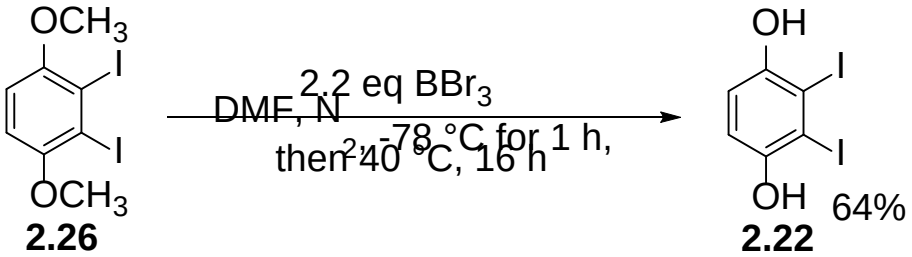
3.2.5 Ether Cleavage of 1,4-Dimethoxy-2,3-diiodobenzene

The demethylation of 1,4-dimethoxy-2,3-diiodobenzene **2.26** required numerous attempts to find effective reaction conditions. After further literature searches, boron tribromide, (BBr_3) reagent, was identified as an effective demethylating reagent.[84] The reagent had brought about demethylation albeit inconsistently. A wide arrange of procedures using various reagents and conditions, some using elevated temperatures at various stages were assessed. Using sodium iodide (NaI), and the 2-(diethylamino)ethanethiol in reactions detected only starting material.[136, 137] The reactions with aluminium trichloride ($AlCl_3$), and 3.1 equivalents of boron tribromide (BBr_3), respectively gave partial conversions and with 3.7 equivalents of boron tribromide (BBr_3), decomposition occurred (Scheme 48).[138,84]



Scheme 48: Demethylation Attempts[84,136,137,138]

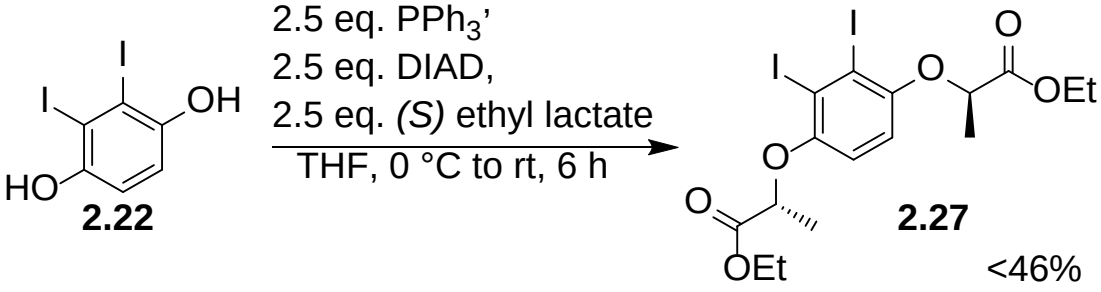
Eventually, with perseverance, a modified literature procedure to access the desired 2,3-diiodohydroquinone **2.22** product consistently was discovered, resulting in a yield of 64% (Scheme 49).[84]



Scheme 49: Demethylation of 1,4-Dimethoxy-2,3-diiodobenzene

3.2.6 Mitsunobu Coupling with 2,3-Diiodohydroquinone

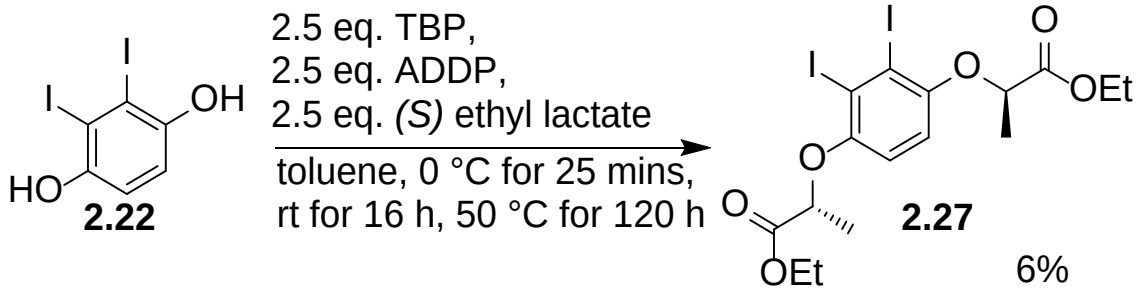
Ishihara's Mitsunobu reaction conditions were used to install the chiral lactate appendages to the 2,3-diiodohydroquinone **2.22** substrate.[22] The reaction was discovered to be unscalable with the diiodo substrate **2.22**, producing large amounts of waste such as triphenyl phosphine oxide (Ph_3PO) and very little product **2.27** hence requiring a great deal of careful purification. Numerous attempts were made to modify the reaction conditions to improve the yield and scalability but were generally unsuccessful. Sonication of the reaction mixture slightly improved the yield to slightly less than 46% at the 50 mg scale (Scheme 50).



Scheme 50: 2,3-Diiodohydroquinone Mitsunobu Coupling

3.2.7 Alternative Robust Mitsunobu Conditions

Given the difficulty in scalability and yield, alternative Mitsunobu conditions for challenging reactions were used. Unfortunately, these conditions were ineffective in improving the yield or scalability (Scheme 51).[85]



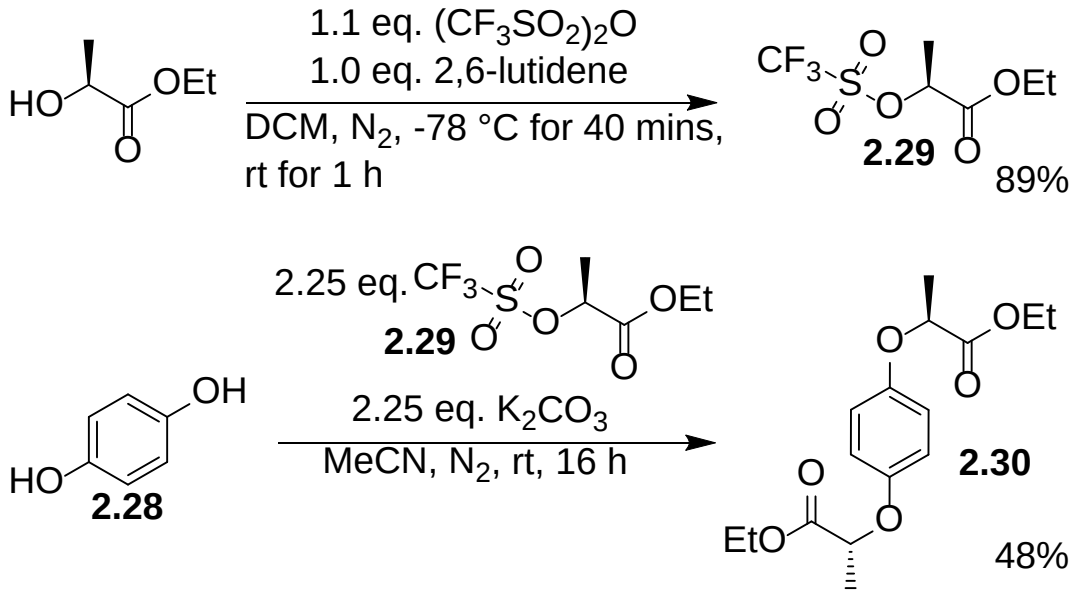
Scheme 51: Robust Mitsunobu Conditions

3.2.8 Mitsunobu Reaction

Mitsunobu reaction is the dehydrative coupling of a secondary, chiral alcohol to a pronucleophile, causing an inversion of the stereocentre.[86] However, the reaction suffers from serious drawbacks such as a lack of atom efficiency. Typical azo reagents, such as diethyl azodicarboxylate, are toxic as well as light and shock sensitive, it produces massive amounts of waste, including hydrazinedicarboxylates and triphenylphosphine oxide (Ph_3PO), making purification of the desired product difficult.[87] In the present case, it is unresponsive to optimisation of yield and scalability. An alternative reaction was desperately sought for progression to access the desired diiodo catalysts.

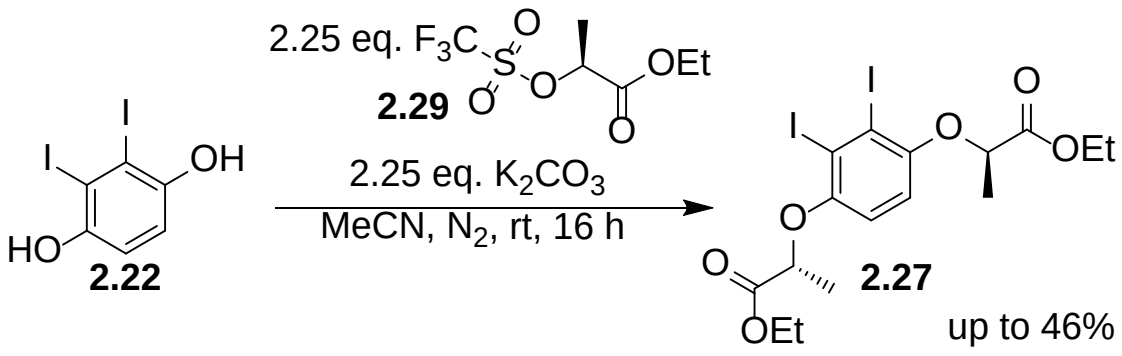
3.2.9 Mitsunobu Reaction Alternative

In 1985, Burkard and Effenberger reported on the promising S_N2 substitution of triflate esters with O and S nucleophiles with inversion of the stereocentre.[88] There was an attempt to evaluate the reaction using commercially available 1,4-hydroquinone **2.28**. Before the coupling of the chiral ethyl (*S*) lactate, the lactate was first converted to the corresponding triflate electrophile **2.29**. The coupling reaction was conducted at 110 mg scale under mild conditions and resulted in the desired product **2.30**, work up and purification was simple and effective due to the significant differences in the polarity of the reactants and product (Scheme 52).



Scheme 52: S_N2 Substitution of Triflate Esters

The reaction had huge potential due to the scalability, further evaluation with the requisite diiodo substrate at the 110 mg scale was conducted. The reaction consistently yielded 46% (Scheme 53). The reaction was repeated on numerous occasions to evaluate the scalability of the reaction. The reaction was scalable up to gram scale, and hence the S_N2 substitution of triflates replaced the Mitsunobu reaction for most of the chiral lactate coupling reactions with single or double iodine substrates.



Scheme 53: 2,3-Diiodohydroquinone S_N2 Substitution

3.3. Chiral Catalyst Synthesis

3.3.1 Synthesis of Chiral Iodoarene Bislactate Analogues

Jacobsen and coworkers in 2016, reported high enantioselectivity in their asymmetric geminal and vicinal difluorination of alkenes with iodoarene catalysts bearing benzyl and para methyl ester groups.[89,90] It was decided a wide range of iodo and diidoarene catalysts with or without para esters, methyl, and benzyl groups would be synthesised using the Mitsunobu reaction or triflate S_N2 substitution reaction (Table 1).

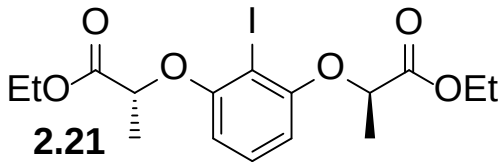
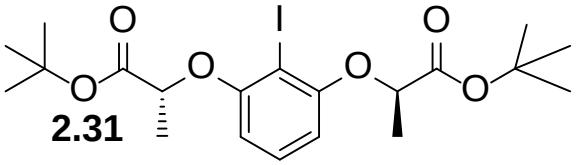
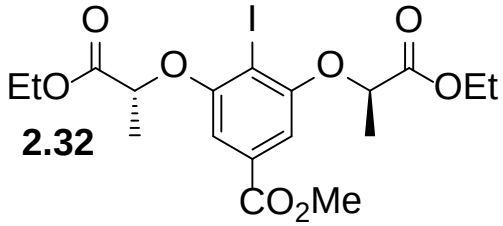
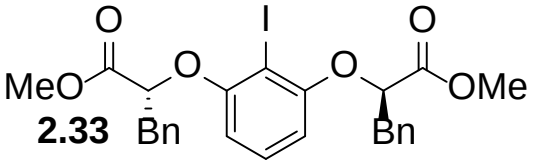
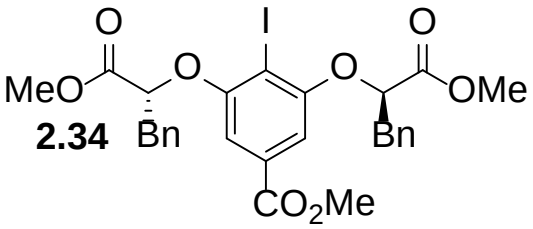
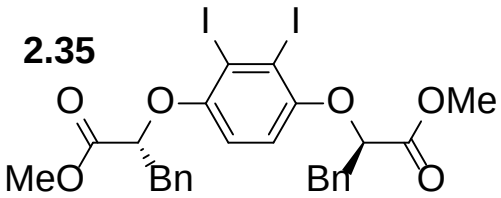
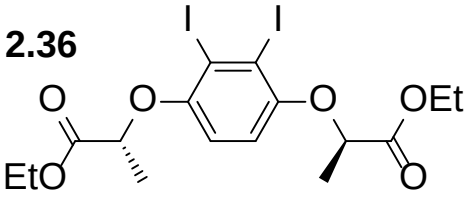
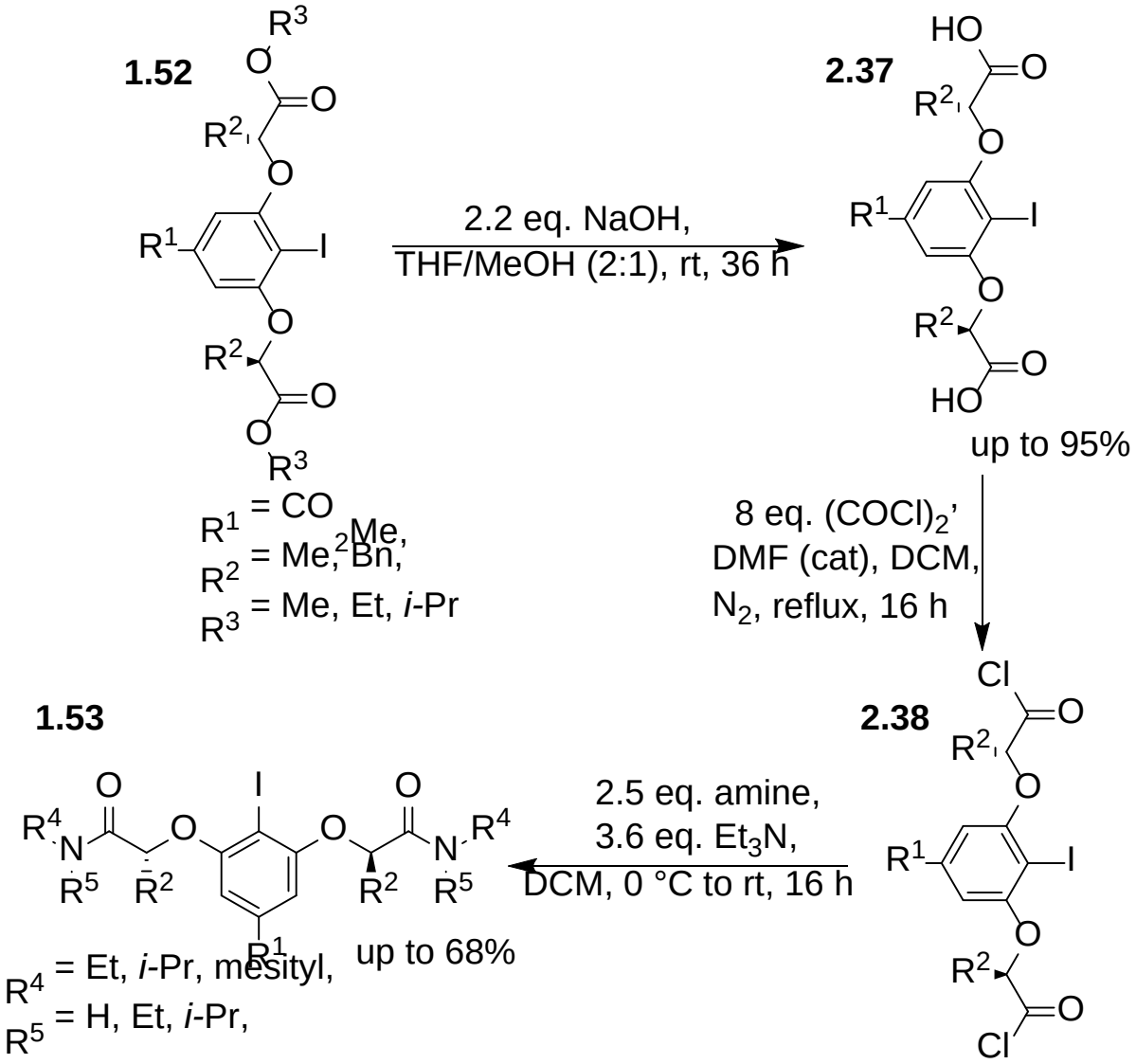
Entry	Reaction	Bislactate Chiral Catalyst	Yield
1	Mitsunobu	 **2.21**	71%
2	Mitsunobu	 **2.31**	76%
3	Triflate S_N2 substitution	 **2.32**	98%
4	Triflate S_N2 substitution	 **2.33**	99%
5	Triflate S_N2 substitution	 **2.34**	99%
6	Triflate S_N2 substitution	 **2.35**	74%
7	Triflate S_N2 substitution	 **2.36**	48%

Table 1: Chiral Iodoarene Bislactatate Catalysts

3.3.2 Synthesis of Chiral Bislactamide Catalysts

Further derivatisation of the iodoarene bislactates **1.52** were performed to take maximum advantage of helical chirality. A range of iodoarene bislactamides **1.53** were produced by first hydrolysing the bislactates **1.52** to the corresponding bislactic acids **2.37**. Then to the reactive bisacyl chloride intermediate **2.38**, which was used without purification, before the amidation reaction to give bislactamides **1.53** (Scheme 54) (Table 2).



Scheme 54: Chiral Bislactamide Preparation

A Mitsunobu reaction was employed to prepare the known dicarbamate Fujita-Ishihara second-generation chiral catalyst **2.40** (entry 3, Table 2).[59]

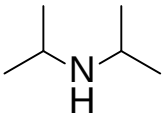
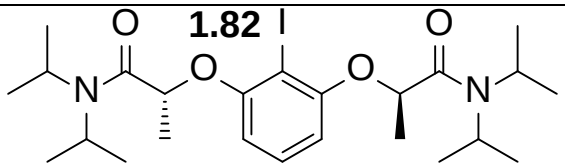
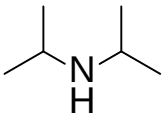
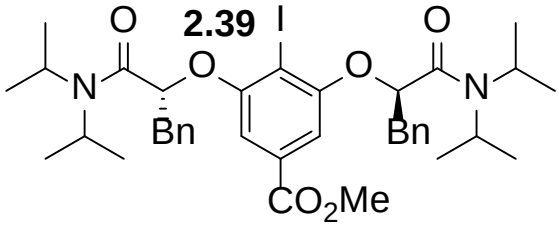
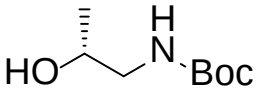
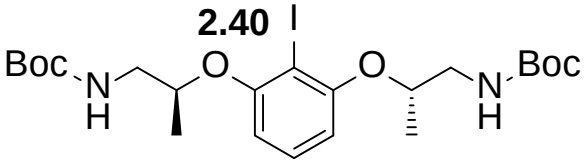
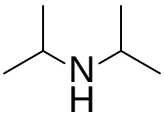
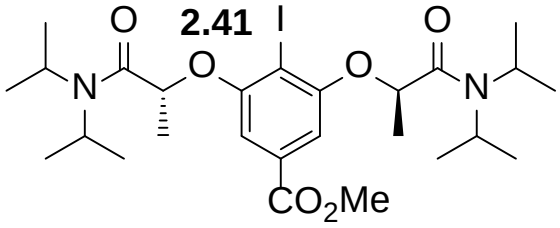
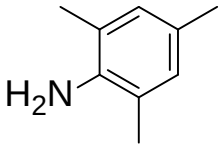
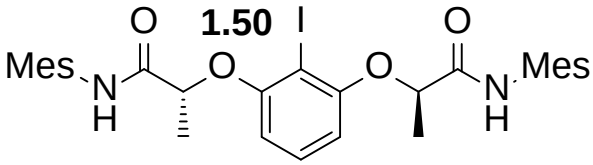
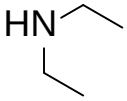
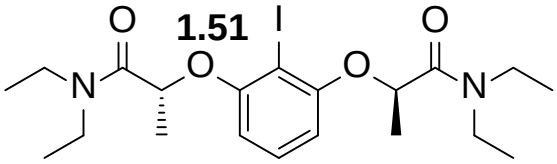
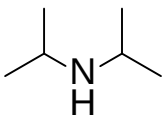
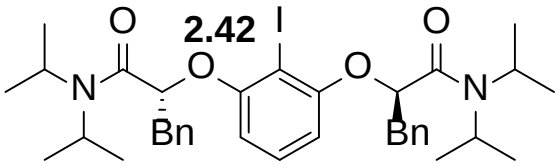
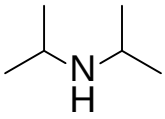
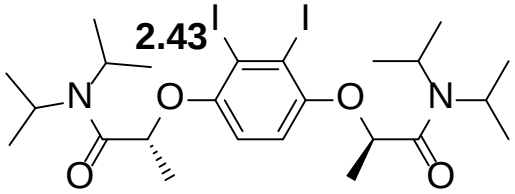
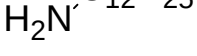
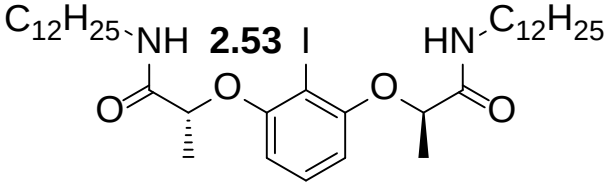
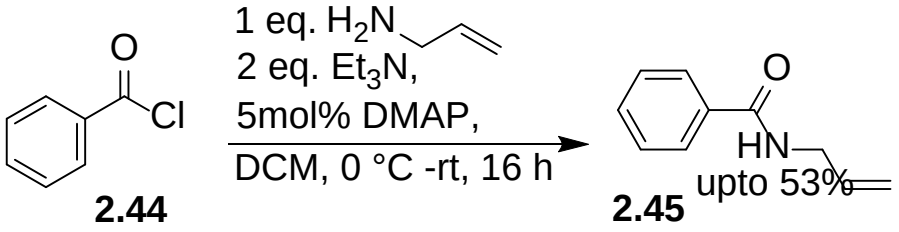
Entry	Reactant	Bislactamide Chiral Catalyst	Yield
1		**1.82** 	76%
2		**2.39** 	56%
3		**2.40** 	67%
4		**2.41** 	56%
5		**1.50** 	48%
6		**1.51** 	42%
7		**2.42** 	48%
8		**2.43** 	42%
9		 **2.53**	68%

Table 2: Chiral Iodoarene Bislacatamide Catalysts

3.4. Chiral Catalyst Evaluation

3.4.1 *N*-allylbenzamide Preparation

Before evaluations could be started the test substrate had to be prepared, reacting benzoyl chloride **2.44** with allylamine to obtained the desired substrate, *N*-allylbenzamide **2.45** (Scheme 55).[64]

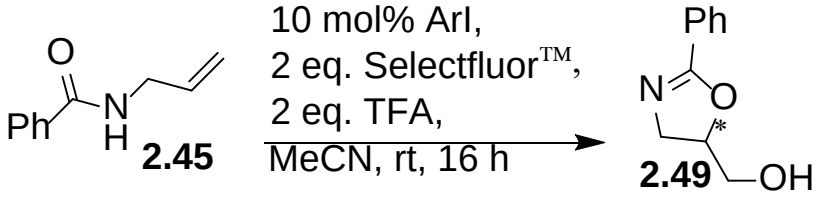


Scheme 55: *N*-allylbenzamide Preparation[64]

3.4.2 Asymmetric Cyclisation Chiral Catalyst Evaluation

A range of chiral catalysts was evaluated in the catalytic cyclisation of *N*-allylbenzamide **2.45** (Table 3). The iododiaryltriflamide **2.12** gave a product **2.49** yield of 31%, however, was ineffective in imparting enantioselectivity (entry 1, Table 3). The iodoarene bislactate bearing a *para* methyl ester **2.32** gave a product **2.49** yield of 41% and 20% *ee* (entry 3, Table 3). The corresponding iodoarene bislactamide **2.41** gave a **2.49** yield of 54% and an *ee* of 19% (entry 2, Table 3), suggesting iodoarene lactates **2.32** and amides **2.41** with *para* esters give similar selectivity. Diiodoarene bislactate with benzyl groups **2.35** gave a **2.49** yield of 39% and the best *ee* of 24% (entry 5, Table 3), compared to a bislactate without the benzyl group **2.36** gave a racemic product **2.49** yield of 60% (entry 6, Table 3). Indicating that benzyl groups influence selectivity probably due to sterics. The diiodoarene bislactamide without the benzyl groups **2.43** gave a **2.49** yield of 29% and an *ee* of 15% (entry 4, Table 3). Implying that diiodoarenes with bislactamide **2.43** give greater

selectivity compared to the diiodoarene bislactate **2.36** (entry 6, Table 3).



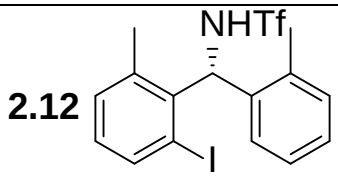
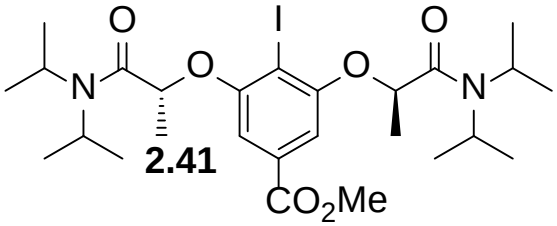
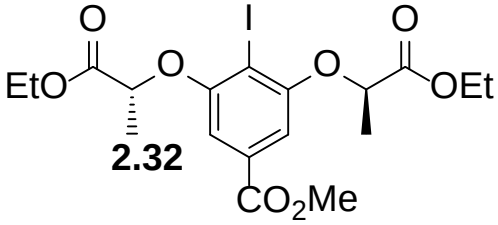
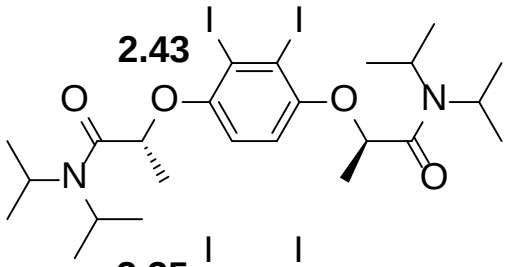
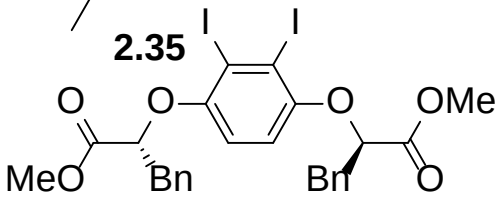
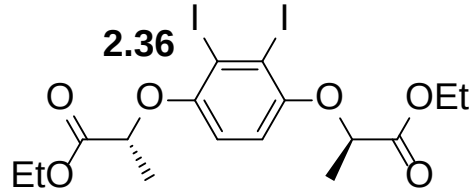
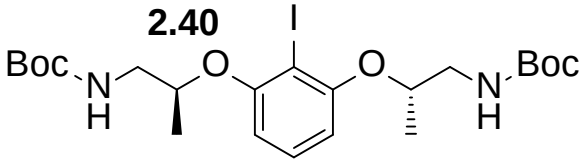
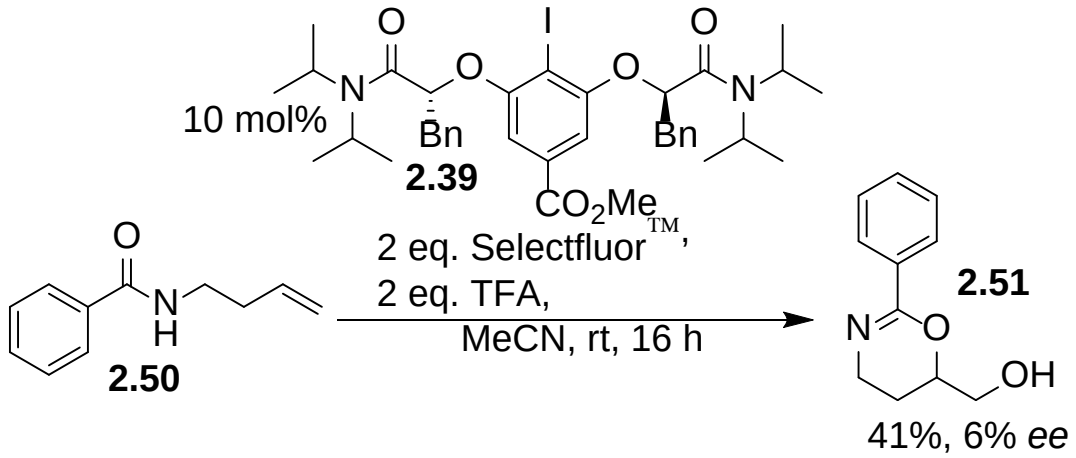
Entry	Chiral Catalyst	Oxazoline Yield	% ee
1	 **2.12**	31%	racemic
2	 **2.41**	54%	19%
3	 **2.32**	41%	20%
4	 **2.43**	29%	15%
5	 **2.35**	39%	24%
6	 **2.36**	60%	racemic
7	 **2.40**	0%	-

Table 3: Enantioselectivity Analysis of Chiral Catalysts

3.4.3 Asymmetric Cyclisation of *N*-(but-3-en-1-yl)benzamide

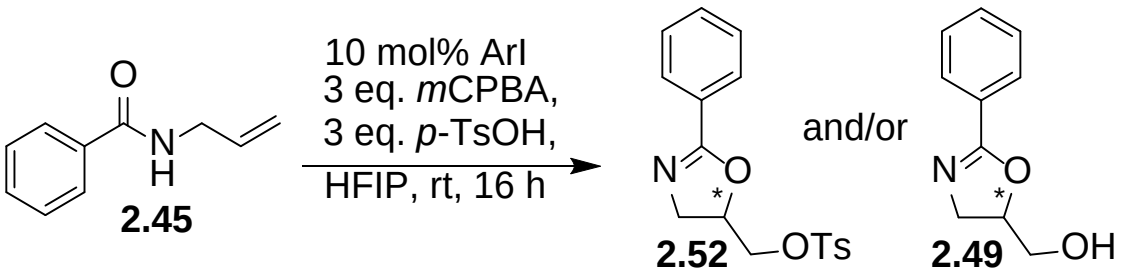
A chiral iodoarene bislactamide bearing the para ester group **2.39** was also evaluated in the asymmetric cyclisation of *N*-(but-3-en-1-yl)benzamide **2.50**, yielding 41% of the 6 membered oxazoline ring **2.51** with 6% *ee* (Scheme 56).



Scheme 56: Asymmetric Cyclisation of *N*-(but-3-en-1-yl)benzamide

3.4.4 Novel *N*-allylbenzamide Cyclisation Reaction Conditions

During the evaluation of the chiral catalysts, a novel set of cyclisation conditions were developed within the Moran research group.[91] It was hypothesised that these conditions may afford superior enantioselectivity with the range of catalysts being evaluated. It was found that in some cases, a mixture of products was produced from the reaction depending on the chiral catalyst used, therefore each product could have entirely different enantioselectivities (Scheme 57).



Scheme 57: Novel Conditions for Cyclisation of *N*-allylbenzamide

3.4.5 Evaluation of Novel Cyclisation Conditions

Using the novel cyclisation conditions a range of chiral catalysts were investigated in terms of imparting enantioselectivity (Table 4). It was found that the chiral diaryltriflamide **2.12** gave a single oxazoline racemic product bearing an OTs substituent **2.52**, yielding 35% (entry 1, Table 4). The iodoarene bislactate **2.33** only produced 62% of the racemic oxazoline bearing an OTs substituent **2.52** (entry 12, Table 4), however, the corresponding bislactate bearing a *para* ester **2.32** (entry 3, Table 4) gave the other oxazoline product with the hydroxy substituent **2.49** with an *ee* of 5%. The chiral iodoarene bislactate with benzyl groups **2.33** (entry 4, Table 4) produced both oxazoline products, giving 34% *ee* concerning the OTs derivative **2.52**, the other oxazoline with the hydroxy substituent **2.49** was racemic. Comparing the iodoarene bislactate without benzyl groups **2.52** (entry 12, Table 4), there is an indication that the benzyl group influences both selectivity and product mixture composition. Iodoarene bislactate bearing benzyl groups and a *para* ester **2.34** gave 20% racemic oxazoline with the OTs substituent **2.52** and 50% of the oxazoline with the hydroxy substituent **2.49** with a 28% *ee* (entry 5, Table 4). The *para* ester group seems to improve the yield with little change to the enantioselectivity in comparison to the bislactate without the *para* ester **2.33** (entry 4, Table 4). The Boc bislactate **2.31** (entry 6, Table 4) gave the single racemic oxazoline bearing the OTs group **2.52** in 35% yield, which was much lower than the ethyl bislactate derivative (entry 12, Table 4). The mesitylene bislactamide catalyst **1.50** gave both products, the OTs product **2.52** having a yield of 38% with 13% *ee*, the minor oxazoline product **2.49** had a yield of 9% with 4% *ee* (entry 2, Table 4).

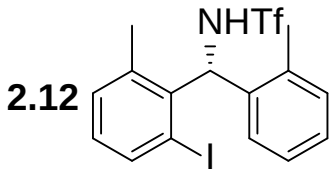
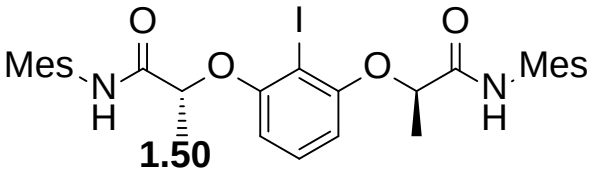
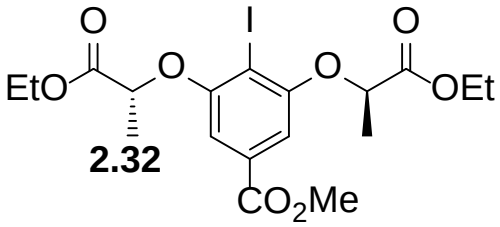
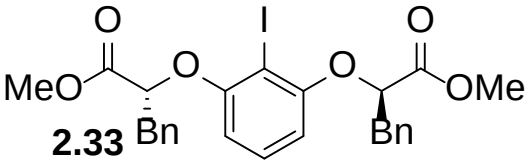
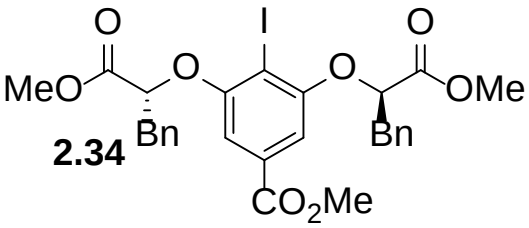
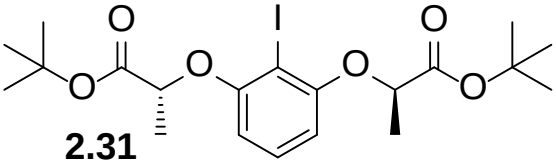
Entry	Chiral Catalyst	Oxazoline Yield OTs	Oxazoline Yield OH	% ee
1	 **2.12**	35%	0%	racemic racemic
2	 **1.50**	38%	9%	13% 4%
3	 **2.32**	0%	48%	- 5%
4	 **2.33**	33%	17%	34% racemic
5	 **2.34**	20%	50%	racemic 28%
6	 **2.31**	35%	0%	racemic -

Table 4: Evaluation of Asymmetric Cyclisation with Chiral Catalysts

The diiodoarene bislactate with benzyl groups **2.35** gave both products in racemic yields 6% and 78% (entry 8, Table 4). The corresponding diiodoarene catalyst without benzyl groups **2.36** gave the single hydroxy product **2.49** in a racemic yield of 88% (entry 7, Table 4). The isopropyl bislactmide **1.82** gave the single OTs product **2.52** in raemic yield of 42%

(entry 9, Table 4). The diethyl bislactamide catalyst **1.51** produced only the OTs product **2.52** at 34% yield with an *ee* of 18% (entry 10, Table 4). The dodecyl bislactamide catalyst **2.53** gave a yield of 53% of the OTs product **2.52** with 8% *ee* (entry 11, Table 4). Generally, bislactates performed better than bislactamides to bring about enantioselectivity under these reaction conditions. *Para* ester groups seem to improve overall yield and benzyl groups seem to aid in enantioselectivity under these novel reaction conditions.

(continued)

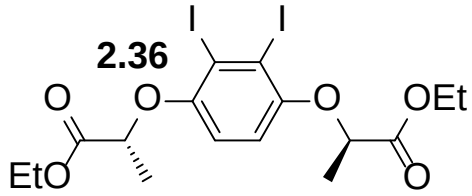
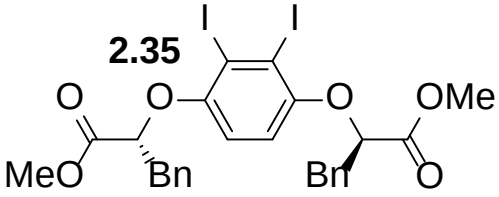
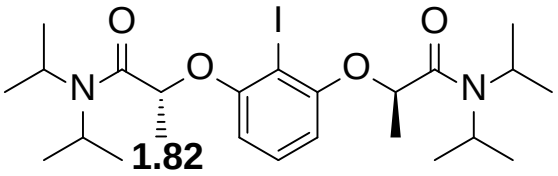
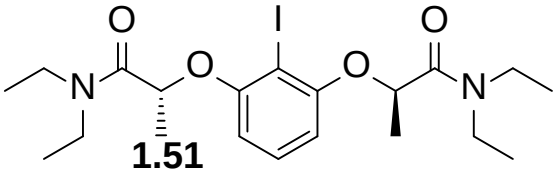
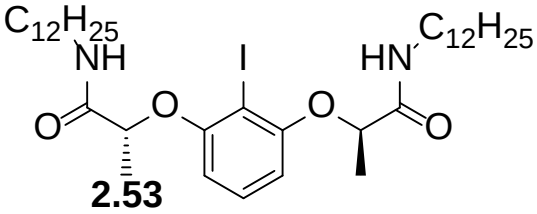
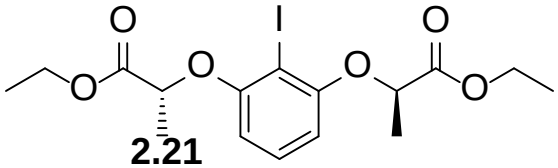
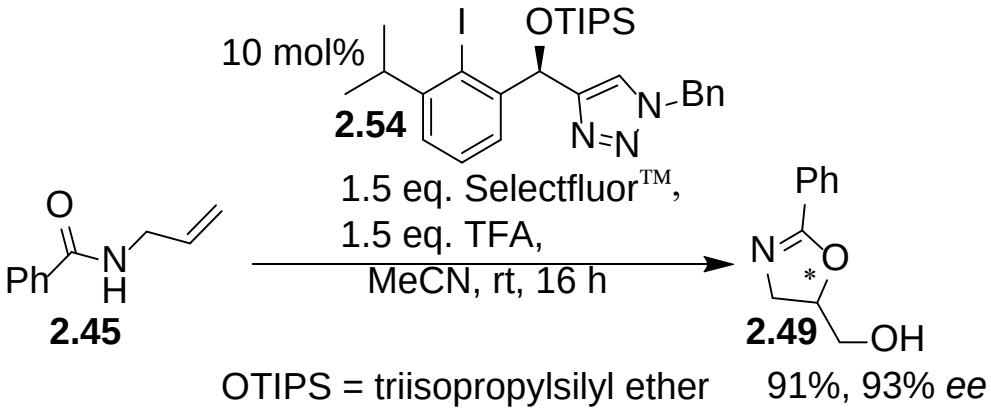
Entry	Chiral Catalyst	Oxazoline Yield OTs	Oxazoline Yield OH	% ee
7	 **2.36**	0%	88%	- racemic
8	 **2.35**	6%	78%	racemic racemic
9	 **1.82**	42%	0%	racemic -
10	 **1.51**	34%	0%	18% -
11	 **2.53**	53%	0%	8% -
12	 **2.21**	62%	0%	racemic -

Table 4: Evaluation of Asymmetric Cyclisation with Chiral Catalysts

3.4.6 Recent Asymmetric Catalytic Cyclisation Developments

Abazid and coworkers reported in 2021, the cyclisation of *N*-allylcarboxamides **2.45**, using a chiral triazole-substituted iodoarene catalyst **2.54**. They suggested the triazole can act as a stabilising donor to the hypervalent iodine centre via coordination between N−I atoms. They managed to achieve impressive oxazoline **2.49** yields of 91% with 93% *ee* (Scheme 58).[92]



Scheme 58: Novel Catalyst Used in *N*-allylbenzamide Cyclisation

3.5 Cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide

3.5.1 Catalytic Cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide

During the development of the cyclisation of *N*-allylbenzamide **2.45** it was identified that the catalytic cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide **2.55** would give access to the oxazoline-pyrrole moiety. The oxazoline-pyrrole motif is found in many natural compounds such as Leupyrrin A_1, which has been shown to be a good inhibitor to various fungi and eukaryotic cells at nanomolar levels with moderate toxicity, *in vivo*. The compound is a very important synthetic target (Figure 19).[78]

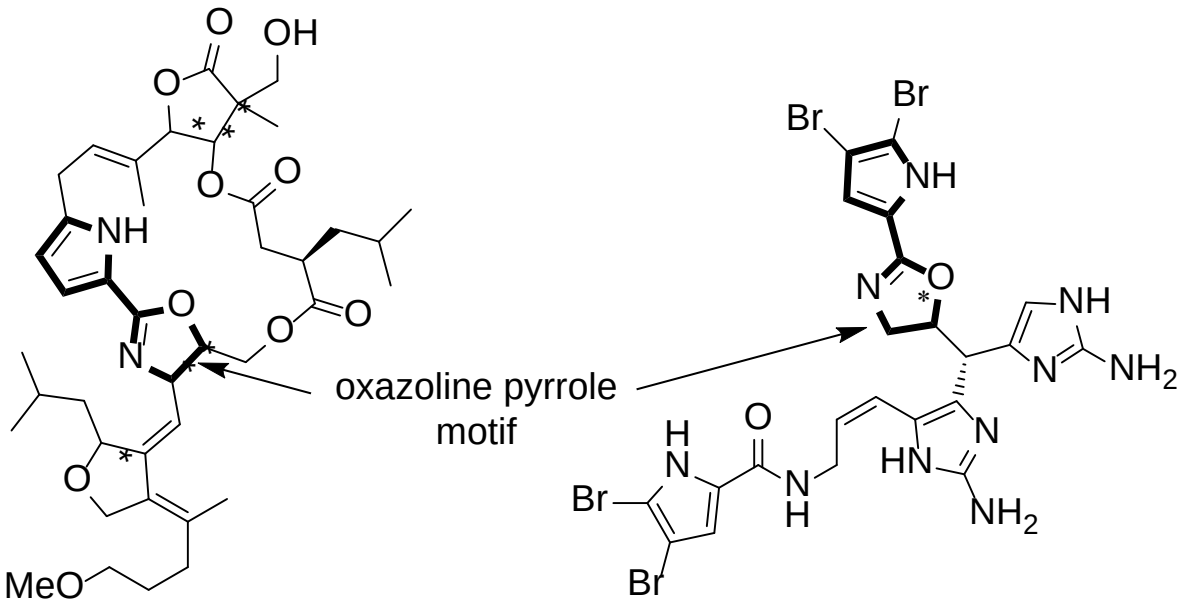
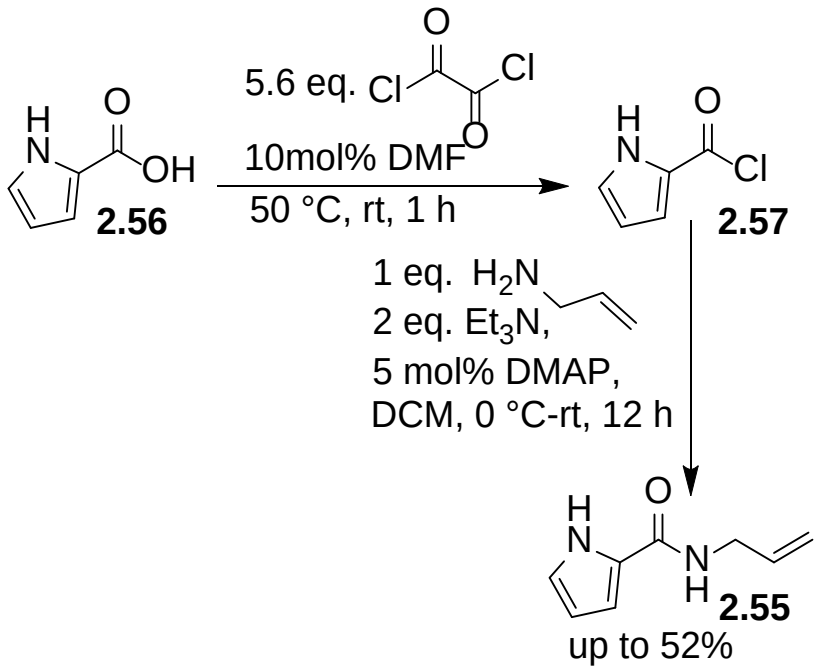


Figure 19: Leupyrrin A_1 and Nagelamide R Natural Products

3.5.2 *N*-allyl-*1H*-pyrrole-*2*-carboxamide Preparation

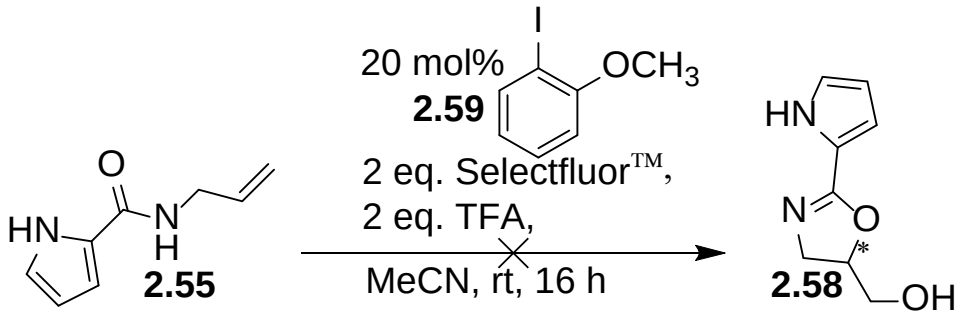
Before the cyclisation conditions could be developed, the preparation of the substrate was required. The synthesis involved converting the commercially available pyrrole-2-carboxylic acid **2.56** into the reactive acyl chloride intermediate **2.57**, followed by amidation with allylamine to *N*-allyl-*1H*-pyrrole-2-carboxamide **2.55** (Scheme 59).[64]



Scheme 59: *N*-allyl-*1H*-pyrrole-*2*-carboxamide Synthesis[64]

3.5.3 Failed Cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide

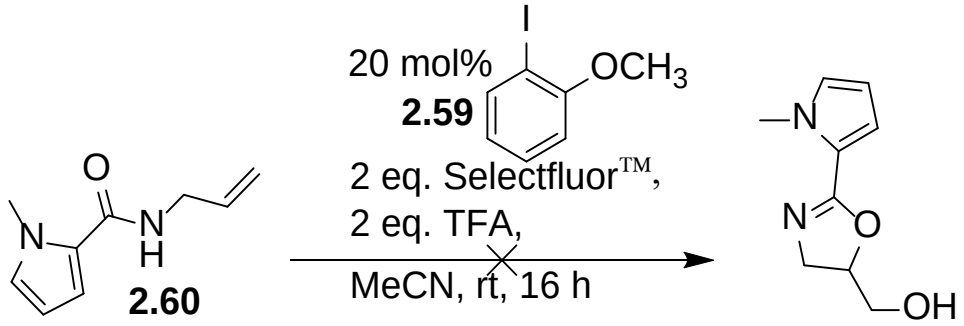
Initially, the standard catalytic conditions for the cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide **2.55** were employed using Selectfluor™ as the oxidant and trifluoracetic acid, TFA, as the ligand source (Scheme 60).[64] Unfortunately, cyclisation did not occur using 2-iodoanisole **2.59** and it was hypothesised that the pyrrole moiety was too electron-rich and was donating electron density to the adjacent carbonyl. This would have the detrimental effect of preventing the carbonyl oxygen from attacking the unactivated alkene.



Scheme 60: Failed Cyclisation of *N*-allyl-*1H*-pyrrole-2-carboxamide

3.5.4 Failed Cyclisation of *N*-allyl-1-methyl-*1H*-pyrrole-2-carboxamide

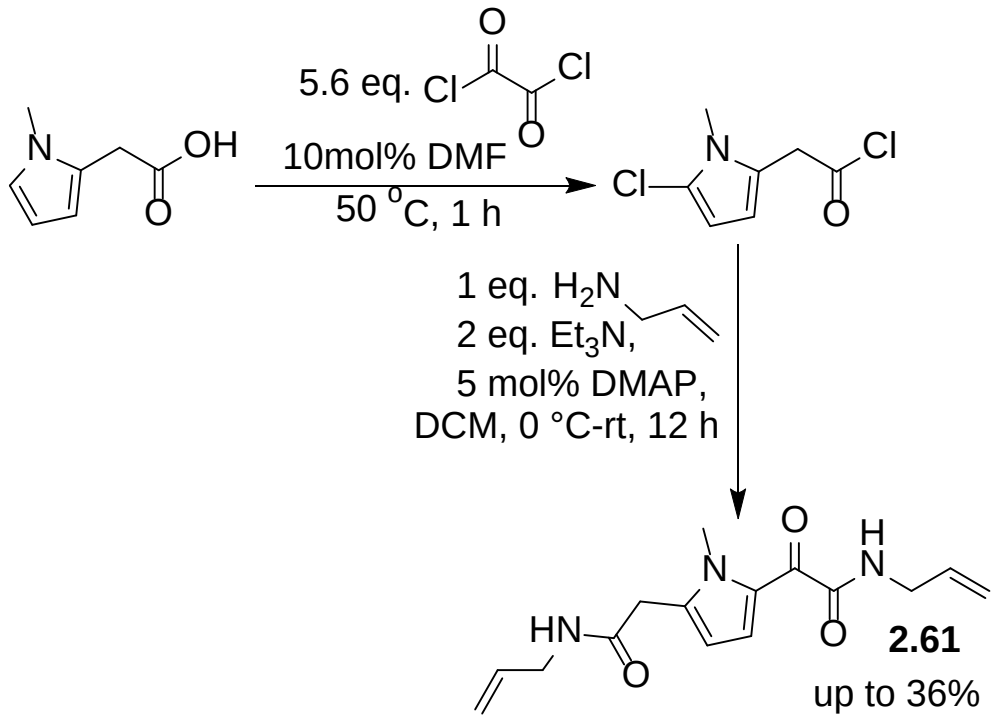
Given the previous failure, an attempt was made to modify the substrate to make the pyrrole less electron-rich by installing a methyl group on the pyrrole nitrogen atom. The substrate **2.60** was made using the same procedure albeit with *N*-methyl-pyrrole-2-carboxylic acid. The modified substrate **2.60** failed to bring about cyclisation (Scheme 61).



Scheme 61: Failed Cyclisation of *N*-allyl-1-methyl-*1H*-pyrrole-2-carboxamide

3.5.5 New Substrate Modification

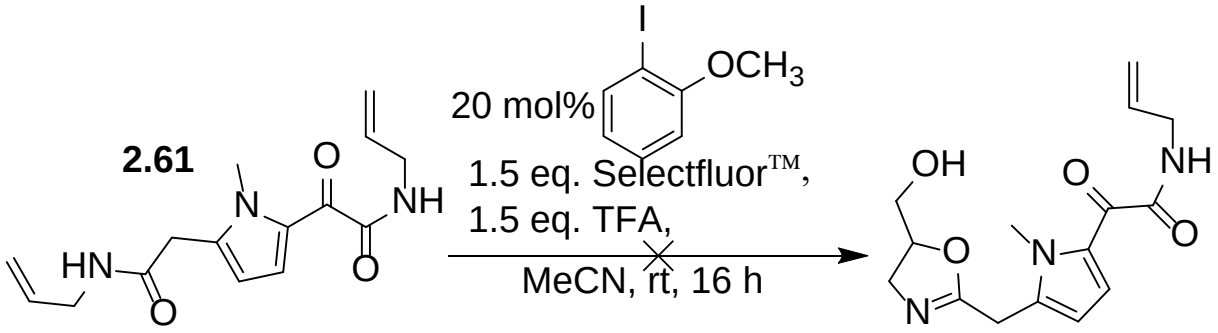
It was still theorised that the pyrrole ring was interfering with the cyclisation process and therefore the carbonyl which is instrumental in the cyclisation mechanism. A strategy of moving the carbonyl further away from the pyrrole ring was tested, by modifying the substrate. The preparation of the substrate did not yield the desired starting material and a second side chain was formed on the opposite side **2.61**. It was discovered that chlorination of the pyrrole ring was favoured over acyl chloride formation (Scheme 62).



Scheme 62: *N*-allyl-2-(1-methyl-1*H*-pyrrol-2-yl)acetamide Derivative Preparation

3.5.6 Cyclisation *N*-allyl-1-methyl-1*H*-pyrrol-2-yl)acetamide Derivative

Nonetheless, there was an attempt to cyclise this substrate **2.61**, as the unwanted side chain would not interfere with a successful cyclisation. The modifications to the substrate **2.61** did not have the desired effect and no cyclised product was detected (Scheme 63).

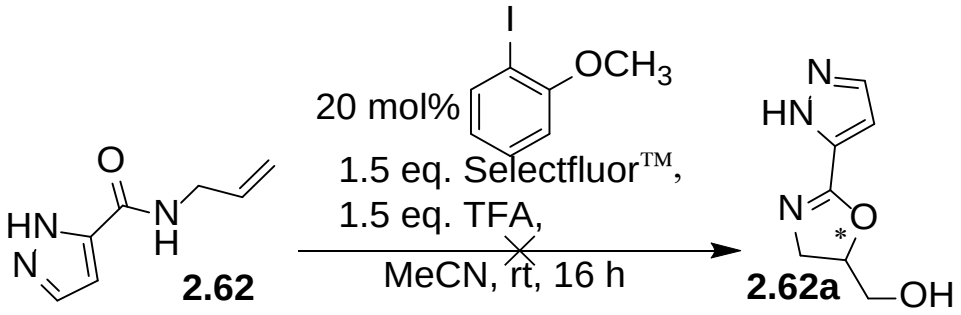


Scheme 63: Failed Cyclisation *N*-allyl-1-methyl-1*H*-pyrrol-2-yl)acetamide Derivative

3.5.7 Pyrrole Ring Oxidation

In 2016, Roth and coworkers, during the development of the catalytic cyclisation of *N*-allyl-pyrrole-carboxamide derivatives, reported on the redox potentials of aromatic heterocycles against a saturated calomel electrode, SCE. They elaborated that pyrrole derivatives have oxidation potentials of approximately +1 V, however, pyrazole derivatives were found to be much harder to oxidise.[93]

Armed with this new thinking, a pyrazole substrate **2.62** was synthesised using the same substrate preparation procedure for *N*-allyl-*1H*-pyrrole-2-carboxamide, and an attempt at cyclisation were made (Scheme 64). Disappointingly, the new substrate did not give the corresponding oxazoline product.

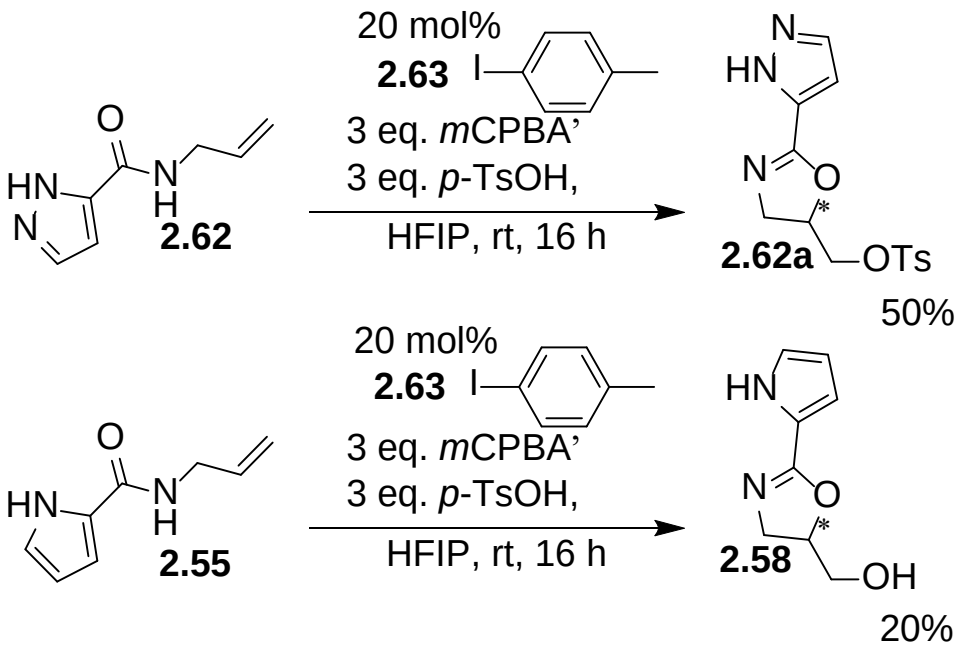


Scheme 64: Unsuccessful Pyrazole Derivative Cyclisation

3.5.8 Novel Cyclisation Conditions

A novel set of cyclisation reaction conditions were developed within the Moran research group for an alternative reaction[91]. Using *meta*-chloroperbenzoic acid (*m*CPBA), as the oxidant, and *para*-toluenesulfonic acid (*p*-TsOH), as the ligand source, and 1,1,1,3,3,3-hexafluoroisopropanol, HFIP solvent. It was decided to trial these mild conditions in the cyclisation of *N*-allyl-*1H*-pyrazole-5-carboxamide **2.62** and *N*-allyl-*1H*-pyrrole-2-carboxamide **2.55**. Both cyclisations successfully produced the desired products albeit in low to moderate yields using 4-

iodotoluene catalyst **2.63** (Scheme 65).[91] Interestingly, the same reaction conditions gave OTs and OH substituents depending on the substrate. The cyclisation conditions required further investigation and optimisation in terms of yield and improving enantioselectivity.

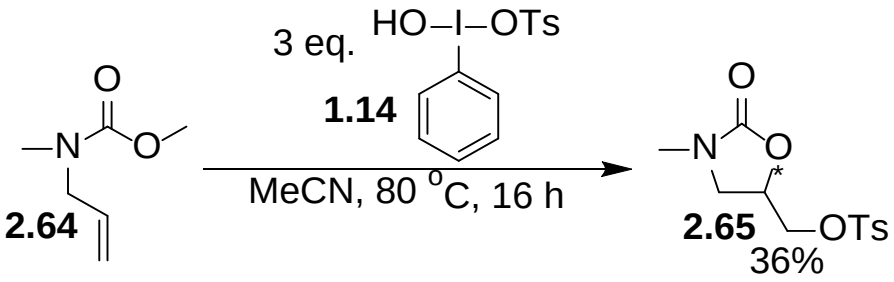


Scheme 65: Cyclisation Pyrazole and Pyrrole Derivatives

3.6 Development of Novel Carbamate Cyclisation

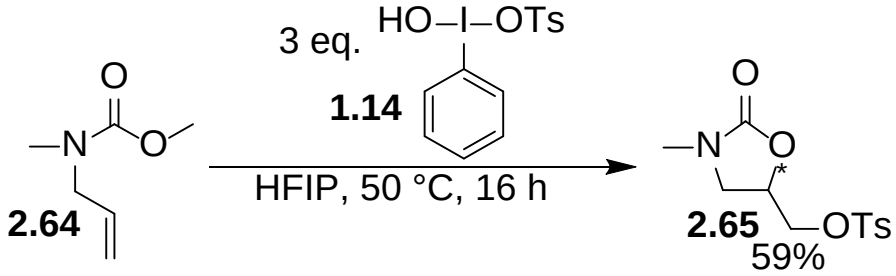
3.6.1 Previous Oxazolidinone Development Work

Moran Group researchers had previously conducted promising, preliminary work with Koser's reagent, [Hydroxy(tosyloxy)iodo]benzene (HTIB) **1.14**, to bring about cyclisation of methyl *N*-allyl (methyl)carbamate **2.64** albeit with poor yields (Scheme 66).



Scheme 66: Koser's Reagent X Mediated Cyclisation

Further development work by the Moran Group managed to lower the reaction temperature to 50 °C and increased the yield to 59% with 3 equivalents and 68% using 5 equivalents of Koser's reagent **1.14**, respectively (Scheme 67).[94]



Scheme 67: Improved Cyclisation Reaction[94]

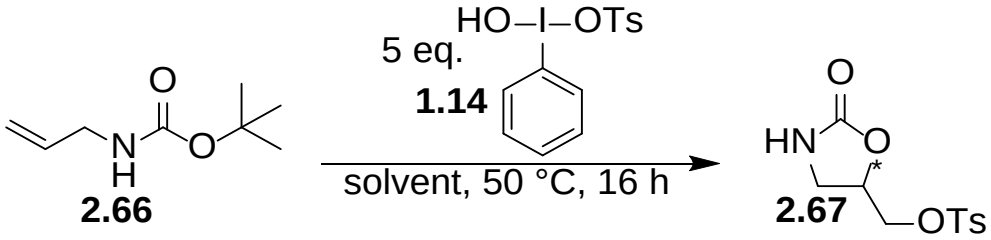
Despite the improvements in the reaction conditions, the reaction was still highly unappealing, it would require approximately a ratio of 10:1 in mass quantities of hypervalent iodoarene **1.14** to substrate **2.64** to give a moderate yield of the cyclised oxazolidinone product **2.65**. Further optimisation work was necessary to address the shortcomings of this promising reaction.

3.6.2 Solvent Screen Rationale

Significant development and optimisation work was conducted and started with a solvent screen. The solvent selection had to take into careful consideration of the solubility of the reactants and the reaction temperature. Acetonitrile (MeCN), methanol (MeOH), trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), 1,2-dichloroethane (DCE) were selected for the cyclisation reaction. The selection of acetonitrile (MeCN) was due to its wide deployment in reactions mediated by Koser's reagent **1.14**. Indeed, Koser and coworkers had shown treatment of ketones with Koser's reagent **1.14** in acetonitrile (MeCN) afforded α-toxyloxy ketones.[31] However, Koser's reagent **1.14** is poorly soluble in acetonitrile (MeCN) at room temperature. Methanol (MeOH) was chosen due to its ability to readily dissolve Koser's reagent **1.14** and the substrate. Koser and Justik had used methanol (MeOH) in their Wittig type ring expansion reaction with Koser's reagent **1.14** to synthesise β-benzocyclo-alkenones.[95] However, its use may lead to a mixture of products containing one or more methoxy substituents. 2,2,2-Trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) were selected because Dohi, Kita, and their colleagues had revealed enhanced reactivity of Koser's reagent **1.14** in fluoroalcohol media.[96] They demonstrated the single electron transfer (SET) oxidation ability of Koser's reagent **1.14**. Togo and Ishiwata employed 2,2,2-trifluoroethanol (TFE) in their cyclisation of *N*-methoxy-2-arylethanesulfonamides with *meta*-chloroperoxybenzoic acid (*m*CPBA).[97] Dichloromethane (DCM) had extensively been employed with Koser's reagent **1.14**, in various reactions such as halogenations, phenyliodinations, oxidative transformations, α-oxytosylations, dioxytosylations, and cyclisations to afford diketolactones and tosyloxylactones.[75] However, dichloromethane (DCM) has a boiling point of approximately 40 °C, which would not allow for the requisite reaction

temperature of 50 ˚C. 1,2-Dichloroethane (DCE) has very similar chemical solvent properties to dichloromethane (DCM) but has a higher boiling point of 83 ˚C, which would allow for heating to 50 ˚C hence was selected as an alternative.

Commercially available *tert*-butyl allyl carbamate **2.66** was the selected cyclisation substrate for the solvent screen, it is readily available and cheap, approximately £30 for 25 g (Scheme 68).



Scheme 68: Solvent Screen Assay

3.6.3 Solvent Screen Results

The solvent screen was performed collectively on a single hotplate to minimise any experimental errors and the yields were determined by quantitative ^{1}H NMR spectroscopy. Hypervalent iodine(III) reagents have been demonstrated to be effective in acetonitrile (MeCN) to mediate the reaction, which justified its initial use in the cyclisation reaction. Using acetonitrile (MeCN) (entry 1, Table 5) in the assay reaction gave a product yield of 32% of the desired oxazolidinone **2.67**, while using 1,2-dichloroethane (DCE) (entry 2, Table 5) slightly reduced the product **2.67** yield to 31%. Employing methanol (MeOH) (entry 3, Table 5) did result in a yield of 45% of a mixture of oxazolidinone products containing distinct substituents such methoxy and tosyl. The methoxy was postulated to have been derived from the disassociation of the methanol (MeOH) solvent and tosylate product **2.67** from the disassociation of the Koser's reagent **1.14**, respectively. 2,2,2-Trifuoroethanol (TFE) (entry 4, Table 5) improved the **2.67** yield to 53% while replacing the reaction solvent with

hexafluoroisopropanol (HFIP) (entry 5, Table 5) gave a superior **2.67** yield of 75%. The above results very much corresponded to assertions made by Koser, Dohi, and Kita, in that methanol did give a mixture of oxazolidinone products, with some containing methoxy substituents.[96] Fluoroalcohol medias did afford the best yields, giving credence to enhanced reactivity of Koser's reagent **1.14**, possibly through a single electron transfer (SET) oxidation mechanism. Comparing the pK_a data for the various solvents, a general trend can be seen that with decreasing pK_a of the solvent there is a gradual increase in product **2.67** yields.[98] Hexafluoroisopropanol (HFIP) (entry 5, Table 5) had the lowest pK_a i.e. the most acidic from the solvent screen, and provided the highest yield as such it was selected as the optimum reaction solvent and taken forward for further optimisation. Other acidic solvents with lower pK_a values such as 2-chlorophenol with a pK_a of 8.5, or 2-fluorophenol with a pK_a of 8.7 could also have been tested if required but these solvents were more expensive and had significantly higher boiling points, making solvent evaporation/work up less appealing.

Entry	Solvent	$pK_{a\ (DMSO)}$	Yield %[a]
1	MeCN	31.3	32
2	DCE	>50	31
3	MeOH	29.0	45(mixture)
4	TFE	23.5	53
5	HFIP	17.9	75

[a] Yields calculated from quantitative ^1H NMR, using TMB as an internal standard

Table 5: *t*-Butyl Allyl Carbamate Cyclisation Solvent Screen

3.6.4 Reagent Selection Rationale

Thus far, the reagent used to bring about *N*-allyl carbamate cyclisation was Koser's reagent (HTIB) **1.14**, an unsubstituted [hydroxy(tosyloxy)iodo]benzene. It was hypothesised that modification of the Koser's reagent **1.14** with electron-withdrawing (EWG) or electron-donating groups (EDG) would alter the electronic effects. These changes could make the reagent more or less reactive and therefore affect the product yield and kinetics of the reaction.

Richter and coworkers discovered complete ionisation of Koser's reagent **1.14** occurred in an aqueous solution affording hydroxy(phenyl)iodonium cations ($PhI^{+}OH$).[99] It was postulated, by modifying the Koser's reagent **1.14**, with an electron-withdrawing group (EWG), the resonance effects would withdraw electron density from the aromatic π system and iodine. The electron-withdrawing group (EWG) could also be conjugated to the iodine atom depending on its position on the phenyl ring. Consequentially, when the electron-deficient Koser's reagent is ionised in solution, the modified iodonium cation could strongly activate the alkene in the substrate. The carbocation created in the intermediate could be intrinsically more electrophilic.[2] Therefore inducing intramolecular ring closure faster by nucleophilic attack from the carbonyl oxygen, and reducing the likelihood of side reactions and products. However, these electronic changes to the iodane may cause partial or less likelihood of ionisation in solution (Figure 20).

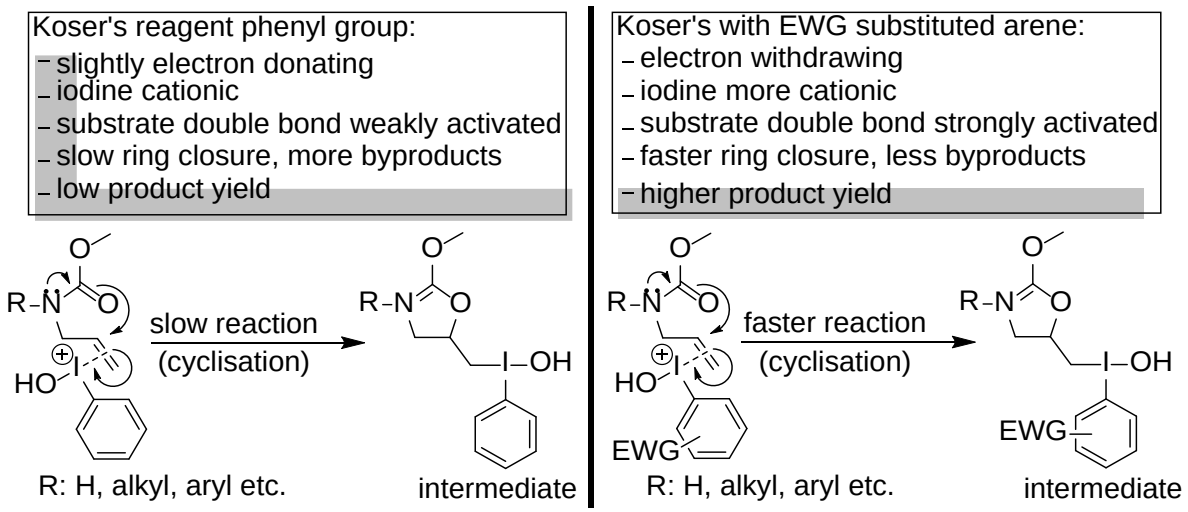


Figure 20: Postulated rationale for the addition of an EWG

Wettach and Koser's crystal structure work on his namesake reagent, **1.14** discovered that the atoms about the T-shaped bond had virtually a planar geometry. They also found that the bond angle for HO–I–C and TsO–I–C was 92.8º was 86.0º, respectively, therefore not precisely perpendicular. Furthermore, the bond length of the I-OTs was longer than the computed covalent single bond distance of 1.99 Å and thus weaker. Empirically the I-OTs and I-OH were found to be 2.47 Å and 1.94 Å, respectively (Figure: 21).[100,101]

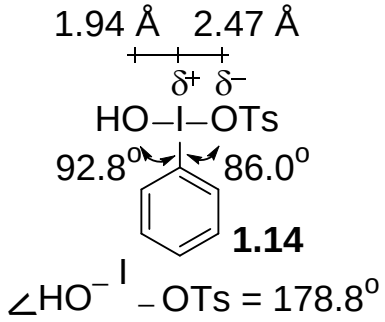


Figure 21: Koser's Reagent Bond Lengths and Bond Angle[100,101]

Both Wettach and Koser and independently, Richter and coworkers have suggested the I–OTs bond is partially ionic and ionises completely in an

aqueous solution.[99,101] Another possible theory might be that this dissociation may occur more readily if an electron-donating group (EDG) was introduced to the phenyl group of the hypervalent iodoarene. The positive resonance effects to the aromatic system could cause the attached iodine atom to consequentially becomes less cationic. Electron density could be shifted to the iodine, causing further weakening of the partially polarised I–OTs bond, causing greater or complete ionisation. Releasing additional –OTs could further drive cyclisation by aiding extraction of the isobutene or methyl leaving group and/or assisting in the S_N2 displacement of the hydroxy(phenyl)iodonium intermediate (Figure 22).

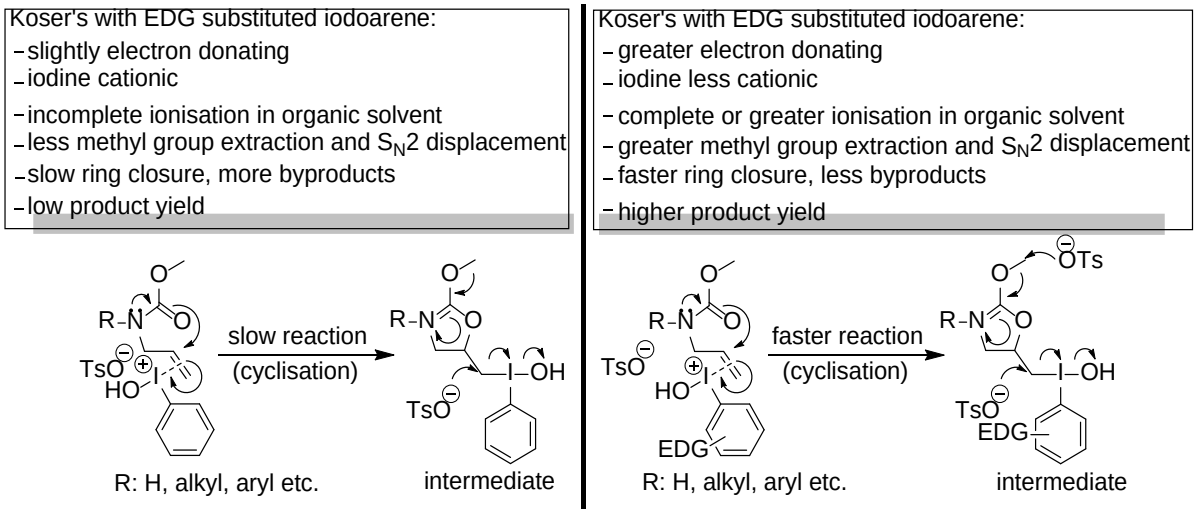
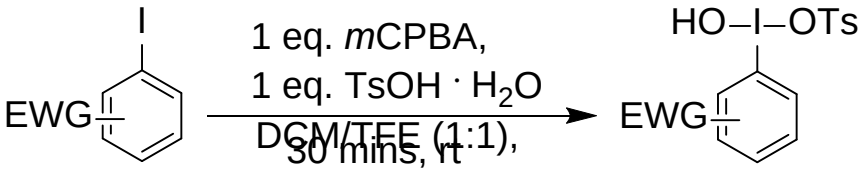


Figure 22: Postulated rationale for the addition of EDG

3.6.5 Electron Deficient Koser's Derivatives Preparation

Koser's reagent derivatives containing electron-withdrawing (EWG) groups were prepared using a literature procedure by Merritt and coworkers. Merritt and coworkers reported enhanced reaction rates and yields in the formation of Koser's derivatives while oxidising iodoarenes with *m*-chloroperbenzoic acid (*m*CPBA) in a 1:1 mixture of

dichloromethane (DCM) and 2,2,2-trifluoroethanol (TFE). (Scheme 69).[102]



Scheme 69: Typical Procedure for Koser's Derivatives with EWGs

Using Merritt's procedure to access the required iodanes, yields varied by a wide range due to the substituted aromatic ring with different electron-withdrawing groups (EWG).[102] Significant drops in yield of the products were seen when there were multiple substituents on the arene ring compared to standard Koser's reagent **1.14** of 92% (entry 1, Table 6). Indeed, the addition of a para fluoro **2.69** or para chloro **2.70** group afforded moderate yields of 67% (entry 3 and 4, Table 6) however with a 2,3,4,5,6-pentafluoro substituted arene ring, the yield was impaired considerably to 28% **2.73** (entry 7, Table 6). With a 1,2-benziodoxol group **2.68**, a moderate yield of 63% was achieved (entry 2, Table 6), with multiple substituents of a 1,2-benziodoxol group and an *ortho*-methyl group **2.72** the yield was nearly halved to 38% (entry 6, Table 6). A single *para*-trifluoromethane group **2.71** gave an average moderate yield of 54% (entry 5, Table 6). The *meta*-methoxy Koser's derivative **2.74** was not successfully produced using Merritt's procedure (entry 8, Table 6).[102]

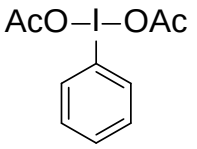
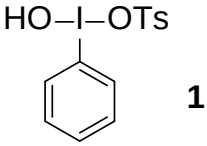
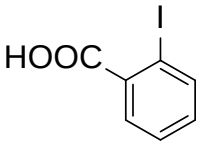
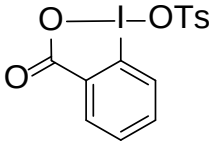
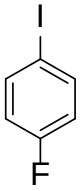
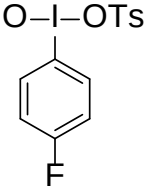
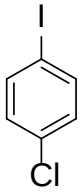
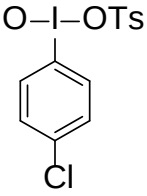
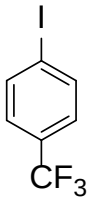
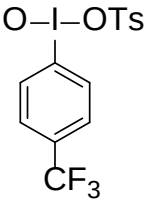
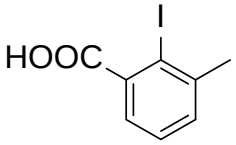
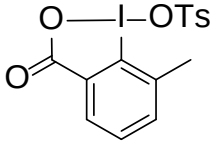
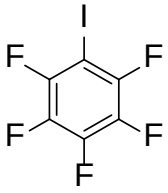
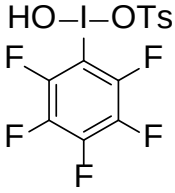
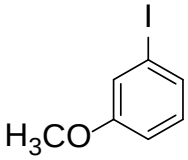
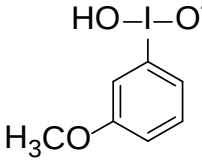
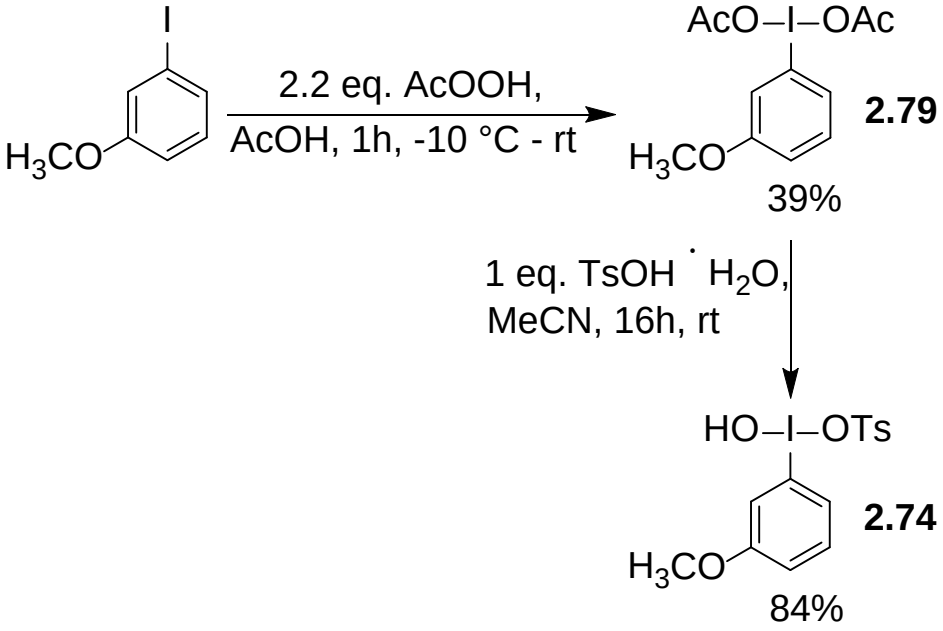
Entry	Starting Material	EWG Koser's Derivative	Derivative Yield %
1		 **1.14**	92
2		 **2.68**	63
3		 **2.69**	67
4		 **2.70**	67
5		 **2.71**	54
6		 **2.72**	38
7		 **2.73**	28
8		 **2.74**	0

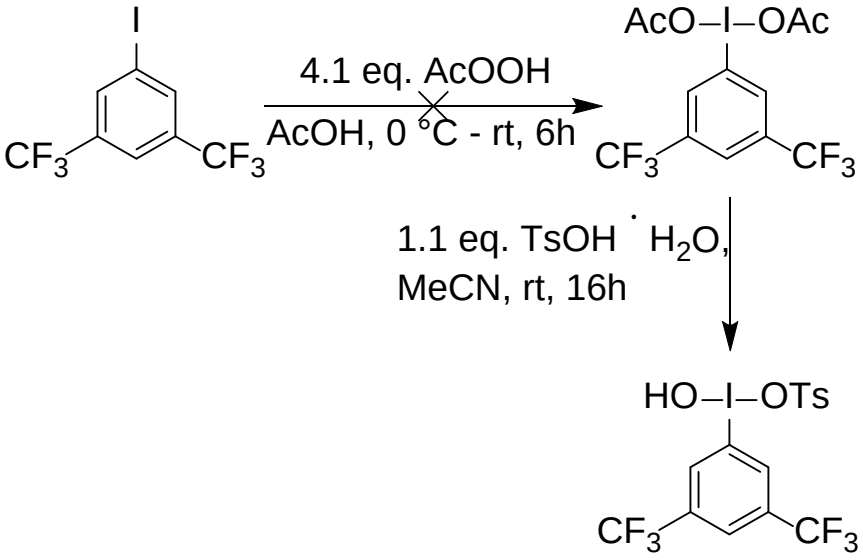
Table 6: **Product Yields of EWG substituted Koser's Derivatives**

A two-step procedure to access the desired *meta*-methoxy derivative **2.74** was used, which involved the production of the diacetate intermediate **2.79** using a procedure by Chun, Lu, and Pike, followed by tosylation to the desired *meta*-methoxy derivative using a procedure by Byung and coworkers.[103,104] The *meta*-methoxy diacetate derivative gave a low yield of 39% and then through ligand exchange to the corresponding *meta*-methoxy iodane, giving an acceptable 84% (Scheme 70).



Scheme 70: Two-Step Koser's Derivative Procedure[103,104]

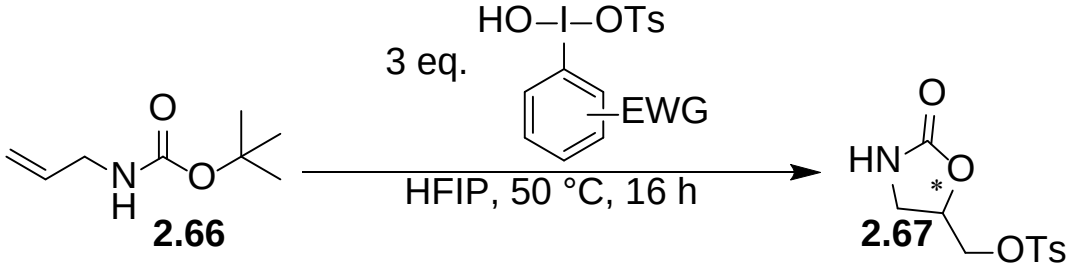
An attempt was made to make the corresponding Koser's derivative from 1-iodo-3,5-bis(trifluoromethyl)benzene using the two-step procedure. Unfortunately, the corresponding diacetate was not formed and hence the requisite Koser's derivative was not obtained (Scheme 71).[103,104]



Scheme 71: Failed Preparation of Koser's Bistrifluoromethyl Derivative[103,104]

3.6.6 Electron Deficient Koser's Derivative Cyclisation

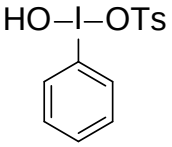
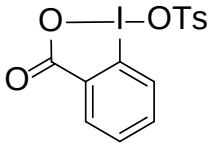
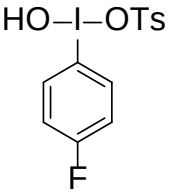
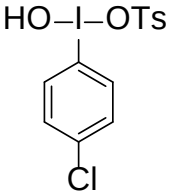
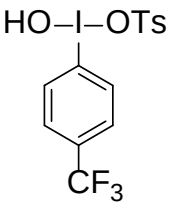
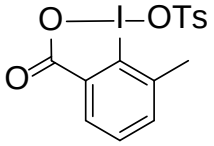
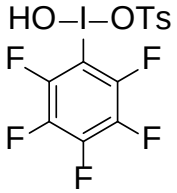
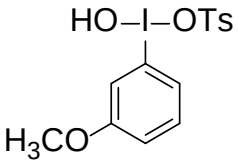
The electron-deficient Koser's derivatives were studied in the carbamate **2.66** cyclisation reaction. Using 3 equivalents of the electron-deficient Koser's derivatives, with HFIP as the optimum solvent choice, at 50 ˚C, for 16 hours (Scheme 72).



Scheme 72: EWG substituted Koser's Derivative Screen

It was found *para*-substituted halogen Koser's derivatives **2.69**, **2.70** gave similar, moderate oxazolidinone **2.67** yields of 66% and 69% (entry 3 & 4, Table 7). Which were slightly less compared to standard Koser's reagent **1.14** oxazolidinone **2.67** yield of 76%, under the same conditions (entry 1, Table 7). However, the residual carbamate starting material from the cyclisation reaction using the *para*-substituted halogen Koser's

derivatives **2.69**, **2.70** gave only a trace of starting material compared to standard Koser's reagent **1.14**, which had 23% residue. The *para*-trifluoromethane substituted derivative **2.71** afforded similar oxazolidinone **2.67** yield of 67%, to the *para*-halogen derivatives **2.69**, **2.70**, interestingly, it left 18% starting material residue **2.66** (entry 5, Table 7). Both the Koser's derivatives containing a 1,2-benziodoxol group **2.68**, **2.72**, did not promote cyclisation, and all the starting material **2.66** was recovered (entry 2 & 6, Table 7). The 2,3,4,5,6-pentafluoro substituted Koser's derivative **2.73** afforded a lowly 50% oxazolidinone **2.67** yield and left 43% of unreacted carbamate **2.66** (entry 7, Table 7). The *meta*-methoxy substituted derivative **2.74** gave a similar oxazolidinone **2.67** yield of 53%, to the 2,3,4,5,6-pentafluoro derivative **2.73**, recovering 29% starting material **2.66** residue (entry 8, Table 7).

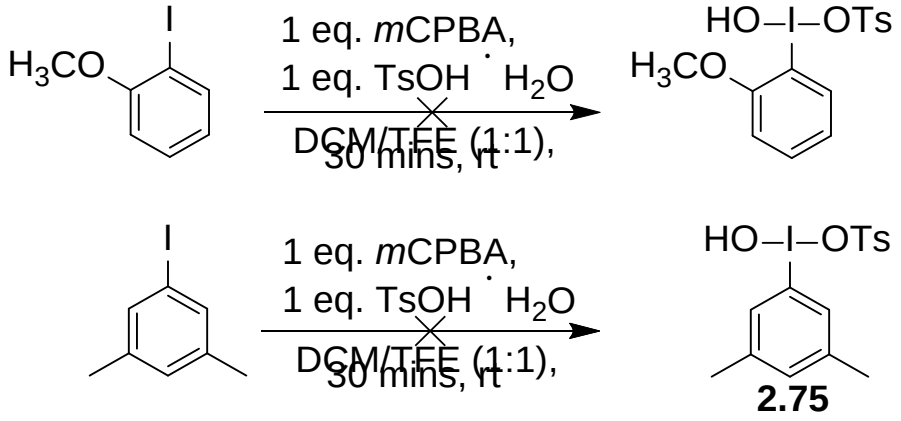
Entry	EWG Koser's Derivative	Residual Substrate[a]	Oxazolidinone Yield[a]
1	 **1.14**	23%	76%
2	 **2.68**	100%	–
3	 **2.69**	trace	66%
4	 **2.70**	trace	69%
5	 **2.71**	18%	67%
6	 **2.72**	100%	–
7	 **2.73**	43%	50%
8	 **2.74**	29%	53%

[a] yields determined by quantitative ^{1}H NMR using internal standard trimethoxybenzene

Table 7: EWG substituted Koser's Derivative Screen

3.6.7 Electron Rich Koser's Derivatives Preparation

The results from the electron-deficient Koser's derivatives screen did not offer any improvements from the standard unsubstituted Koser's reagent **1.14**. Progression was then made to preparing a range of electron-donating group (EDG) substituted Koser's derivatives for evaluation. Merritt and coworker's previously successful procedure was attempted to obtain *ortho*-methoxy and xylyl substituted Koser's derivatives **2.75**. Unfortunately, their procedure didn't provide the desired Koser's derivatives probably due to the electron-rich nature of the substrates (Scheme 73).[102]



Scheme 73: Failed Preparation of EDG Substituted Derivatives[102]

After a further literature search for another procedure, electron-donating group (EDG) substituted Koser's derivatives were prepared using a two-step synthesis and a single-step process. Reacting the requisite iodoarene with peroxyacetic acid to obtain the corresponding iodoarene-diacetate intermediate **2.76**, followed by ligand exchange with *para*-toluenesulfonic acid ($TsOH.H_2O$) gave the desired tosylated Koser's derivative **2.75**. The *meta*-xylyl diacetate **2.76** was obtained at 87% yield and the corresponding Koser's derivative **2.75** was achieved at 82% yield (entry 2, Table 8). A single-step procedure to obtain the mesitylene Koser's derivative **2.77**, involved reacting mesitylene, iodine, *meta*-

chloroperoxybenzoic acid (*m*CPBA), and *para*-toluenesulfonic acid ($TsOH.H_2O$), giving a reasonable yield of 63% (entry 1, Table 8).

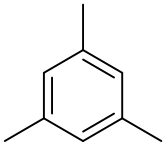
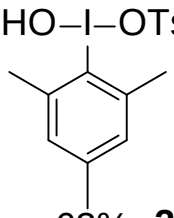
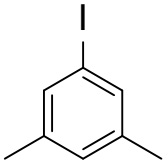
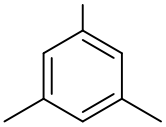
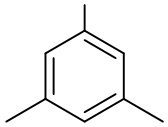
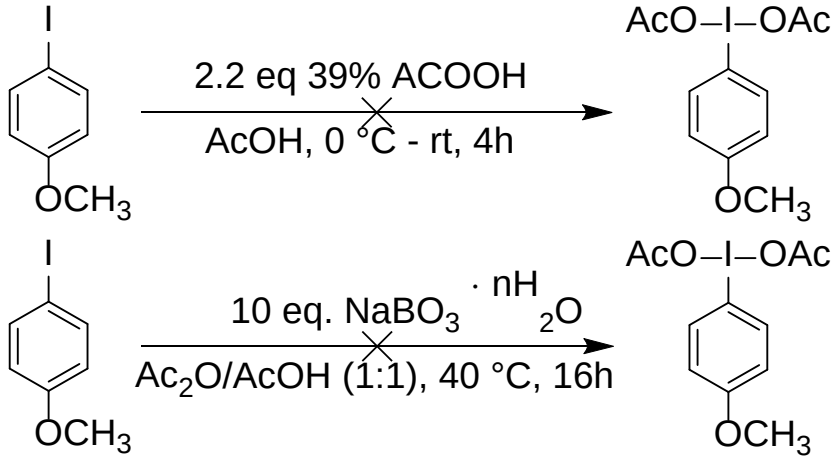
Entry	Substrate	Intermediate	EDG Koser's Derivative
1		–	 HO–I–OTs 63% **2.77**
2	 I	AcO–I–OAc  87% **2.76**	HO–I–OTs  82% **2.75**

Table 8: Yields of EDG substituted Koser's Derivatives

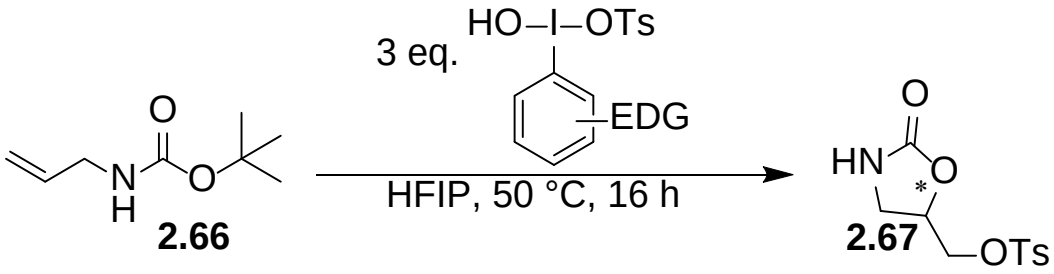
Further attempts were made to prepare *para*-methoxyphenyl-iodo-diacetate by reacting with peroxyacetic acid or with sodium perborate and acetic anhydride, neither method was successful (Scheme 74).



Scheme 74: Failed Preparation of diacetate Intermediates

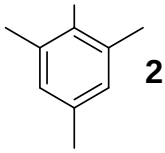
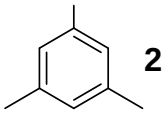
3.6.8 Electron Rich Koser's Derivative Screening

The prepared electron-rich Koser's derivatives **2.75**, **2.77** were evaluated in the cyclisation reaction (Scheme 75).



Scheme 75: EDG Koser's Derivative Screening Reaction

The mesitylene Koser's derivative **2.77** disappointingly only produced a trace of the oxazolidinone product **2.67** and nearly all the carbamate starting material **2.66** was recovered (entry 1, Table 9). The *meta*-xylyl Koser's derivative **2.75** gave a surprisingly high yield of 95% of oxazolidinone **2.67** and no starting material **2.66** was detected (entry 2, Table 9).

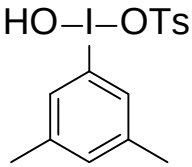
Entry	EDG Koser's Derivative	Residual Substrate[a]	Oxazolidinone Yield[a]
1	HO–I–OTs  **2.77**	99%	trace
2	HO–I–OTs  **2.75**	0%	95%

[a] Yields determined by quantitative ^{1}H NMR using internal standard trimethoxybenzene

Table 9: EDG substituted Koser's Derivative Screen

3.6.9 Stoichiometric Studies

Further stoichiometry studies were conducted using the *meta*-xylyl Koser's derivative **2.75** to find the optimum ratio of reagent to bring about the optimum yield of the cyclised product **2.67**. Using 1 equivalent each of *meta*-xylyl Koser's derivative **2.75** and the substrate **2.66** resulted in only a 49% conversion to product **2.67** and left 48% substrate **2.66** residue (entry 4, Table 10). With 1.2 equivalents of the novel reagent **2.75**, an improved product **2.67** yield of 65% was achieved with 34% starting material **2.66** detected (entry 3, Table 10). With 2 equivalents of the novel reagent **2.75** an impressive 90% yield **2.67** was had and 2% substrate **2.66** was found (entry 2, Table 10).

Entry		**Residual Substrate**[a]	**Oxazolidinone Yield**[a]
1	3 eq.	0%	95%
2	2 eq.	2%	90%
3	1.2 eq.	34%	65%
4	1.0 eq.	48%	49%

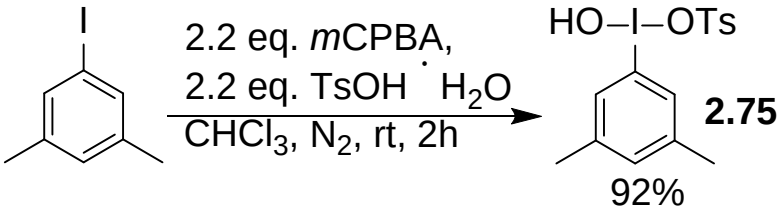
[a] Yields determined by quantitative ^{1}H NMR using internal standard trimethoxybenzene

Table 10: Stoichiometry Study of *m*-Xylyl Koser's Derivative

Given the serendipitous discovery of the novel *meta*-xylyl Koser's derivative **2.75** and the very high conversion to the cyclised product **2.67**. The search for other electron-deficient and electron-rich Koser's derivatives was discontinued, given the unlikelihood of finding a superior Koser's derivative. Given the modest increase in yield by using 3 equivalents of the novel Koser's derivative **2.75**, it was decided 2 equivalents were economically more desirable.

3.6.10 One-Step *m*-Xylyl Koser's Derivative Preparation

Give the significant improvements in product yield afforded by the novel *meta*-xylyl Koser's derivative **2.75**, further persistent attempts to generate the reagent in one step did bear fruit. Using a procedure by Yamamoto and Togo, iodo-3,5-dimethylbenzene and *meta*-chloroperoxybenzoic acid (*m*CPBA) in chloroform were reacted with *para*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$).[105] Pleasingly, a 92% yield of the novel *meta*-xylyl Koser's derivative **2.75** was achieved after 2 hours of stirring (Scheme 76).

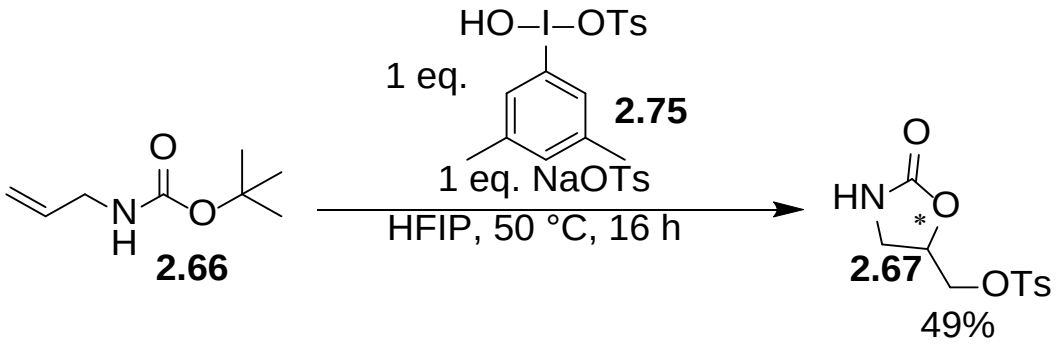


Scheme 76: One-Step Preparation of *m*-Xylyl Koser's Derivative[105]

3.6.11 Further Cyclisation Optimisation

From the results from the stoichiometry study, a further theory was put forward that the cyclisation reaction required a minimum of 2 equivalents of *meta*-xylyl Koser's derivative **2.75** to achieve high conversion. It was hypothesised that two tosylate anions were required to facilitate effective cyclisation. It was postulated that one of the tosylate anions aided in

extracting the *tert*-butyl leaving group from the iodonium intermediate. The other tosylate anion would be used in S_N2 displacement of the iodonium substituent. However, it was envisaged that a separate tosylate source could be added to further reduce the required amount of the *meta*-xylyl Koser's derivative **2.75**. An investigation into the cyclisation conditions with a separate source of tosylate anions in the form of sodium tosylate was conducted, to assess if this had any impact on the reaction. Unfortunately, the tosylate source did not have the desired effect of driving cyclisation with less *meta*-xylyl Koser's derivative **2.75** and gave a meager **2.67** yield of 49%. This result suggested that a minimum of 2 equivalents of the *meta*-xylyl Koser's derivative **2.75** were crucial in mediating cyclisation to completion in high yields (Scheme 77).

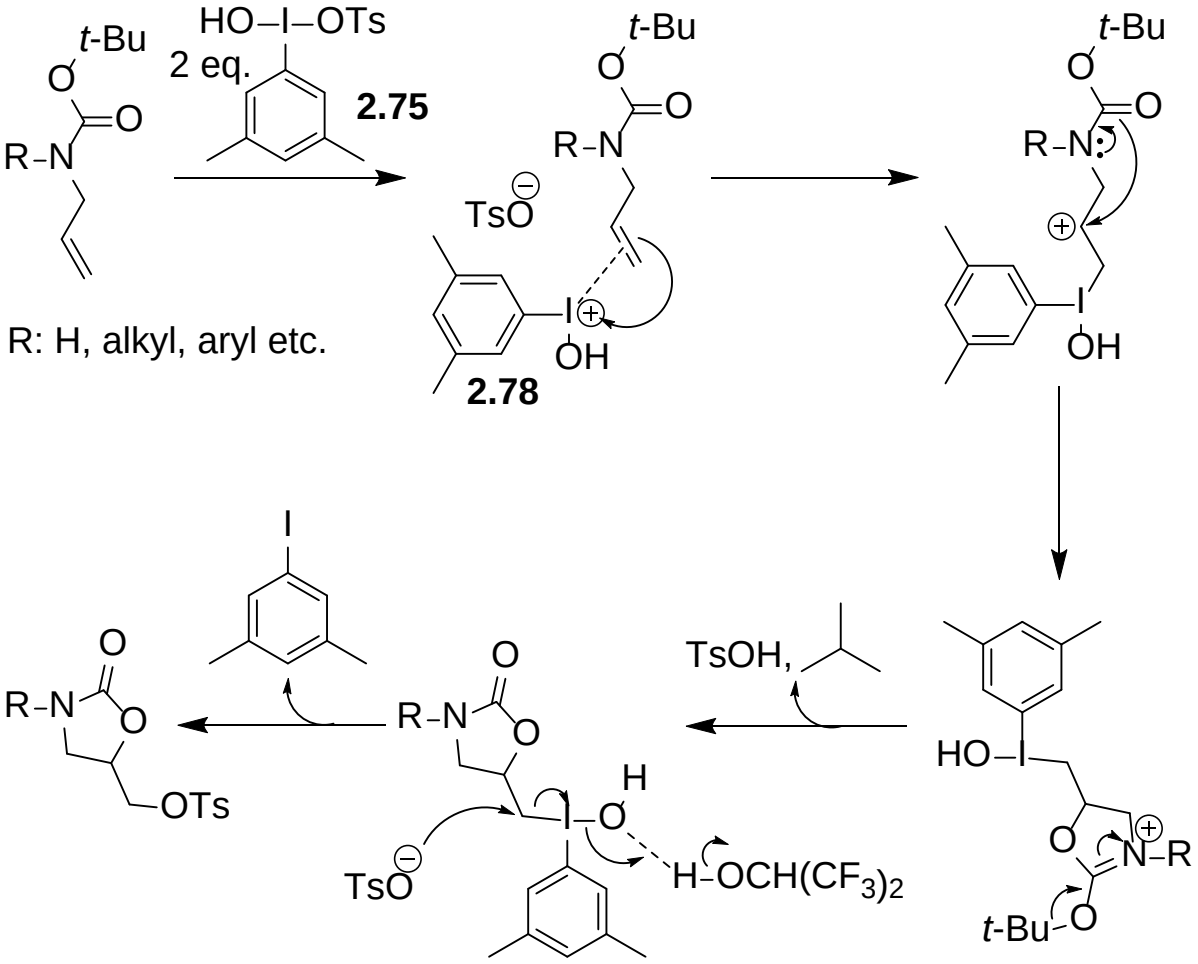


Scheme 77: Modified Reaction Conditions

3.6.12 Cyclisation Mechanism

Through the range of empirical observations and analysis, it was proposed the intramolecular cyclisation mechanism. It was postulated this was a disassociative mechanism, given the ^{1}H NMR analysis showed the presence of tosyl substituent on the oxazolidinone ring **2.67**. It was proposed that the hexafluoroisopropanol (HFIP) solvent with a low pK_a causes partial or complete disassociation of the ionic ArI(OH)-OTs bond from the *meta*-xylyl Koser's derivative **2.75** as reported by Wettach and

Koser. In solution, the corresponding free iodonium cations **2.78** can then activate the olefin of the substrate, creating a carbocation. Cyclisation would be induced by an attack from the carbonyl oxygen on the carbocation resulting in a heterocyclic ring formation. The positive charge would be shifted to the carbon of the former carbonyl and the positive charge would be transferred to the neighbouring nitrogen, due to the donation of a lone pair of electrons. It was observed that electron-rich substituents attached to the nitrogen greatly aided yield suggesting electron lone pair donation to the carbon is a critical step. A free tosylate anion could then deprotonate the isobutane cation to give the loss of isobutene and *para*-toluenesulfonic acid. A new carbonyl is formed in the five-membered ring causing the return of the donated lone pair of electrons to quench the positively charged nitrogen. After the completed heterocyclic ring formation, a second tosylate anion could initiate S_N2 nucleophilic substitution of iodonium cation, aided by the reaction solvent, to afford the final oxazolidinone product (Scheme 78).[67]



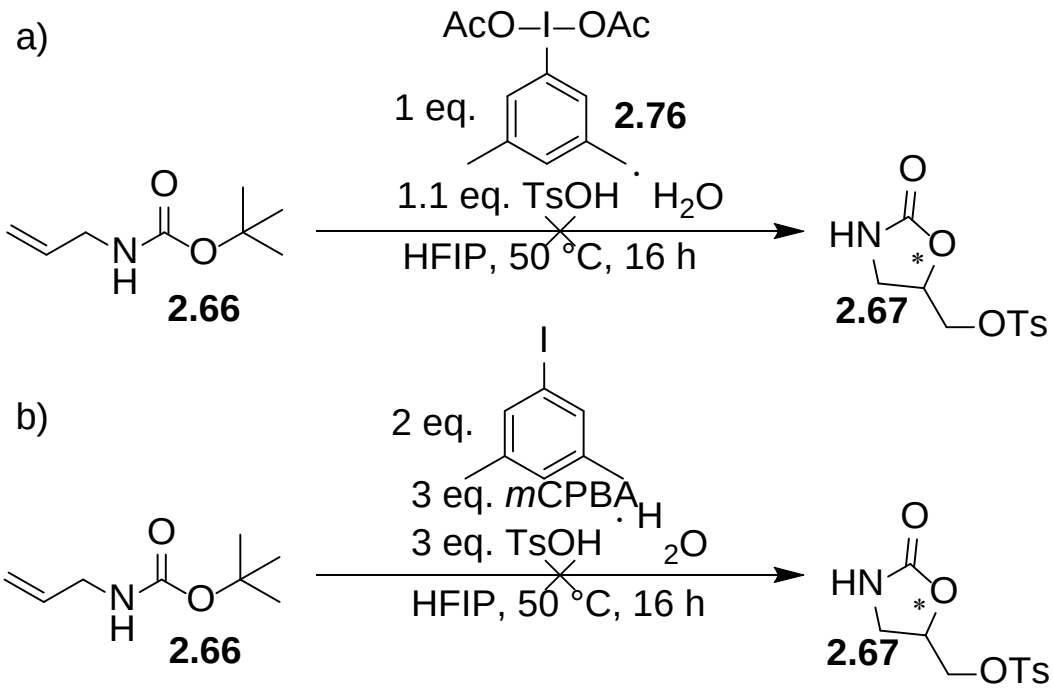
Scheme 78: Postulated Cyclisation Mechanism[67]

3.6.13 One-Pot Iodoarene Mediated Cyclisation

There are many examples of *in situ* formation of hypervalent iodine(III) species to mediate cyclisation such as the one-pot iodoarene catalysed cyclisation of *N*-alkenylamides developed within the Moran Group[64]. One-pot transformations are very effective, efficient, simplified procedures, minimising chemical waste, saving time and effort, and circumventing the need for work up or purification of the hypervalent iodine(III) reagent.[106]

Given the significant utility of a one-pot synthesis, there was an attempt to try and make a one-pot cyclisation by trying to generate the *meta*-xylyl Koser's derivative **2.75** *in situ*. The first strategy trialed, involved iodo-3,5-dimethylbenzene-λ^3-diacetate **2.76** and *para*-toluenesulfonic acid ($TsOH \cdot H_2O$) added to the carbamate substrate **2.66** in

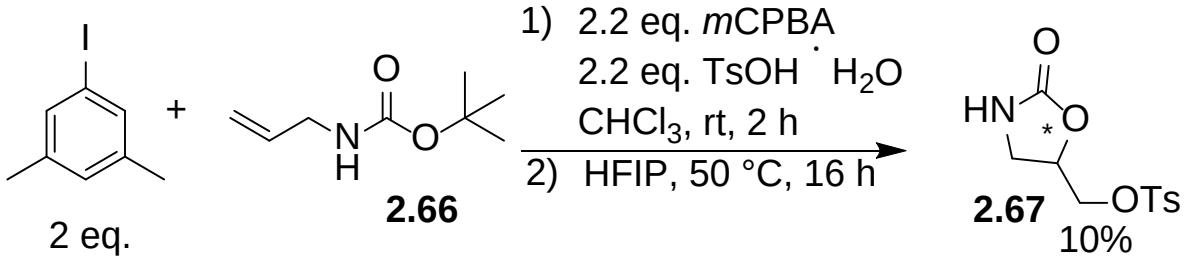
hexafluoroisopropanol (HFIP) under the optimum cyclisation conditions (Scheme 79a). The second strategy trialed, comprised of Koser's conditions developed by Yamamoto and Togo, iodo-3,5-dimethylbenzene, *para*-toluenesulfonic acid ($TsOH \cdot H_2O$) add to an oxidant *meta*-chloroperoxybenzoic acid (*m*CPBA) and the carbamate substrate **2.66** in hexafluoroisopropanol (HFIP) under the optimum cyclisation conditions (Scheme 79b).[105] Unfortunately, neither set of reaction conditions brought about cyclisation and this was probably due to the failed formation of the novel Koser's derivative. It was thought to be due to the incompatibility of hexafluoroisopropanol (HFIP) to mediate the *in situ* formation of the *meta*-xylyl Koser's derivative **2.75**.



Scheme 79a&b: Unsuccessful One-Pot Carbamate Cyclisation

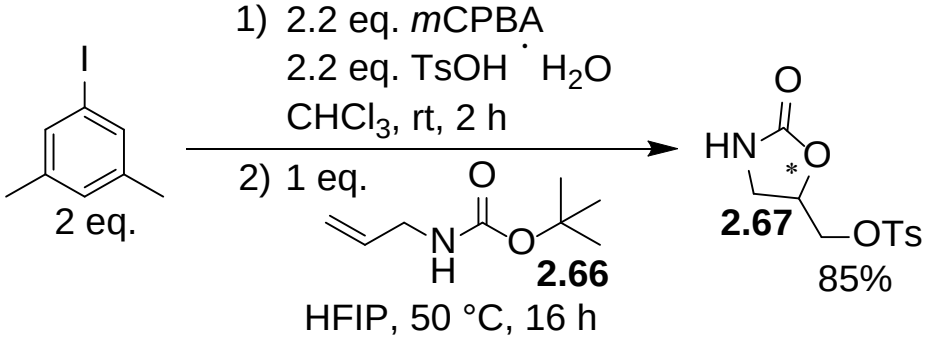
Given the incompatibility of hexafluoroisopropanol (HFIP) to mediate the *in situ* formation of the *meta*-xylyl Koser's derivative **2.75**, new one-pot strategies were devised to access the desired product. The first strategy involved adding all the materials in chloroform and stirring at room

temperature for 2 hours, then adding hexafluoroisopropanol (HFIP) and heating at 50 °C, for 16 hours. The reaction produced 10% of the desired oxazolidinone **2.67** with no detected starting material **2.66**, oxidation by *meta*-chloroperoxybenzoic acid (*m*CPBA) of the alkene within the substrate **2.66** could have occurred (Scheme 80).



Scheme 80: Successful One-Pot Carbamate Cyclisation

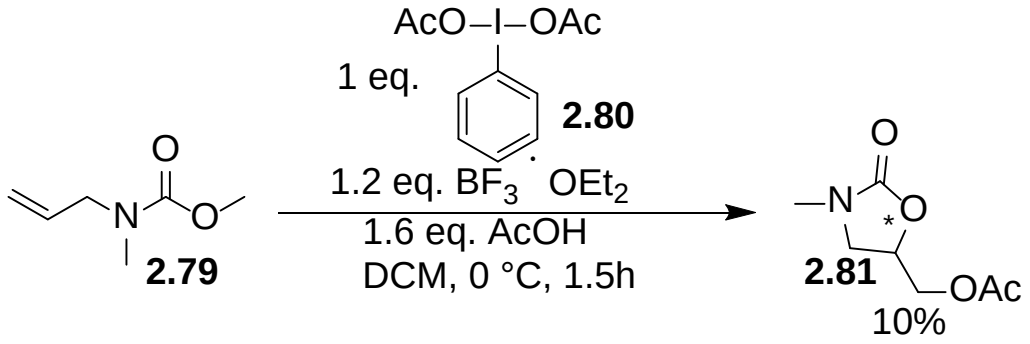
The second strategy involved adding iodo-3,5-dimethylbenzene, *para*-toluenesulfonic acid (TsOH.H_2O) with *meta*-chloroperoxybenzoic acid (*m*CPBA) in chloroform and stirring at room temperature for 2 hours. Then adding by canula, the substrate **2.66** dissolved in hexafluoroisopropanol (HFIP) and heating at 50 °C, for 16 hours. This one-pot procedure produced 85% of the oxazolidinone **2.67** with no detected starting material **2.66**, supporting the hypothesis that the substrate **2.66** could have been epoxidised during *in situ* formation of the *meta*-xylyl Koser's derivative **2.75** (Scheme 81).



Scheme 81: Improved One-Pot Carbamate Cyclisation

3.6.14 Alternative Reaction Conditions

While investigating alternative reaction conditions, it was found using unoptimised conditions developed by Fujita and coworkers, cyclisation could be achieved albeit in low yields of 10%. These alternative conditions employed phenyliodine(III) diacetate (PIDA) **2.80** and boron trifluoride dietherate Lewis acid and were interesting due to the product **2.81** containing acetate substituent that could be used as a handle for further functionalisation.[107] These conditions were not further investigated due to the success of the optimised conditions using the *meta*-xylyl Koser's derivative **2.75** (Scheme 82).

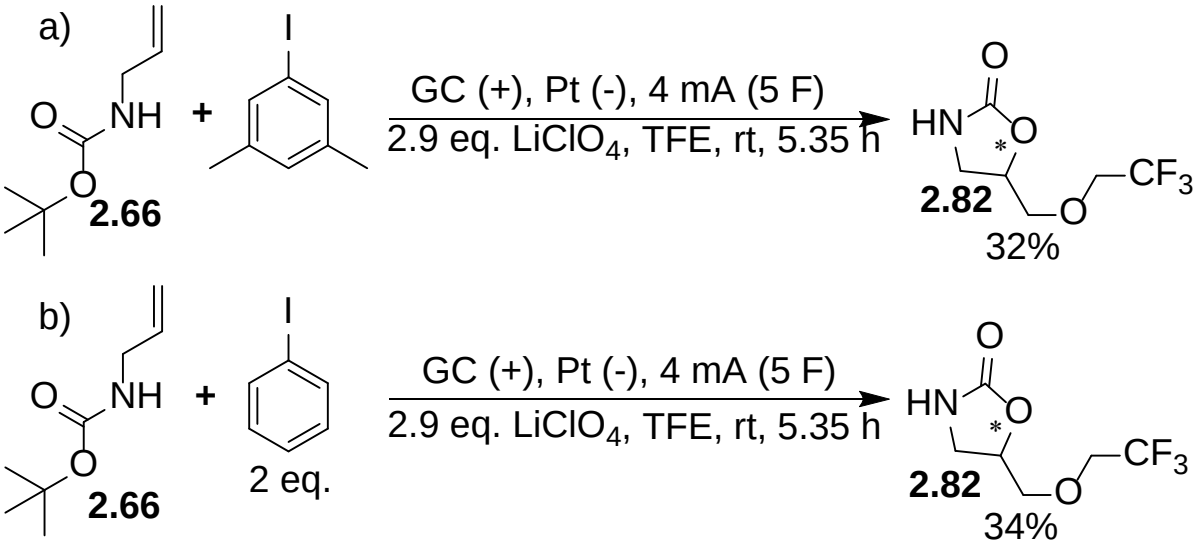


Scheme 82: Alternative Cyclisation Reaction Conditions[107]

3.6.15 Electrochemical-Mediated Cyclisation

Electrosynthesis has many advantages over conventional reagent-based processes, such as mild conditions, high yields, ease of scale-up, functional group tolerance, and selective transformations. Electrons can act as a mass-free reagent, stoichiometric amounts of oxidant in reactions are unnecessary, thus reducing the production of waste. Developments in various cyclisations have been reported through a variety of electrochemical annulations for the use in pharma-, agro- and fine chemicals as well as the total synthesis of complex molecules derived from natural products.[108]

While experimenting with electrochemical synthesis with assistance, it was found using a glassy carbon (GC) working electrode and a platinum (Pt) cathode, with a constant current of 4 mA and 5 F per mole, cyclisation occurred. A **2.82** yield of 32% was achieved with 27% residual substrate **2.66**, after 5 hours and 21 minutes, the conditions were not further optimised (Scheme 83a). 2 equivalents of iodobenzene were also found to be effective in mediating cyclisation, affording a **2.82** yield of 34% and recovering 68% starting material **2.66** (Scheme 83b).



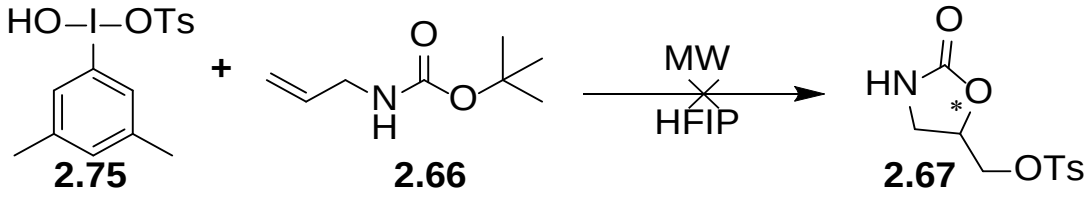
Scheme 83a&b: Electrochemical Mediated Carbamate Cyclisation

3.6.16 Microwave-Assisted Synthesis

Microwave irradiation has been widely utilised in organic chemistry as an efficient energy source, microwave irradiation has advantages over conventional heating which includes homogeneous and deep internal heating, remarkable reaction kinetics due to high heating rates, and selective heating. Subsequently, microwave-assisted organic reactions produce high yields and low amounts of side-products, easier purification of products, and in some instances, modified selectivity. Microwave radiation has two main effects on a reaction, thermal effect and non-

thermal effect. The thermal effect involves the friction and collisions of molecules resulting in heat generation. The non-thermal effect relates to the interaction or alignment of the dipoles of the molecules and charges of the electric field.[109] It was thought that microwave-assisted heating could reduce reaction times, maintain high yields and reduce the production of byproducts in the cyclisation of carbamates. There was an attempt to use microwave irradiation to assist in carbamate cyclisation (Scheme 84).

Using a Milestone MicroSYNTH microwave reactor, an initial microwave power of 100 W, the reaction mixture was heated to 130 ˚C, in HFIP and held at this temperature for 20 minutes, working at a 6 mmol scale, no product **2.67** was formed (Entry 1, Table 11). Extending the reaction temperature and time, and increasing the microwave energy, the reaction was repeated. Using an initial microwave power of 150 W, the reaction mixture was heated to 150 ˚C and held at this temperature for 90 minutes, working on a 6 mmol scale, no product **2.67** was formed (Entry 2, Table 11). Increasing the reaction conditions further, a final attempt was made. Using an initial microwave power of 200 W, the reaction mixture was heated to 180 ˚C and held at this temperature for 6 hours, working on a 6 mmol scale, no product **2.67** was formed (Entry 3, Table 11).



2.75 **2.66** **2.67**

Scheme 84: Failed Microwave Promoted Cyclisation

Entry	Reaction Conditions	Scale (mmol)	Residual Substrate[a]	Oxazolidinone Yield[a]
1	10 mL vessel, initial power 100 W, heating ramp to 130 °C in 15 mins., 130 °C maintained for 20 mins.	6	99%	0%
2	10 mL vessel, initial power 150 W, heating ramp to 150 °C in 20 mins., 150 °C maintained for 90 mins.	6	99%	0%
3	10 mL vessel, initial power 200 W, heating ramp to 180 °C in 30 mins., 180 °C maintained for 6 hours.	6	99%	0%

Table 11: Microwave Assisted Cyclisation Results

From ^{1}H NMR analysis, there was no λ^3 iodane or cyclised product **2.67** identified, suggesting that the *meta*-xylyl Koser's derivative **2.75** was destroyed before facilitating the cyclisation reaction. This hypothesis is further reinforced by Differential Scanning Calorimetry (DSC) studies that show two discrete decompositions. At approximately 140 °C the first decomposition starts, a second decomposition of the residue then occurs at approximately 177 °C, which completely destroys the λ^3 iodane (Figure 23).

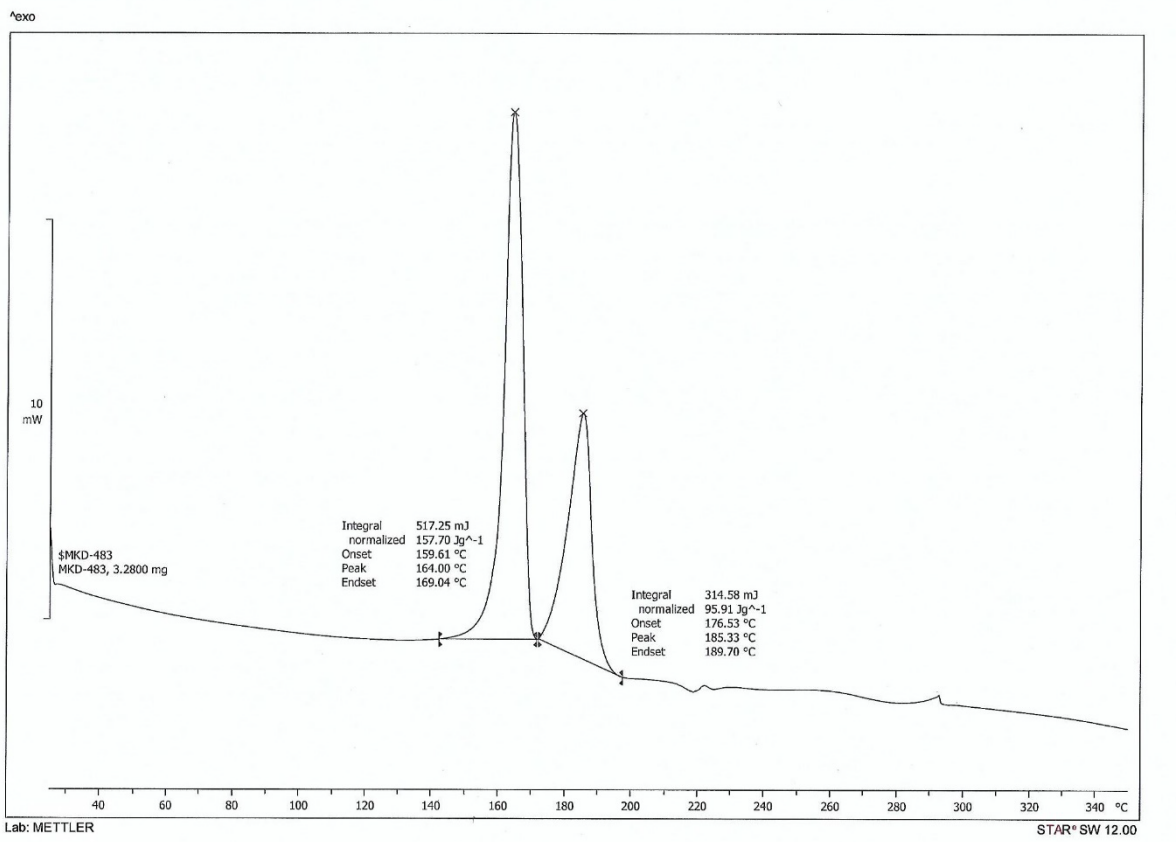
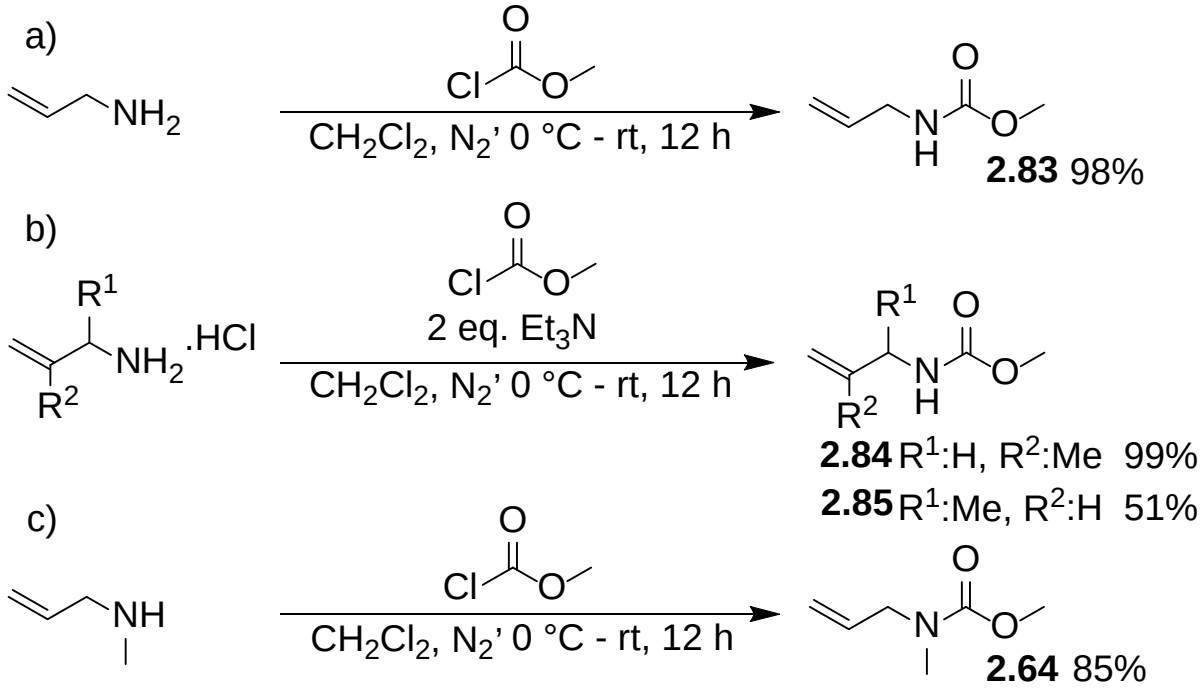


Figure 23: DSC Graph of Iodane Decomposition

3.6.17 Carbamate Scope Development

To demonstrate the utility of the carbamate cyclisation reaction, it was essential to create a scope of oxazolidinone analogues. However, a diverse range of carbamate substrates would need to be synthesised to undergo cyclisation. After careful consideration of literature strategies to access interesting carbamates, it was decided to use simple, robust reactions to obtain the corresponding substrates. Employing a carbamoylation procedure by Kozmin and coworkers, methyl *N*-allylcarbamate **2.83** was prepared, or a modified procedure was used to prepare analogues **2.79**, **2.84**, **2.85** (Scheme 85a-c).[110]

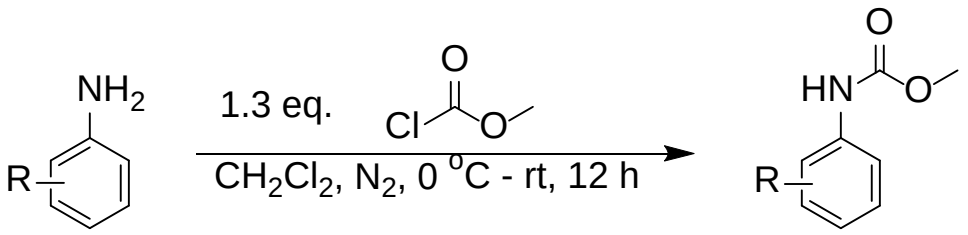


Scheme 85a,b,&c: *N*-Allylcarbamate Preparations

3.6.18 Carbamoylation of Anilines

It was thought it would be very important to further derivatise the *N*-allylcarbamates to allow access to the substrates that could then be cyclised into oxazolidinones. The *N* position is a key position for derivatisation for oxazolidinone antibacterial, drug development. Kozmin's

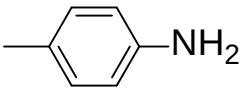
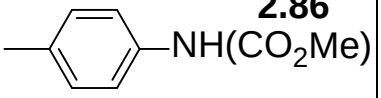
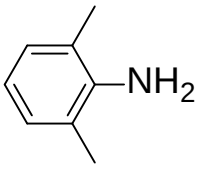
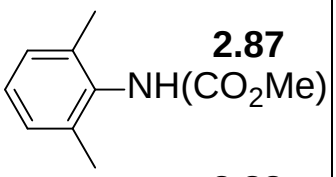
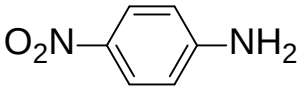
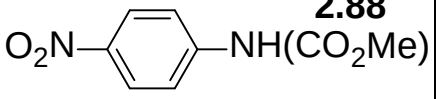
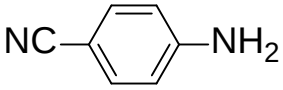
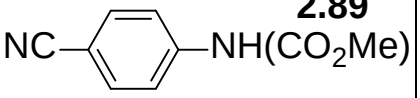
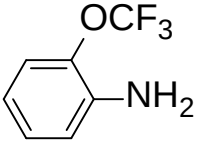
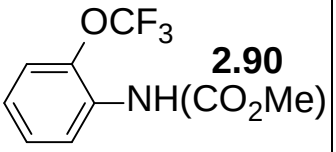
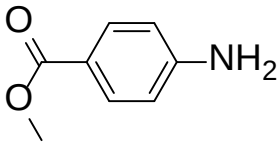
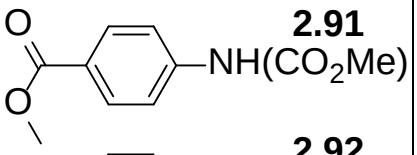
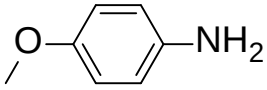
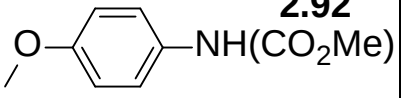
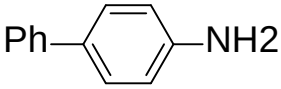
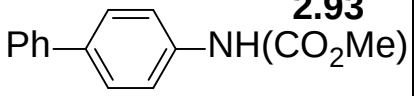
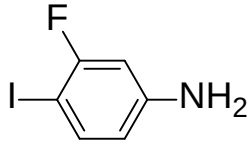
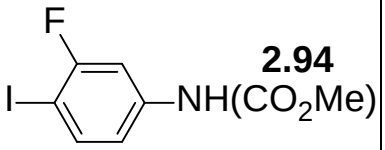
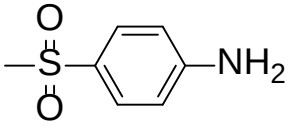
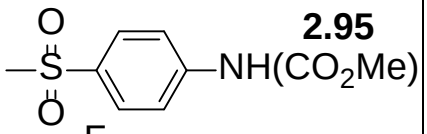
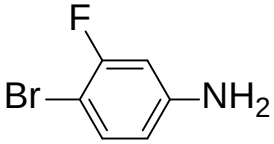
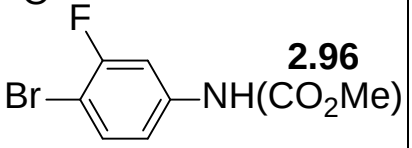
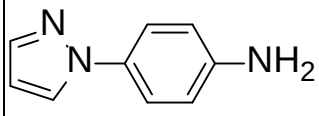
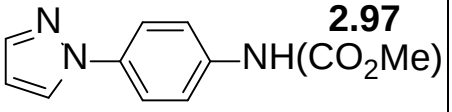
carbamoylation was again employed to access a range of substituted aryl carbamates from their corresponding anilines (Scheme 86).[110]



R: H, CH_3, NO_2, CN, OCF_3, CO_2Me, Ph, F, I, Br, SO_2Me etc.

Scheme 86: Carbamoylation of Anilines

The carbamoylation reaction was simple to perform and resulted generally in high yields with some exceptions (Table 12). (4-methylsulfonyl)phenyl carbamate **2.95** yielded only 33% and methyl (4-(*1H*-pyrazol-1-yl)phenyl)carbamate **2.97** gave 49% (entry 10 and 12, Table 12). However, (4-methyl)phenyl carbamate **2.86** gave a pleasing 96% and (4-nitrile)phenyl carbamate **2.89** 98% (entry 1 and 4, Table 12). Both electron-deficient substituted phenyl and electron-rich substituted phenyl carbamates gave excellent yields.

Entry	Substrate	Carbamate	Yield
1		**2.86** 	96%
2		**2.87** 	55%
3		**2.88** 	84%
4		**2.89** 	98%
5		**2.90** 	63%
6		**2.91** 	62%
7		**2.92** 	93%
8		**2.93** 	82%
9		**2.94** 	93%
10		**2.95** 	33%
11		**2.96** 	77%
12		**2.97** 	49%

(continued)

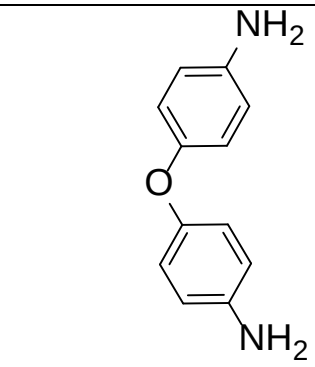
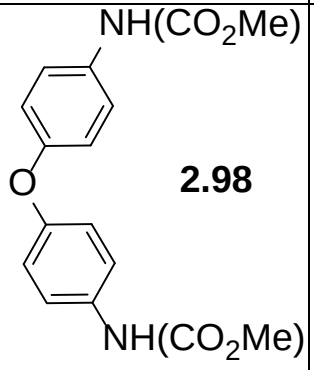
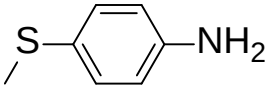
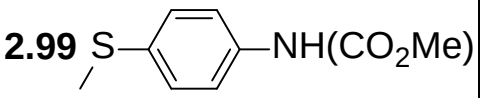
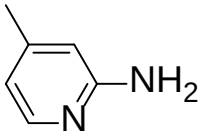
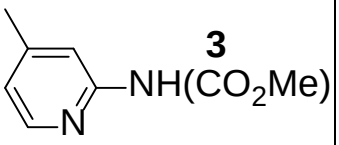
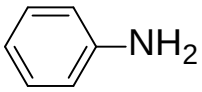
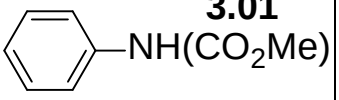
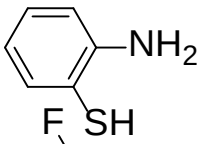
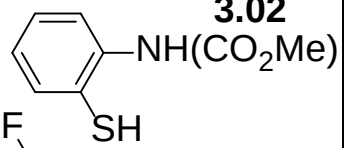
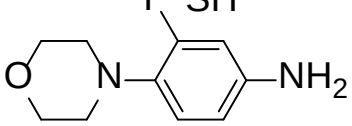
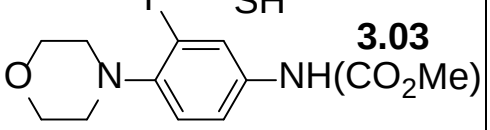
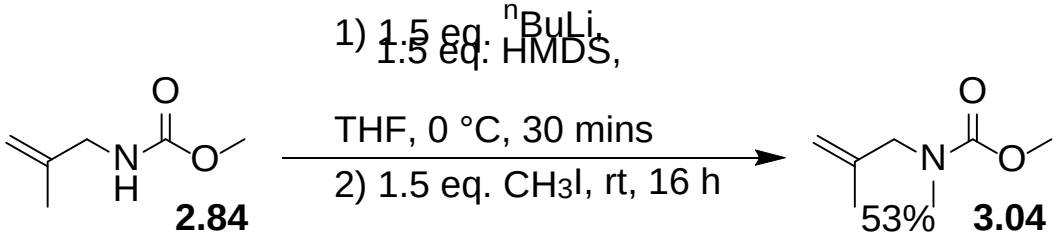
Entry	Substrate	Carbamate	Yield
13		 **2.98**	55%
14		 **2.99**	99%
15		 **3**	46%
16		 **3.01**	94%
17		 **3.02**	43%
18		 **3.03**	87%

Table 12: Carbamoylation of Substituted Anilines

3.6.19 Derivatisation of Carbamates

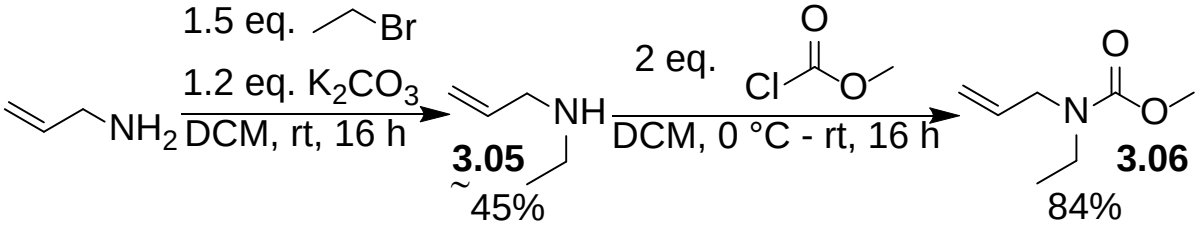
From literature searches, various strategies could be employed to access derivatised carbamates. Jeschke and coworkers offered *N*-alkylation of the carbamate using a strong base to deprotonate before nucleophilic attack of a haloalkane.[111] Akinleye's patent suggested a method to prepare alkylated secondary allylamines before carbamoylation.[112] Murphy and coworkers offered *N*-allylation of the secondary amine carbamate using sodium hydride (NaH) and allyl bromide.[113] All the

methods were utilised to access a diverse range of allyl carbamates. Using Jeschke's *N*-alkylation procedure, methyl (2-methylallyl)carbamate was methylated successfully with a yield of 53% (Scheme 87).[111]



Scheme 87: *N*-Alkylation of Methyl (2-methylallyl)carbamate

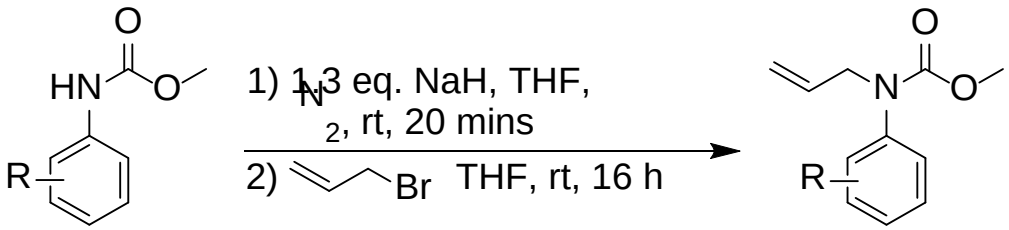
An alternative strategy to Jeschke's *N*-alkylation procedure was Akinleye's patent method, which involves preparing a secondary amine from allylamine.[111] It was used to prepare an ethylated secondary allylamine **3.05** in approximately 45% yield. The ethyl secondary allylamine **3.05** was then used without purification in Kozmin's carbamoylation reaction to create the corresponding carbamate **3.06**, in 84% yield (Scheme 88).[110]



Scheme 88: Preparation of Methyl allyl(ethyl)carbamate

3.6.20 Carbamate Allylation

Murphy's allylation procedure was extensively used to synthesise a range of starting materials for the cyclisation reaction. It was necessary to wash the mineral oil from the sodium hydride to initiate an effective allylation reaction of the carbamates (Scheme 89).[113]



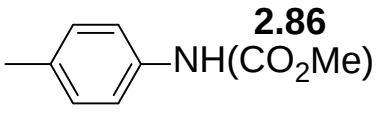
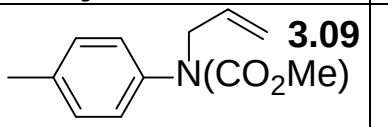
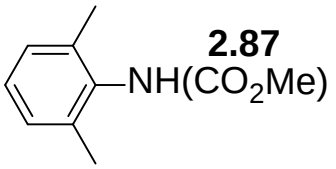
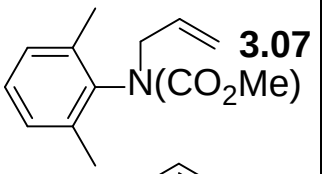
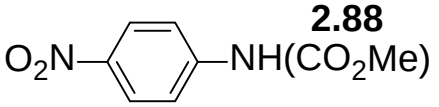
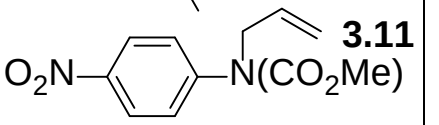
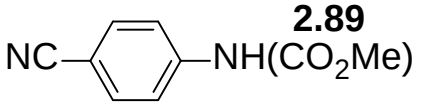
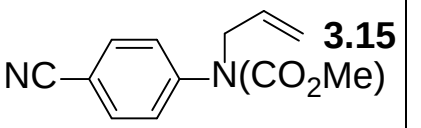
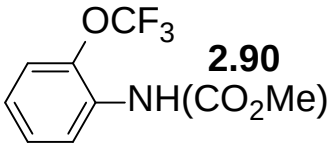
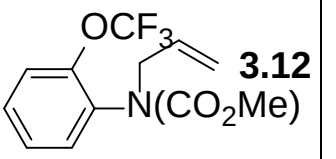
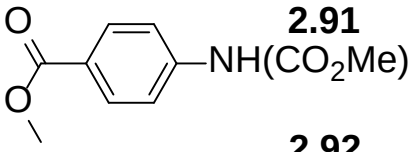
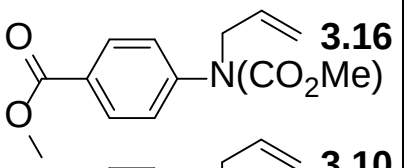
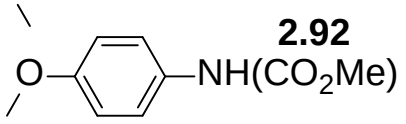
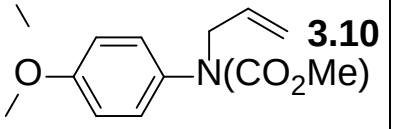
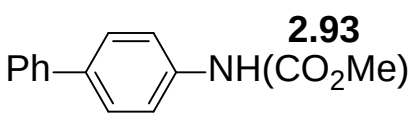
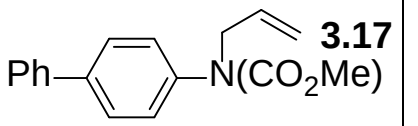
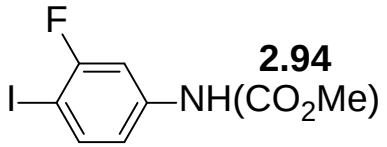
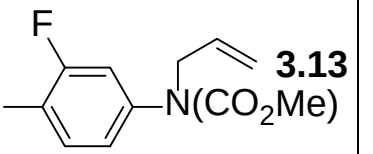
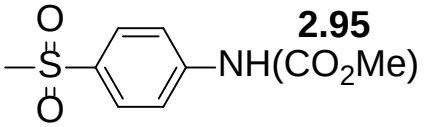
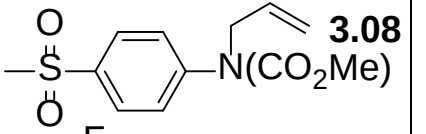
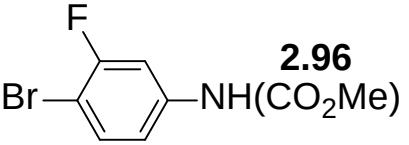
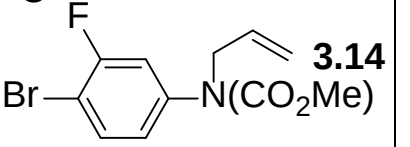
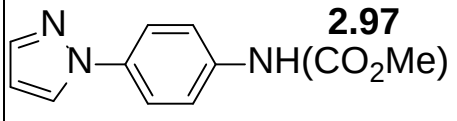
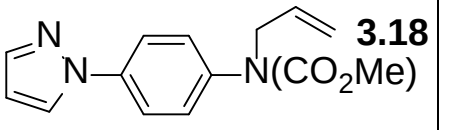
R: H, CH_3, NO_2, CN, OCF_3, CO_2Me, Ph, F, I, Br, SO_2Me etc.

Scheme 89: General *N*-allylation of Carbamates Procedure

Very high yields were obtained with the (3,5-dimethyl)phenyl *N*-allylcarbamate **3.07** and (4-methylsulfonyl)phenyl *N*-allylcarbamate **3.08** derivatives, 99%, and 96%, respectively (entry 2 and 10, Table 13). The (4-methyl)phenyl *N*-allylcarbamate **3.09** derivative gave an unexpectedly low yield of 40%, however, the (4-methoxy)phenyl *N*-allylcarbamate **3.10** obtained a 76% yield (entry 1 and 7, Table 13). In general, the trend was that electron-donating groups (EDGs) substituted phenyl *N*-allylcarbamates gave moderate to excellent yields. The (4-nitro)phenyl *N*-allylcarbamate **3.11** gave a meager yield of 36% and (2-trifluoromethoxy)phenyl *N*-allylcarbamate **3.12** gave a reasonable 57% yield (entry 3 and 5, Table 13). The (4-iodo, 3-fluoro)phenyl *N*-allylcarbamate **3.13** gave a similar yield to (4-bromo, 3-fluoro)phenyl *N*-allylcarbamate **3.14** of 78% and 80%, respectively (entry 9 and 11, Table 13). Methyl allyl(2-mercaptophenyl)carbamate was not produced in the allylation reaction, deprotonation and allylation of the thiol group resulted in producing methyl (2-(allylthio)phenyl)carbamate and was thus discontinued. In general, there was a trend that electron-withdrawing groups (EWGs) substituted phenyl *N*-allylcarbamates gave low to moderate yields.

It was found during experimentation that increasing the sodium hydride (NaH) concentration to 5 equivalents had an adverse impact on the

carbamate. From ^{1}H NMR studies, the carbamate was found to have been demethylated or hydrolysed to an *N*-allylcarbamic acid.

Entry	Substrate	*N*-Allylcarbamate	Yield
1	 **2.86**	 **3.09**	40%
2	 **2.87**	 **3.07**	99%
3	 **2.88**	 **3.11**	36%
4	 **2.89**	 **3.15**	60%
5	 **2.90**	 **3.12**	57%
6	 **2.91**	 **3.16**	70%
7	 **2.92**	 **3.10**	76%
8	 **2.93**	 **3.17**	64%
9	 **2.94**	 **3.13**	78%
10	 **2.95**	 **3.08**	96%
11	 **2.96**	 **3.14**	80%
12	 **2.97**	 **3.18**	73%

(continued)

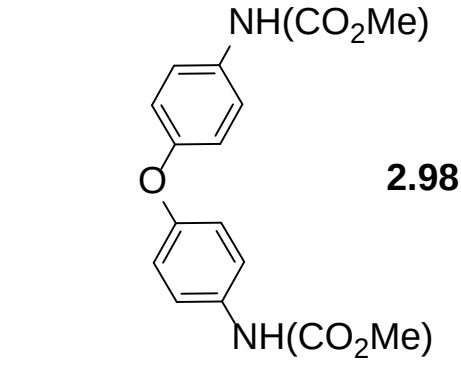
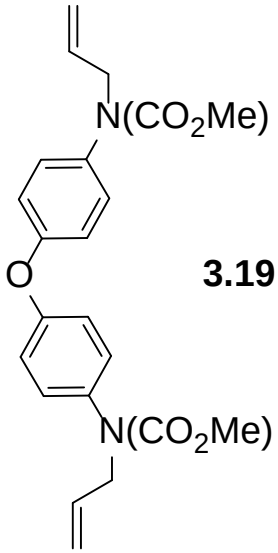
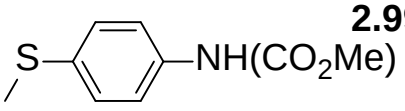
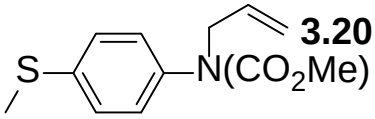
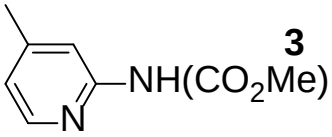
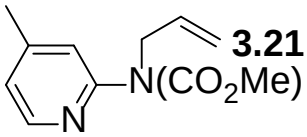
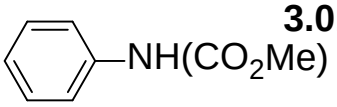
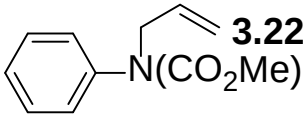
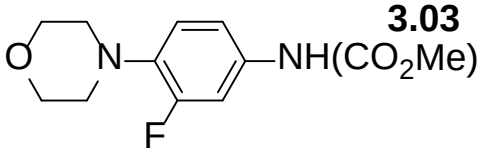
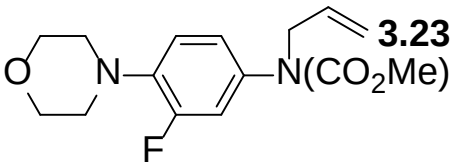
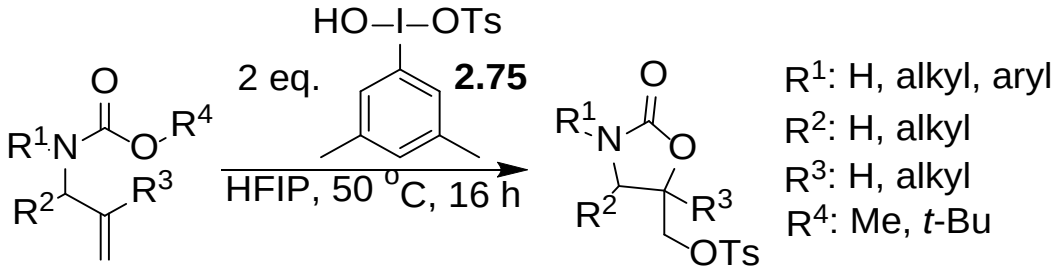
Entry	Substrate	*N*-Allylcarbamate	Yield
13	 **2.98**	 **3.19**	87%
14	 **2.99**	 **3.20**	48%
15	 **3**	 **3.21**	55%
16	 **3.01**	 **3.22**	59%
17	 **3.03**	 **3.23**	58%

Table 13: Carbamate Allylation Yields

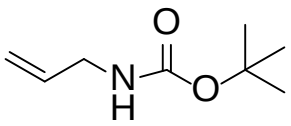
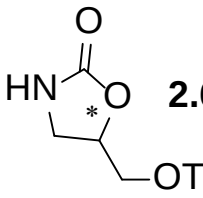
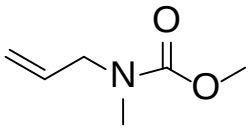
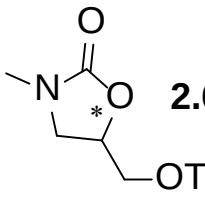
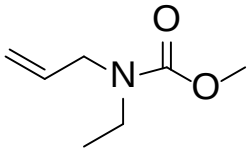
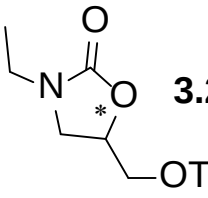
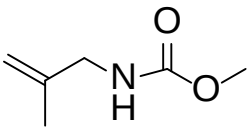
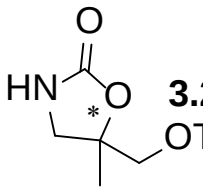
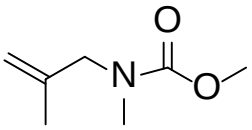
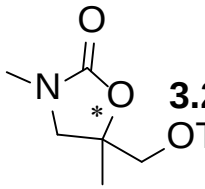
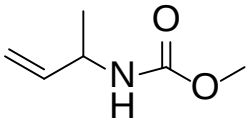
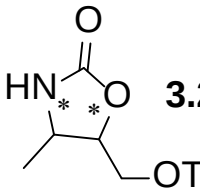
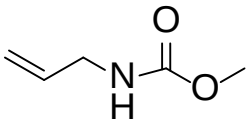
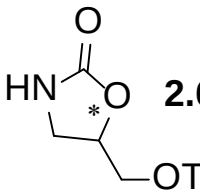
3.6.21 Oxazolidonone Scope of Alkyl Derivatives

Using the optimised carbamate cyclisation conditions, all of the prepared allylated substrates were subjected to the reaction conditions (Scheme 90).



Scheme 90: Cyclisation Scope of Alkyl derivatives

The results varied but in general, were good to excellent. Using *tert*-butyl allylcarbamate **2.66** at the 1 mmol scale, the corresponding oxazolidinone **2.67** was produced at 97%, suggesting that the *tert*-butyl group could be a better leaving group (entry 1, Table 14). Using the methyl allylcarbamate **3.24** starting material in the same reaction conditions only produced 26% **2.67** with no residual substrate **3.24** (entry 7, Table 14). Methyl **3.25** and ethyl **3.26** *N*-substituted oxazolidinones produced 67% and 81%, respectively, which could be due to the resonance effects of alkyl groups (entry 2 and 3, Table 14). Comparing the cyclisation of methyl (2-methylallyl)carbamate **2.84** and methyl methyl(2-methylallyl)carbamate **3.04** resulted in a significant difference in oxazolidinone yield. The 5-methyl oxazolidinone **3.27** gave a low yield of 36%, compared to the 3,5 dimethyl oxazolidinone **3.28** which produced 74% (entry 4 and 5, Table 14). This further adds credence to the idea that inductive effects influence cyclisatiion and product formation. The 4-methyl oxazolidinone **3.29** yielded only 44%, which further reinforces that *N*-substituted allylcarbamates perform better in the reaction (entry 6, Table 14).

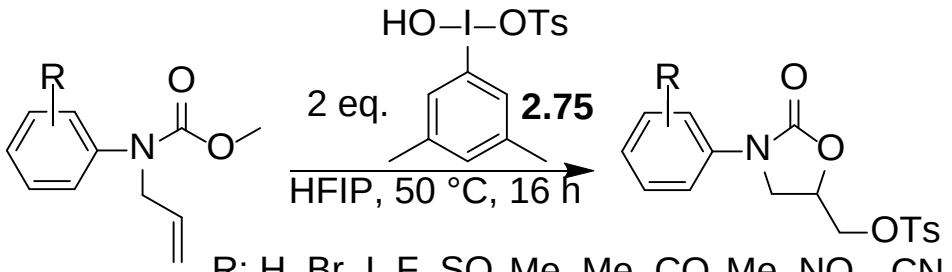
Entry	*N*-Allylcarbamate		Oxazolidinone		Yield
1		**2.66**		**2.67**	97%[a]
2		**2.79**		**2.65**	67%
3		**3.06**		**3.26**	81%
4		**2.84**		**3.27**	36%
5		**3.04**		**3.28**	74%
6		**2.85**		**3.29**	44%
7		**3.24**		**2.67**	26%

[a] using *tert*-butyl allylcarbamate substrate at 1 mmol scale

Table 14: Cyclisation Scope of Alkyl derivatives

3.6.22 Oxazolidinone Scope of Aryl Derivatives

The prepared *N*-aryl substituted allylcarbamates were subjected to the cyclisation conditions, the results were generally very good to excellent with a few unexpected results (Scheme 91).

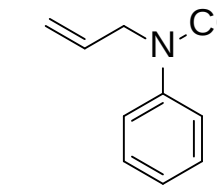
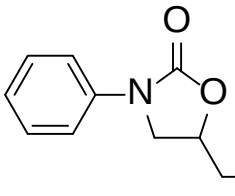
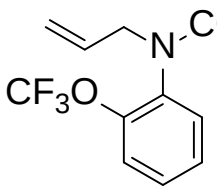
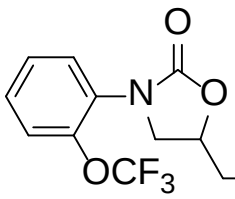
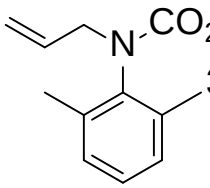
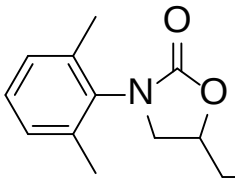
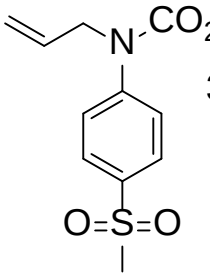
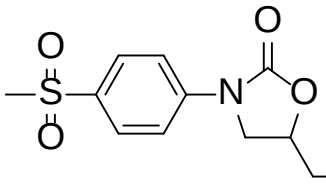
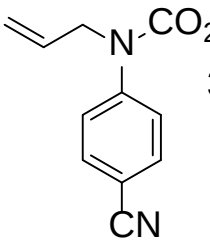
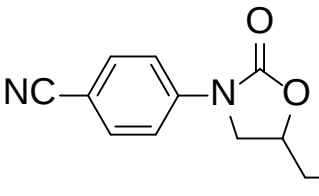
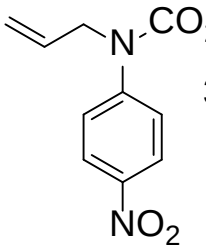
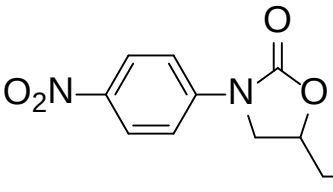
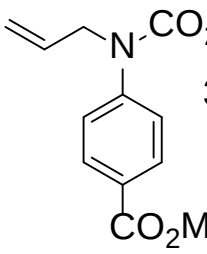
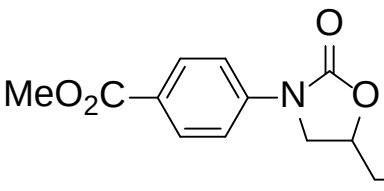


R: H, Br, I, F, SO_2Me, Me, CO_2Me, NO_2, CN, OCF_3, OCH_3, Ph, pyrazolyl etc.

Scheme 91: Cyclisation Scope of Aryl derivatives

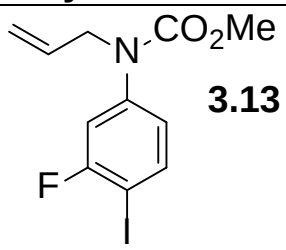
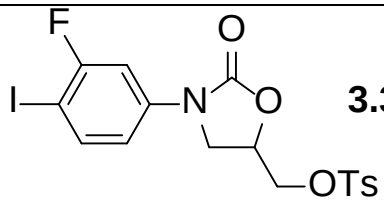
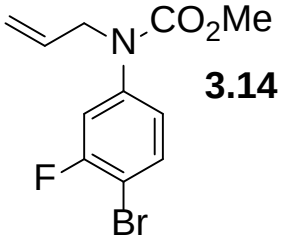
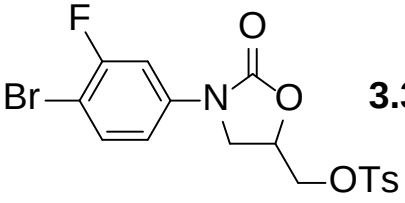
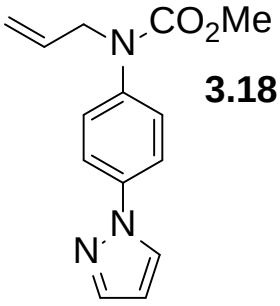
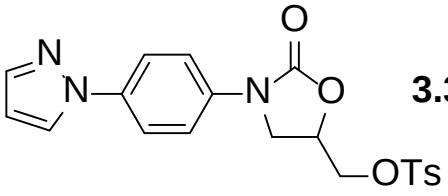
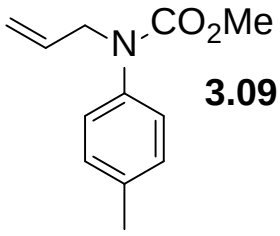
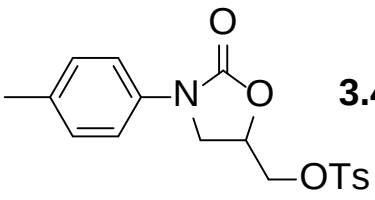
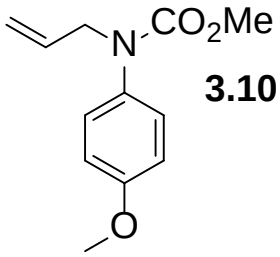
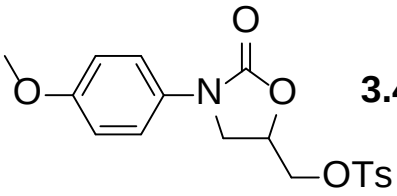
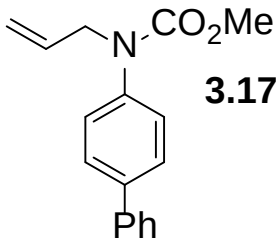
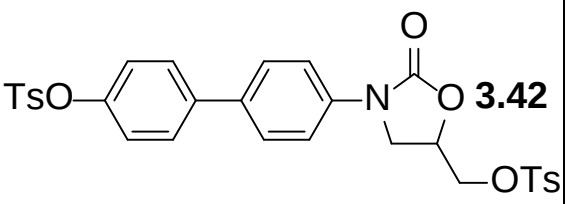
N-phenyl oxazolidinone **3.30** only yielded 16% with 2 equivalents *meta*-xylyl Koser's derivative **2.75**, however using 5 equivalents of standard Koser's reagent **1.14**, yielded 61% (entry 1, Table 15). (2-trifluoromethoxy)phenyl oxazolidinone **3.31** yielded an impressive 95%, there was concern that the ortho position may interfere with cyclisation, however, it was unfounded (entry 2, Table 15). The (2,6-dimethyl)phenyl oxazolidinone **3.32** was also produced in 95% yield, further reinforcing that efficient cyclisation is possible where the substituents are in the *ortho* positions. This could be due to the positive inductive effects of the *ortho* electron-donating groups (EDGs) on the nitrogen (entry 3, Table 15). (4-methylsulfonyl)phenyl oxazolidinone **3.33** only gave a 55% yield, however, the (4-cyano)phenyl oxazolidinone **3.34** gave a very good yield of 87%. Demonstrating that *para* electron-donating groups (EDGs) perform slightly worse than *para* electron-withdrawing groups (EWGs) (entry 4 and 5, Table 15).

(4-nitro)phenyl oxazolidinone **3.35** gave a good yield of 70%, and the 4-benzoate oxazolidinone **3.36** produced 87% yield (entry 6 and 7, Table 15). Reinforcing the premise that generally *para* positioned electron-withdrawing groups (EWGs) perform slightly better than *para* electron-donating groups (EDGs). There were doubts whether the *para* iodo-substituted phenyl *N*-allylcarbamate **3.13** would be efficiently cyclised, due to oxidation of the iodine substituent, hence, the *para* bromo-substituted phenyl *N*-allylcarbamate **3.14** was added to the *N*-allylcarbamate scope. Fortunately, those concerns were not realised and both (3-fluoro-4-iodo)phenyl oxazolidinone **3.37** and (3-fluoro-4-bromo)phenyl oxazolidinone **3.38** were produced consistently in good yields of 84% and 85%, respectively (entry 8 and 9, Table 15). The (3-(4-4-(*1H*-pyrazol-1-yl)phenyl) oxazolidinone **3.39** was formed in a moderate to good yield of 67%, as on trend with previous cyclisations (entry 10, Table 15). (4-methyl)phenyl oxazolidinone **3.40** gave a good yield of 85%, and the (4-methoxy)phenyl oxazolidinone **3.41** produced a similar 75% yield (entry 11 and 12, Table 15). Suggesting *para* electron-donating groups (EDGs) have less of a positive resonance effect compared to *ortho* electron-donating groups (EDGs), which could be due to the distance from the nitrogen. Cyclisation of the 1,1-biphenyl *N*-allylcarbamate **3.17** resulted in the unexpected double oxytosylation of both the oxazolidinone ring and the biphenyl substituent **3.42**, resulting in a poor yield of 16% (entry 13, Table 15). Given the double oxytosylation, it was thought that increasing the *meta*-xylyl Koser's derivative **2.75** from 2 equivalents to maybe 3 or 4 equivalents would improve the yield.

Entry	*N*-Allylcarbamate	Oxazolidinone	Yield
1	 **3.22**	 **3.30**	61%[a]
2	 **3.12**	 **3.31**	95%
3	 **3.07**	 **3.32**	95%
4	 **3.08**	 **3.33**	55%
5	 **3.15**	 **3.34**	87%
6	 **3.11**	 **3.35**	70%
7	 **3.16**	 **3.36**	87%

[a] using 5 eq. Koser's Reagent

(continued)

Entry	*N*-Allylcarbamate	Oxazolidinone	Yield
8	 **3.13**	 **3.37**	84%
9	 **3.14**	 **3.38**	85%
10	 **3.18**	 **3.39**	67%
11	 **3.09**	 **3.40**	85%
12	 **3.10**	 **3.41**	75%
13	 **3.17**	 **3.42**	16%

(continued)

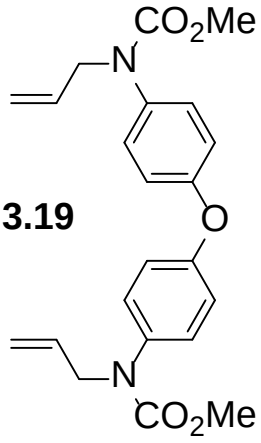
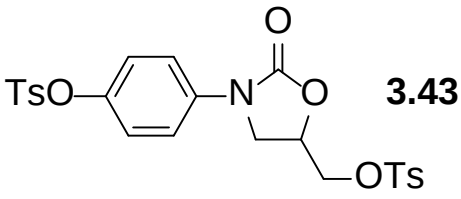
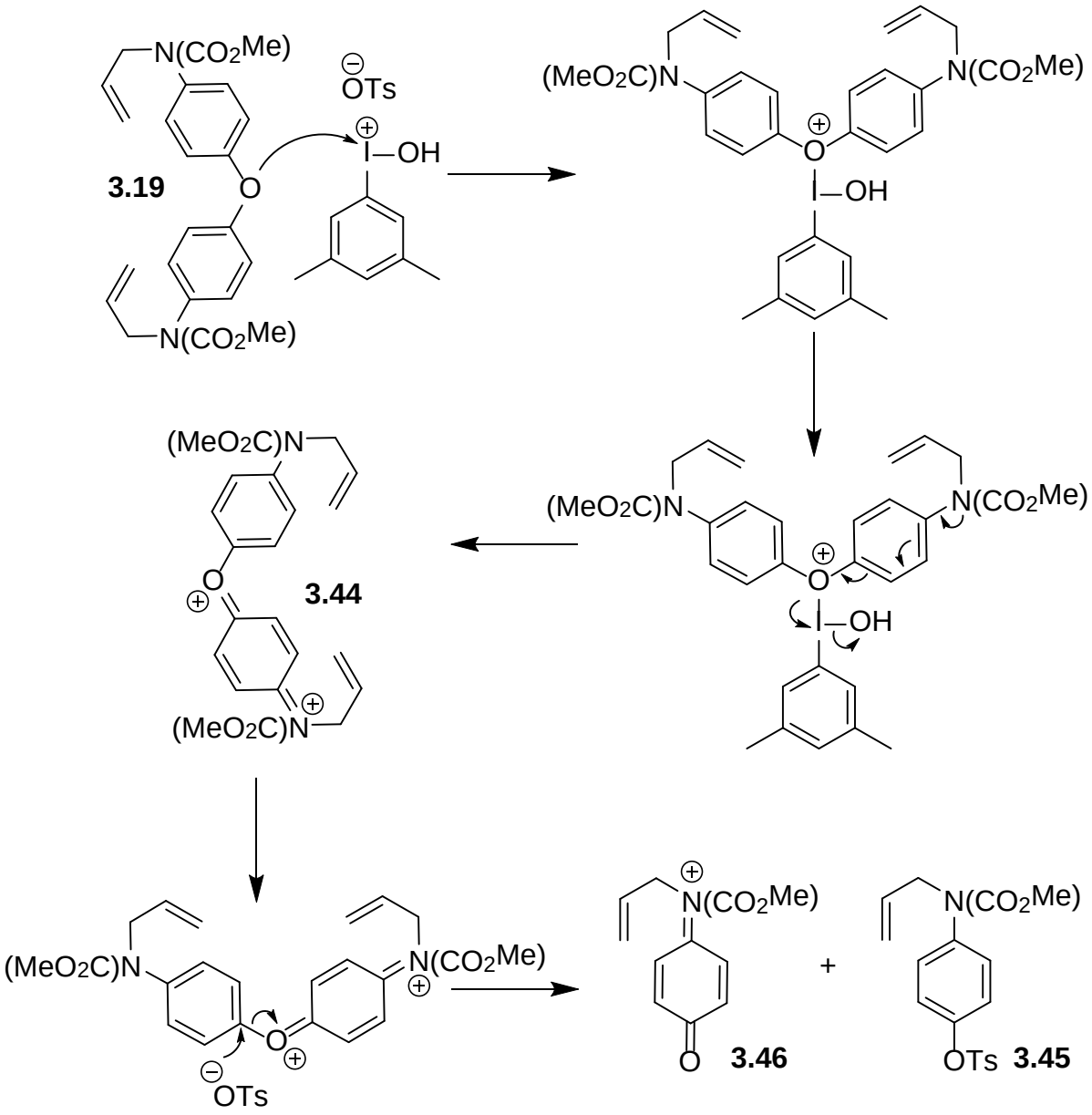
Entry	*N*-Allylcarbamate	Oxazolidinone	Yield
14	 **3.19**	 **3.43**	26%

Table 15: Cyclisation Scope of Aryl derivatives

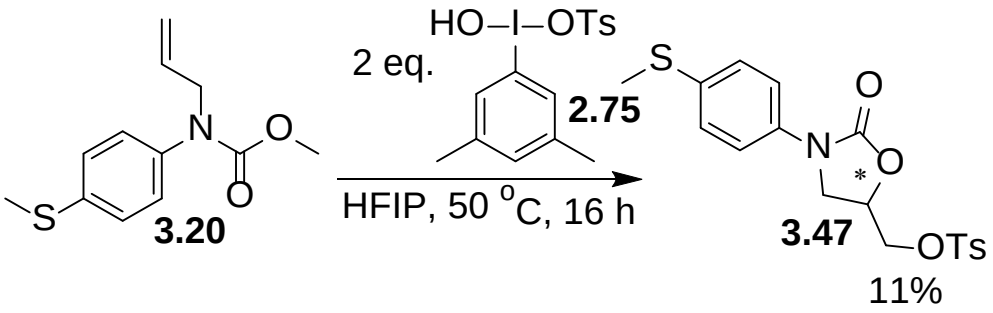
Oxybis(4,1-phenylene) bis(*N*-allylcarbamate) **3.19** also gave an unexpected result, it was anticipated that a double oxazolidinone ring would be formed. The oxybis 4,1-phenylene was cleaved at the oxygen bridge, resulting in a single cyclisation, forming (4-(tosyloxy)phenyl oxazolidinone **3.43** in 26% yield (entry 14, Table 15). It was proposed that an oxidation of the electron rich arene had occurred to the substrate **3.19**. Via ligand exchange with a tosylate anion, resulting in deromatisation of one of the arenes and reductive elimination of an iodoarene. This was followed by an S_N2 substitution of a free tosylate anion to the para carbon of the arene **3.44** and the cleaving of the ether to form the *para*-tosylated phenyl allylcarbamate **3.45** and an iminium cation **3.46**(Scheme 92). Possibly increasing the concentration of the iodane **2.75** would improve the yield of the cyclised product. However, due to the ether cleavage of the substrate before cyclisation, the product yield would be capped to 50%, as only one half of the substrate would be cyclised.



Scheme 92: Postulated Ether Cleavage Mechanism of Substrate

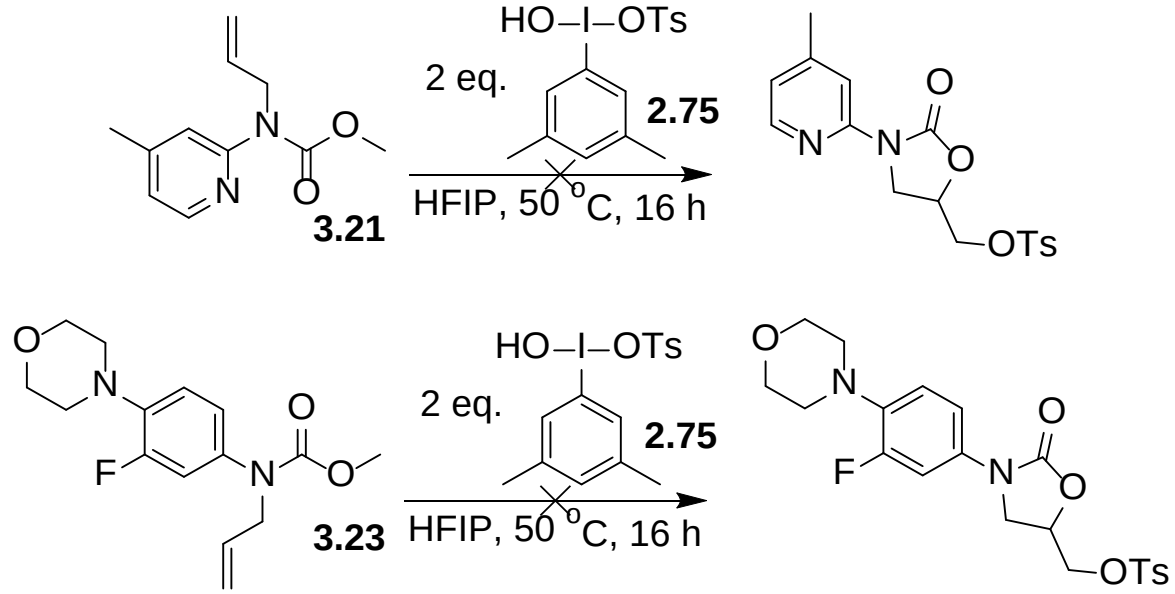
3.6.23 Miscellaneous Cyclisations

(4-(methylthio)phenyl *N*-allylcarbamate **3.20** did cyclise, producing a yield 11% of oxazolidinone product **3.47** and recovering 82% of the starting material **3.20**. Further development of (4-(methylthio)phenyl oxazolidinone **3.47** was discontinued given the poor yield and mixtures of products (Scheme 93).



Scheme 93: Low Yielding (4-(methylthio)phenyl Oxazolidinone

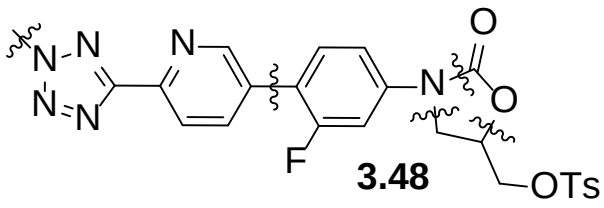
(4-methylpyridin-2-yl) *N*-allylcarbamate **3.21** did not cyclisation probably due to the pyridine nitrogen removing electron density from the critical *ortho* and *para* carbons via resonance effects. (3-fluoro-4-morpholino)phenyl *N*-allylcarbamate **3.23** also did not cyclise, suggesting other adverse electronic effects could be involved (Scheme 94).



Scheme 94: Failed Cyclisations of *N*-phenyl derivatives

3.6.24 Retrosynthesis of Tedizolid Analogue

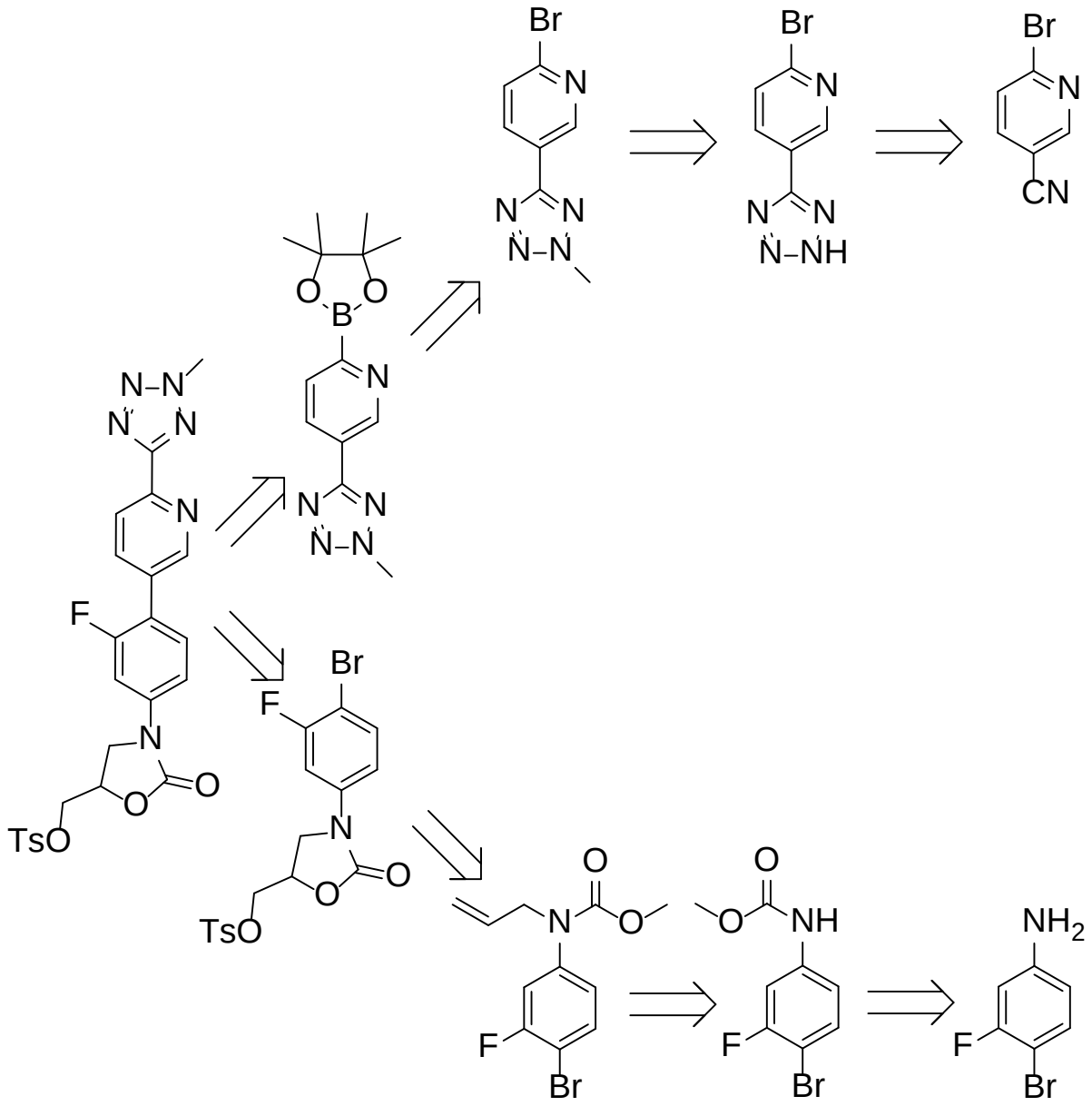
It was desirable to demonstrate real-world cyclisation applications in a total synthesis setting. A procedure was developed for the total synthesis of a Tedizolid, antibiotic drug analogue containing the all-important oxazolidinone moiety. A disconnect approach was employed to find a synthetic route to the target molecule (Figure 24).[114]



3.48

Figure 24: Disconnect Approach of Target Molecule

Using the disconnect approach it was clear that a cross-coupling reaction could be used to install the pyridyl tetrazole moiety to the oxazolidinone. The *N*-aryl oxazolidinone would therefore need to incorporate a *meta*-fluoro and a *para*-bromo or iodo substituent to facilitate a Suzuki-Miyaura reaction. The corresponding pyridyl tetrazole moiety would require a boronic ester to bring about the effective coupling of the two aromatic fragments. It was proposed that the bromo pyridyl-tetrazole intermediate could be formed via a cycloaddition of the corresponding bromo-pyridyl nitrile substrate before the selective methylation of one of the nitrogens. The formation of the oxazolidinone ring would be through the novel hypervalent iodine mediated cyclisation, and the subsequent starting material could be formed by carbomoylation of the di-substituted aniline, followed by allylation (Scheme 95).

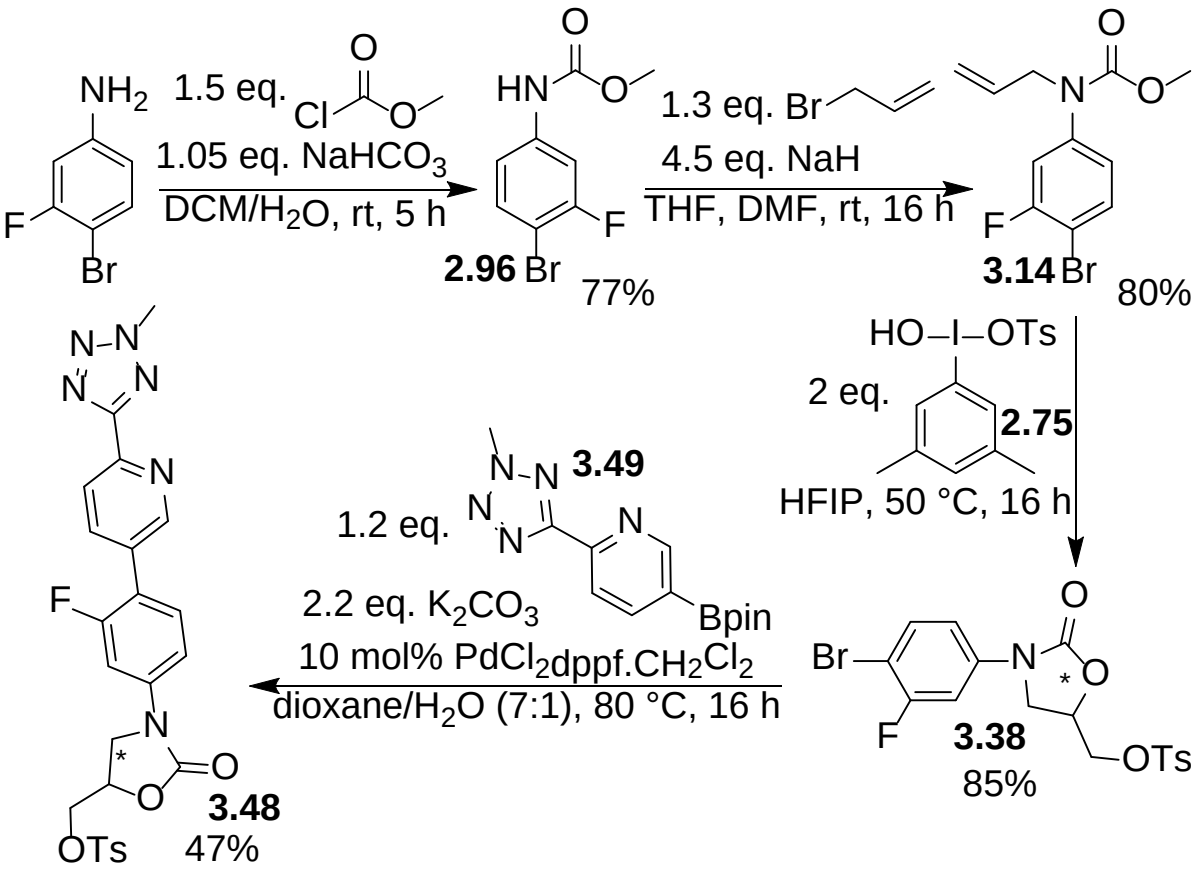


Scheme 95: Retrosynthesis of Tedizolid Analogue

3.6.25 Total Synthesis of Tedizolid Analogue

Starting with (3-fluoro-4-bromo)phenyl aniline **3.49** and using a known literature carbamoylation reaction, a 77% carbamate **2.96** yield was achieved, followed by Murphy's allylation procedure to give the corresponding *N*-allylcarbamate **3.14**, affording an 80% yield. The *N*-allyl carbamate **3.14** was then cyclised using the novel *meta*-xylyl Koser's derivative **2.75** to give the corresponding oxazolidinone **3.38**, in 85% yield.

Fortuitously, 5-bromo-2-(2-methyl-2*H*-tetrazol-5-yl) pyridine was commercially available which avoid the need to synthesise it. The 5-bromo-2-(2-methyl-2*H*-tetrazol-5-yl) pyridine was converted to the boronic ester **3.49** displacing the bromine atom using a procedure by Mahy and coworkers. The oxazolidinone intermediate **3.38** underwent Suzuki-coupling with the boronic ester pyridyl-tetrazole reagent **3.49**, using a palladium catalyst to give a 47% yield of the target Tedizolid analogue **3.48** (Scheme 96).[114,115]



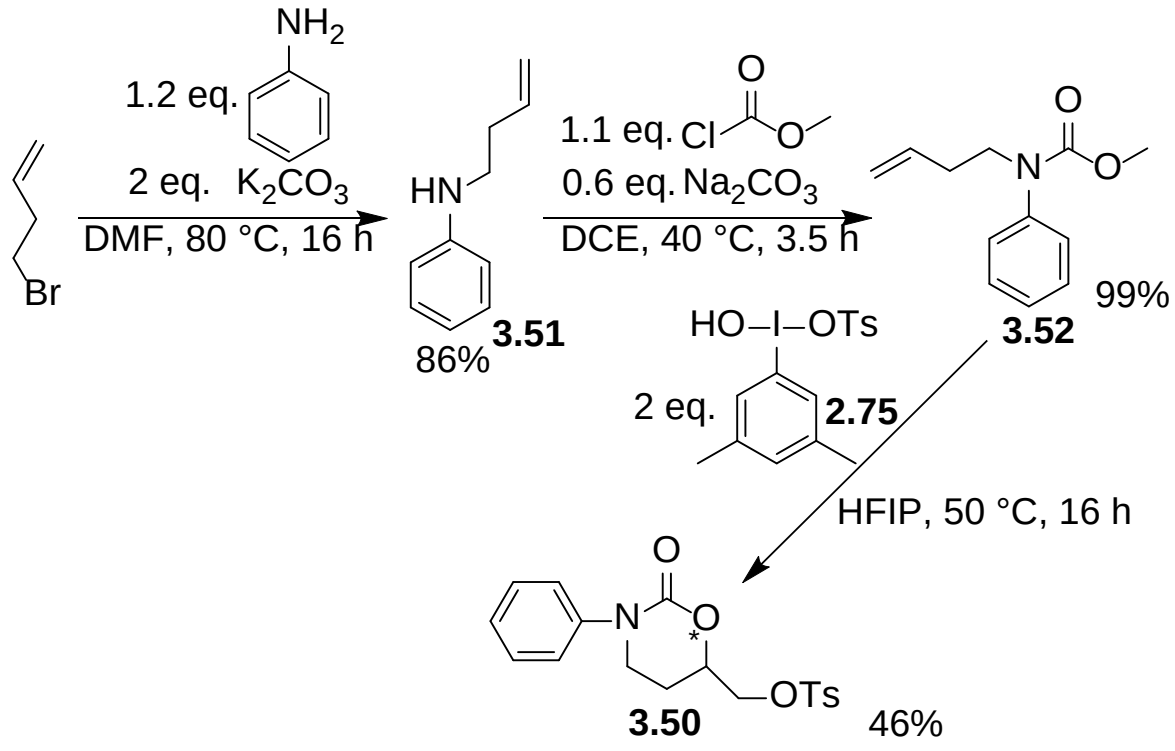
Scheme 96: Total Synthesis of Tedizolid Analogue

3.6.26 Six-Membered, *N*-Aryl-1,3-Oxazinan-2-one Preparation

1,3-Oxazinan-2-one derivatives exhibit a range of biological activities, they are being investigated for the treatment of inflammation, ulcers, allergies, asthma, arthritis, and diabetes. 1,3-Oxazinan-2-ones have been applied as crucial intermediates in the total synthesis of erythromycin A

and natural products, in the synthesis of thrombolytic agents, and the synthesis of liquid crystal displays (LCDs). The 6-membered 1,3-oxazinan-2-ones have found utility as chiral auxiliaries or elements for chiral control. However, 1,3-oxazinan-2-ones are not used as widely as oxazolidinones, due to difficulties in synthesising them.[116]

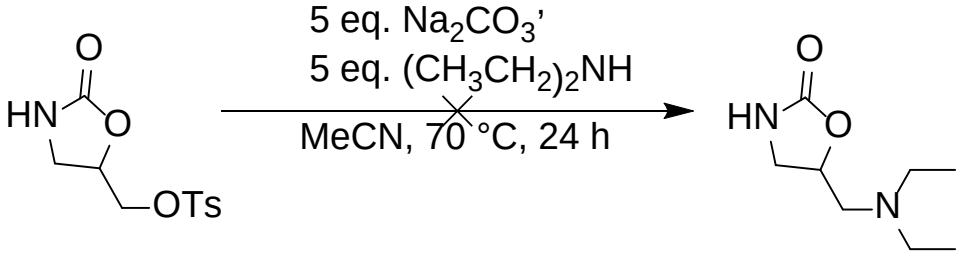
It was postulated that the modified Koser's derivative **2.75** mediated cyclisation could give access to 1,3-oxazinan-2-ones as easily as oxazolidinones. To further demonstrate the attractive utility of the novel cyclisation reaction, there was an attempt to prepare an *N*-aryl-1,3-oxazinan-2-one **3.50**. Aniline was butenylated **3.51** with 4-bromobut-1-ene using a literature procedure by Zeng and coworkers, followed by a modified carbamoylation procedure by Uhlig and Li.[117,118] The carbamate substrate **3.52** was subjected to the optimised cyclisation conditions and the desired *N*-aryl-1,3-oxazinan-2-one **3.50** was isolated in 46% yield (Scheme 97).



Scheme 97: 3 Step Preparation of *N*-Aryl-1,3-oxazinan-2-one

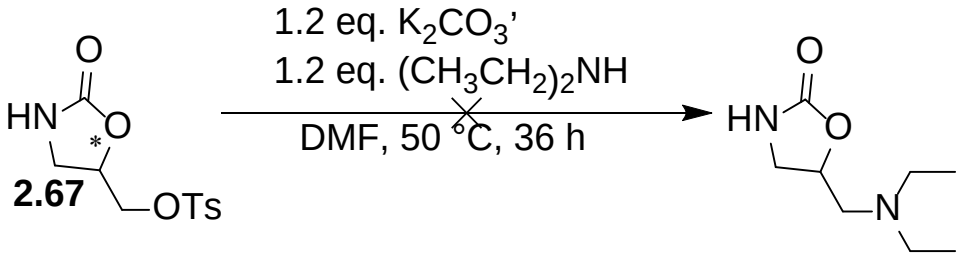
3.6.27 Derivatisation of Oxazolidinones

It was thought that it would be useful if the tosylate could be displaced to demonstrate derivatisation is possible and to facilitate the development of desirable analogues. Using a procedure by Morin and coworkers an attempt was made using diethylamine to displace the tosylate group in an S_N2 substitution.[119] Disappointingly, the tosylate was not displaced and the starting material was recovered (Scheme 98).



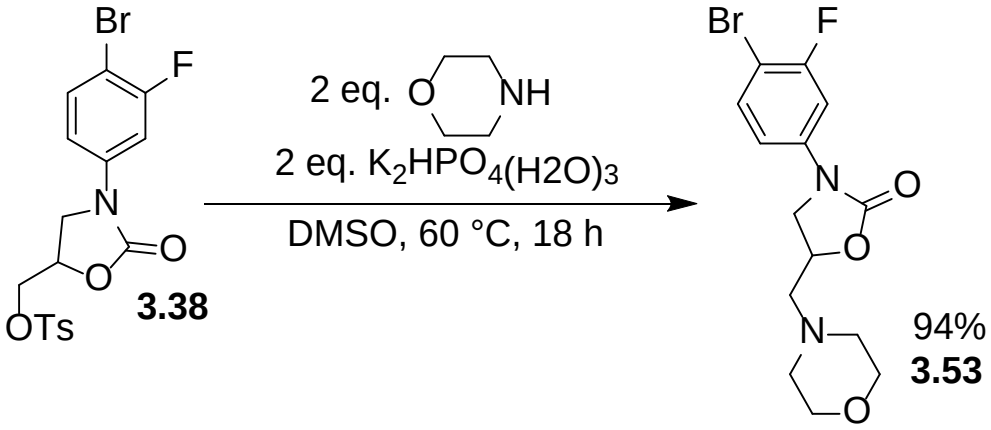
Scheme 98: Failed S_N2 Substitution of Tosylate

Using a modified procedure by Leonard and Woerpel, another attempt was made to displace the tosylate group, using different reaction conditions and diethylamine as the nucleophile.[120] Unfortunately, S_N2 displacement did not occur and the starting material remained unchanged (Scheme 99).



Scheme 99: Failed S_N2 Displacement of Tosylate

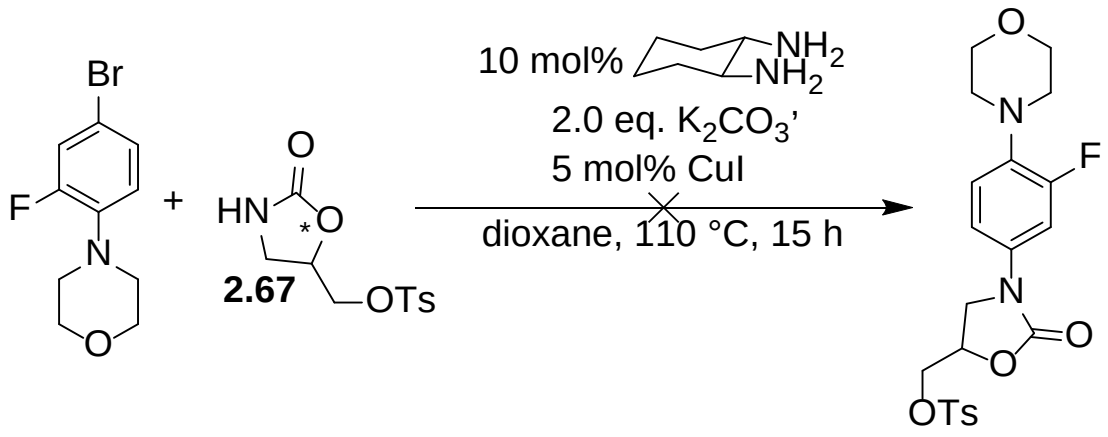
After further literature searches, a modified procedure by Wagner and coworkers was used to install a morpholine group **3.53**, displacing the tosylate.[121] It involved using dibasic potassium phosphate base to remove the proton and quench the charge on the oxazolidinone-morpholinium intermediate (Scheme 100).



Scheme 100: Smooth S_N2 Displacement of Tosylate

3.6.28 *N*-Coupling of Oxazolidinones

Another key position of interest that could be a powerful handle for derivatisation of oxazolidinone is the nitrogen position. *N*-aryloxazolidinones constitute an important class of pharmacologically active compounds, hence a strategy for *N*-arylation could be very useful. Using a Ullman coupling protocol, copper iodide (CuI) mediated *N*-arylation procedure by Mallesham and coworkers, an attempt was made to couple 4-(4-bromo-2-fluorophenyl)morpholine to (2-oxazolidin-5-yl)methyl 4-methylbenzenesulfonate **2.67.**[122] Despite using the identical conditions, the procedure did not produce the desired *N*-arylated oxazolidinone. Further work would be required to facilitate this important transformation (Scheme 101).

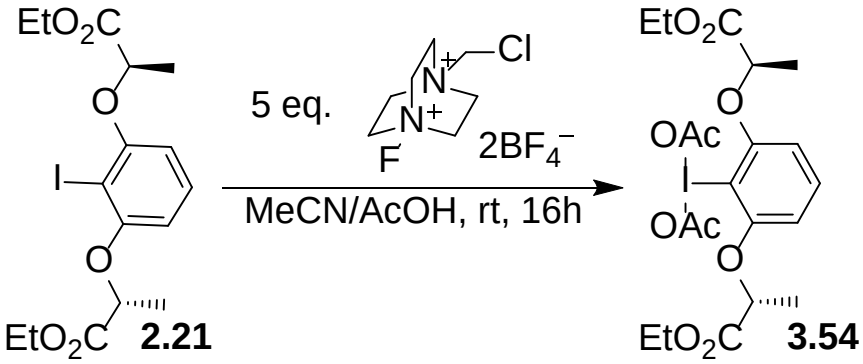


Scheme 101: Unsuccessful *N*-arylation of 2-Oxazolidinone

3.6.29. Enantioselective Carbamate Cyclisation

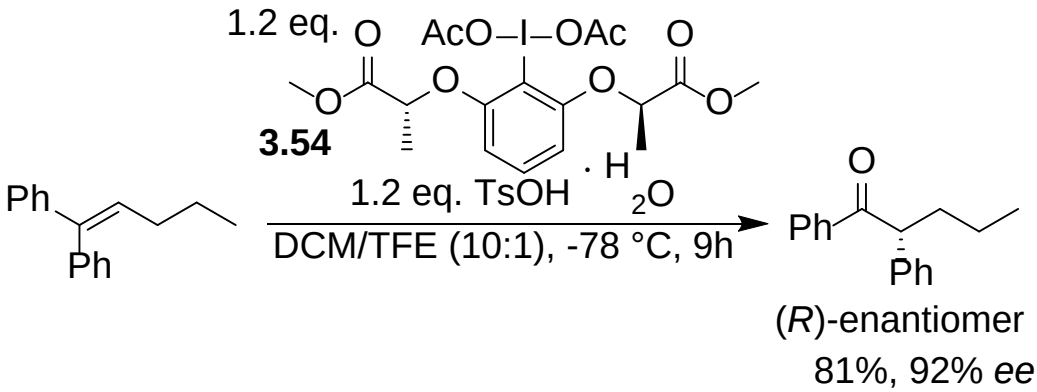
3.6.29.1 Asymmetric Cyclisation

Oxazolidinone compounds have found an important use as a novel class of antibiotics, however (*R*)-enantiomer is biologically active. It was thought to demonstrate real-world applications it would be advantageous if the cyclisation reaction could be possibly made enantioselective. To convey enantioselectivity, it would be necessary to create a chiral Koser's type reagent. From literature searches, there are examples of hybrid Ishihara-phenyliodine(III) diacetate type reagents **3.54** created by Wirth and coworkers (Scheme 102).[123]



Scheme 102: Wirth's Hybrid Ishihara-Phenyliodine(III) Diacetate

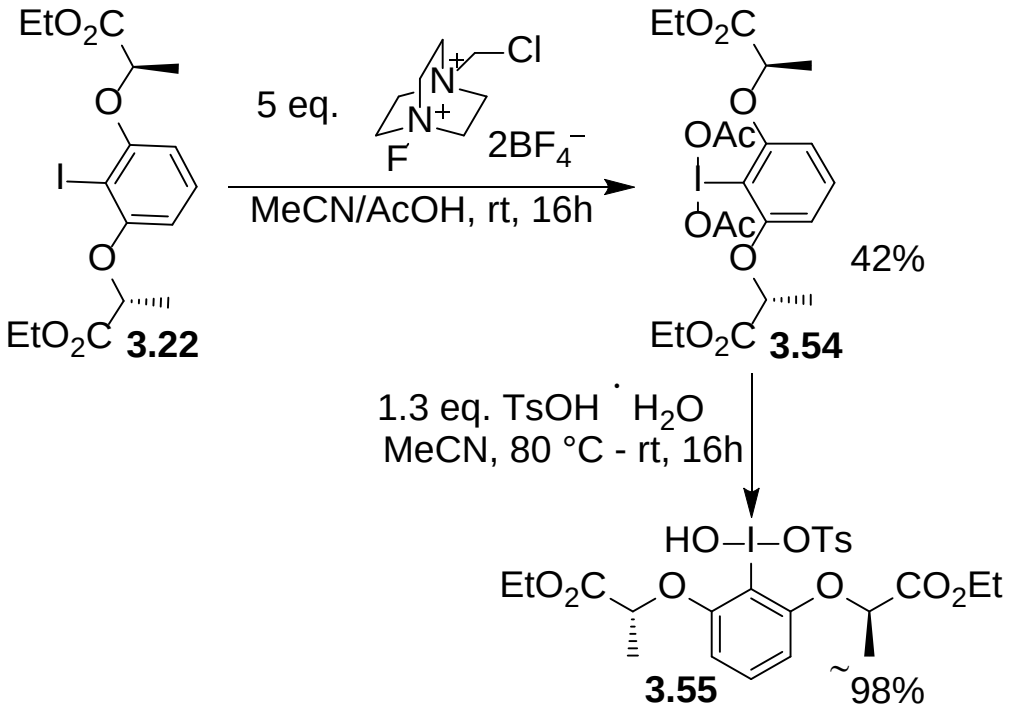
They also managed to generate *in situ* the chiral Ishihara-Koser's derivative for use in their reaction by ligand exchange with the diacetate precursor **3.54**.[62] Achieving an impressive 92% *ee* in the oxidative rearrangement of 1,1-disubstituted alkenes (Scheme 103).



Scheme 103: Oxidative Rearrangement of 1,1-disubstituted Alkenes[62]

3.6.29.2 Asymmetric Cyclisation Strategy

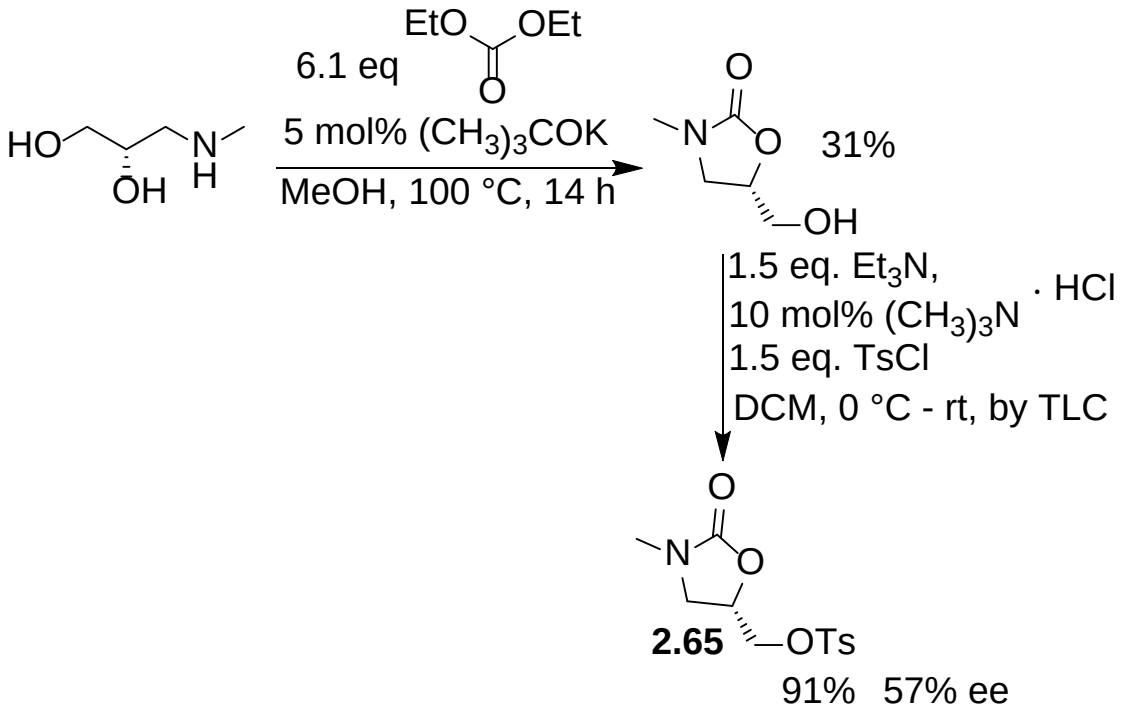
Wirth's and coworker's reaction conditions were not applicable to our reaction conditions given that it had been demonstrated dichloroethane (DCE) and 2,2,2-trifluoroethanol (TFE) gave poor yields. Dichloromethane (DCM) would be problematic due to the reaction temperature being above its boiling point. Wirth's reaction was performed at -78 ˚C in DCE/TFE, compared to the novel optimised reaction temperature of 50 ˚C in hexafluoroisopropanol (HFIP). After careful consideration of the relevant factors, it was decided to use Wirth's procedure to create the hybrid Ishihara-phenyliodine(III) diacetate **3.54** type reagent. Then use the reliable ligand exchange procedure to generate the chiral Ishihara-Koser's derivative and use the reagent without further purification (Scheme 104).



Scheme 104: Wirth's Chiral Ishihara-Koser's Reagent Preparation

3.6.29.3 Known Chiral Conditions

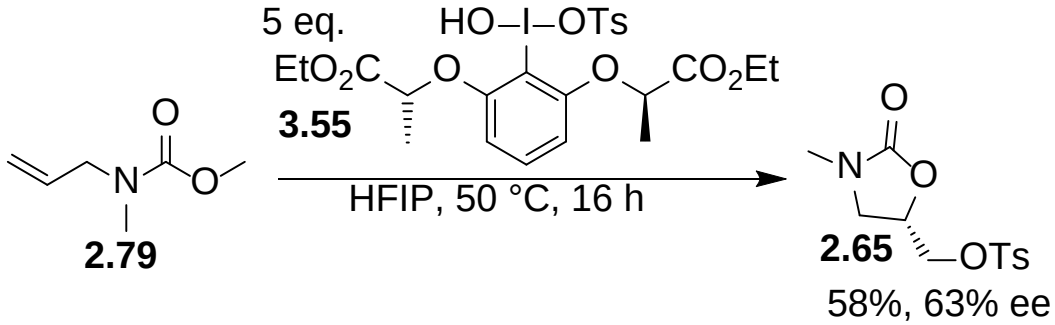
A literature search discovered a patent by Davenport and coworkers. It included the development of analytical chiral HPLC conditions to separate the enantiomers of (3-Methyl-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate **2.65** for their reaction (Scheme 105).[124]



Scheme 105: *N*-Methyl 2-Oxazolidinone Prep and Chiral Separation

3.6.29.4 Novel Asymmetric Cyclisation

It was reasonable to use those separation conditions to evaluate the enantioselectivity of the carbamate cyclisation reaction using the enantiopure Ishihara-Koser's reagent **3.55**. Hence the corresponding substrate *N*-methyl allyl(methyl)carbamate **2.79** was selected for cyclisation. The unpurified chiral Ishihara-Koser's reagent **3.55** was formed and used immediately in the asymmetric *N*-methyl allyl(methyl)carbamate **2.79** cyclisation reaction due to the uncertainty of the stability of the reagent (Scheme 106).



Scheme 106: Asymmetric Carbamate Cyclisation

3.6.29.5 Development of Modified Chiral Conditions

Using Davenport's conditions was not possible due to the longer chiral column being used, which created technical issues.[124] The longer chiral column generated higher back pressure exerted on the HPLC pump which was beyond the instrument's safe working parameters. Therefore, a lower flow rate of 1.0 mL per minute was an unfortunate necessity that would affect the retention times. Furthermore, the longer column would mean the enantiomers would interact with the stationary phase over a longer distance, further increasing the retention times.

3.6.29.6 Enantioselectivity Excess Calculations

From the peak area integrations, it was calculated that the enantiomeric excess (*ee*) for the racemic cyclisation product was as expected, 0% *ee*, and the asymmetric cyclisation product was calculated to be 63% *ee* (Figure 27). It was noted that the *ee* value was higher than Davenport's asymmetric reaction, which only yielded 57% *ee*.[124]

Racemic Cyclisation Product:

$$ee = \frac{A - B}{A + B} \times 100 = \frac{50.001 - 49.999}{50.001 + 49.999} \times 100 = \mathbf{0\%}$$

Asymmetric Cyclisation Product:

$$ee = \frac{A - B}{A + B} \times 100 = \frac{81.324 - 18.676}{81.324 + 18.676} \times 100 = \mathbf{62.6\%}$$

*where A and B are the enantiomer peak areas

Figure 25: Oxazolidinone Enantiomeric Excess Calculations

4. Conclusion and Future Work

4.1 Conclusion

In conclusion, a conformationally rigid chiral hypervalent iodine(III) catalyst **2.11** was generated and investigated in the asymmetric cyclisation of *N*-allybenzamide **2.45** and the diacetoxylation of styrene **2.46**, the catalyst did bring about cyclisation and diacetoxylation, however, produced no enantioselectivity. A range of monoiodo and diiodoarene bislactate **1.52, 2.35, 2.36** and bislactamide **1.53, 2.43** catalysts were designed, developed and prepared and evaluated, yielding low to moderate enantioselectivity in the cyclisation of *N*-allylbenzamide. Both *N*-allyl-1*H*-pyrrole-2-carboxamide and *N*-allyl-1*H*-pyrazole-5-carboxamide were cyclised albeit with modified reaction conditions, unfortunately, due to time constraints, the investigation of enantioselectivity was not possible. A novel carbamate cyclisation was developed comprehensively, providing a scope of substrates and cyclised products. The reaction was developed into an asymmetric cyclisation reaction using stoichiometric quantities of the chiral hypervalent iodine(III) species **3.55**, achieving good selectivity. The carbamate cyclisation was developed into a one-pot reaction with the novel hypervalent iodine(III) species **2.75** generated *in situ*.

4.2 Future Work

A range of conformationally rigid chiral hypervalent iodine(III) compounds could be developed based on the current iododiarylmethylamine structure with various substituents capable of forming coordinate bonds with the iodine. Then their enantioselectivity could be investigated in a wider range of hypervalent iodine(III) mediated asymmetric reactions.

The existing range of novel monoiodo and diiodoarene bislactate and bislactamide catalysts could be screened for selectivity in a wider range of asymmetric reactions. Further catalysts could be developed and tested based on the reaction screening results.

The carbamate cyclisation was exhaustively investigated and developed; however, it was not possible to catalytically perform the reaction. Further development of the chiral Ishihara-Koser's type reagents and reaction conditions could be conducted to improve enantioselectivity and develop into a catalytic carbamate cyclisation. Possibly, a scope of 6-membered 1,3-oxazinan-2-ones products could be prepared from the corresponding carbamate substrates. The preparation of the basic oxazolidinone ring was high yielding, approximately 97%, there were failed attempts to *N*-arylate the oxazolidinone ring using a Buchwald protocol. An important and powerful handle for derivatisation of oxazolidinones is the nitrogen position and further development of *N*-alkylation and *N*-arylation of the oxazolidinone is crucial for the reaction to find ubiquitous use. Alternative reactive conditions were discovered using phenyliodine(III) diacetate (PIDA) and boron trifluoride dietherate, these conditions could be optimised further and investigated in the asymmetric carbamate cyclisation. Electrochemical synthesis experiments showed that cyclisation could be performed in an electrochemical cell. Investigation into an electrochemical oxidation reaction could provide a superior enantioselective catalytic carbamate cyclisation reaction in the future.

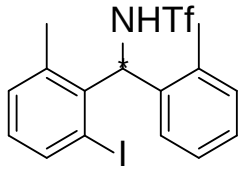
5. Experimental

5.1 General Experimental Information

^{1}H NMR spectra were recorded on Bruker Ascend 400 or 600 MHz instrument, in $CDCl_3$ unless otherwise stated. Chemical shifts are stated in ppm from tetramethylsilane with the solvent resonance of the internal standard at 7.26 ppm, in $CDCl_3$. Data is reported in the following order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet etc.), integration, and then coupling constants, in Hertz. ^{13}C NMR was recorded at 100 MHz in $CDCl_3$ unless otherwise reported with complete proton decoupling. Chemical shifts are stated in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.4 ppm). Mass spectrometry (m/z) was performed in electrospray ionisation, ESI, mode, reporting the molecular ions by measuring time of flight, TOF. Fourier Transform Infrared (FT-IR) spectroscopy was performed using a Thermo Fisher Scientific Nicolet 380, FT-IR spectrometer, reported in cm^{-1}. Bands are defined as broad (br), strong (s), medium (m) and weak (w). Melting points were determined on a Stuart SMP10 or by Differential Scanning Calorimetry (DSC) technique using a Mettler Toldeo DSC 3 instrument. All procured reagents were used without further purification unless otherwise stated. Petroleum ether 40-60 refers to the boiling of the fraction at 40-60 $^{\circ}C$. HPLC solvents used were hexane, ethanol, 2-propanol, acetonitrile and water (all were HPLC grade purity, procured from Fisher Scientific). HPLC analysis was performed using an Agilent Technologies 1100 series instrument fitted with multiple wavelength, diode array detector, DIAD, using wavelength, 254 nm. Oxazolidinone chiral HPLC resolution was performed on a Shimadzu LC-40 instrument. Chiral Analytical chiral columns used were Chiralpak IA, IB, IF and Chiralpak OD-H.

5.2 Procedures and Characterisation Data

(2-iodo-6,2-dimethyl)-diphenylmethyl-trifluoromethanesulfonamide, 2.12



According to literature procedure reported by Chu *et al*.[80] To a 10 ml round bottom flask was added *N*-(di-o-tolylmethyl)-1,1,1-trifluoromethane sulfonamide (0.27 g, 0.8 mmol), palladium(II)acetate (0.02 g, 0.08 mmol), *N*-benzoyl-DL-leucine (0.08 g, 0.32 mmol), caesium(I) acetate (0.46 g, 2.4 mmol), iodine (0.62 g, 2.4 mmol), sodium carbonate (0.26 g, 2.4 mmol) and DMSO (0.86 mL, 12 mmol) with *t*-amyl alcohol (8 mL). The mixture was stirred at 30 °C for 48 hours under air, the resulting mixture was diluted in ethyl acetate (20 mL), filtered through a pad of celite, and washed with the aqueous sodium thiosulfate (50 mL). The product was extracted with ethyl acetate (3 x 20 mL) and the combined organic was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography at petrol : ethyl acetate 15 : 1, yielding a cream solid (0.28 g, 75%), (69% *ee*).

Characterisation data in accordance with the literature[80]

Chiral Separation Conditions:

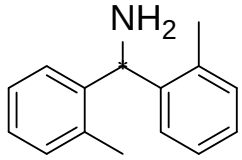
instrument: Agilent HPLC 1260;

column: Chiralpak AS-H; solvent: 95:5 hexane:IPA;

flow: 0.3 mL/min, temperature: 25 °C;

MWD @ 210 nm, R_t: 22.0 : 33.6 mins.

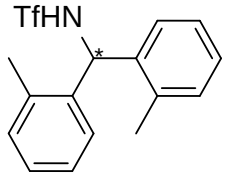
di-*o*-tolylmethanamine, 2.15



According to literature procedure reported by Chu *et al*.[80] 2M *o*-tolylmagnesium bromide in ether (26.0 mL, 50.7 mmol) was dissolved in dry THF (35 mL) under a nitrogen atmosphere and *o*-tolunitrile (5.1 mL, 42.4 mmol) was added by syringe. The resulting solution was stirred and refluxed for 48 hours under nitrogen before cooling to room temperature. Then a suspension of lithium aluminium hydride (4.00 g, 51 mmol) in dry THF (40 mL) was added by syringe and then refluxed for a further 40 hours under nitrogen, then quenched carefully with water (2 mL), 20% aqueous sodium hydroxide solution (2 mL) and then with water (8 mL). The product was extracted with ether (3 x 30 mL) and dried over $MgSO_4$ and concentrated under reduced pressure yielding a light yellow, transparent oil. (8.09 g, 90%).

Characterisation data was in accordance with the literature[80]

***N*-(Di-*o*-tolylmethyl)-1,1,1-trifluoromethanesulfonamide, 2.16**

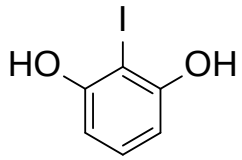


According to literature procedure reported by Chu *et al*.[80] To a stirred solution of di-*o*-tolylmethanamine (1.06 g, 5 mmol) in dry DCM (20 mL) was added triethylamine (0.7 mL, 5 mmol) at -78 °C, under nitrogen. After stirring for 20 minutes at -78 °C, trifluoromethanesulfonic anhydride (0.9 mL, 5.3 mmol) was added dropwise and the mixture was stirred for 1 hour at -78 °C before being quenched with water (20 mL). The organic layer

was extracted with DCM (3 x 20 mL). The combined organic layer were washed with brine (20 mL) and then dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product of a light yellow solid. The crude was purified by column chromatography with a 20:1 petrol:ethyl acetate mobile phase, affording a cream coloured solid. (1.20 g, 70%).

Characterisation data was in accordance with the literature[80]

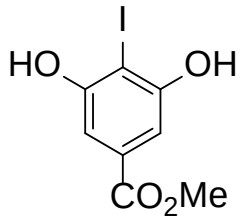
2-iodobenzene-1,3-diol, 2.20a



According to literature procedure reported by Muniz *et al*.[55] Resorcinol (1.00 g, 9.08 mmol) in 7 mL water was added to a 50 mL r.b. flask and stirred for 15 mins in an icebath, followed by the addition of iodine (2.42 g, 9.54 mmol) and stirred for 10 mins. Sodium bicarbonate (0.84 g, 9.99 mmol) was added slowly over 20 mins, the resulting mixture was stirred at 0 ˚C for 10 mins and at r.t. for 30 mins. The reaction was quenched with saturated sodium thiosulfate solution and extracted with ethyl acetate (3 x 20 mL) and washed with brine over $MgSO_4$ and concentrated under reduced pressure. It was recrystallised from cold chloroform yielding a beige solid (1.46 g, 68%).

Characterisation data was in accordance with the literature[55]

methyl 3,5-dihydroxy-4-iodobenzoate, 2.20b



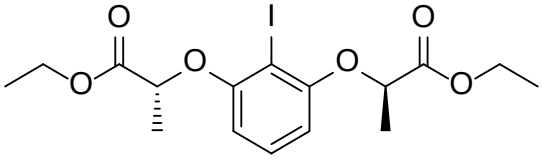
Using the literature procedure reported by L. Gao *et al*.[125] To a solution of methyl-3,5-dihydroxybenzoate (0.76 g, 4.46 mmol) in 10 mL anhydrous methanol was slowly added to a solution of *N*-iodosuccinimde (1.13 g, 4.90 mmol) in 10 mL of anhydrous methanol at 0 ˚C. The reaction mixture was warmed to r.t. and stirred for 16 h. The reaction mixture was diluted with ice-water and quenched with saturated sodium sulfite solution and extracted with ethyl acetate. (3 x 20 mL) The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure and purified by column chromatography with dichloromethane and ethyl acetate, yielding a beige solid (1.23 g, 94%).

Characterisation data was in accordance with the literature[125]

General Mitsunobu Procedure

The iodoarene-diol (1 eq.) is dissolved in anhydrous THF and purged with nitrogen. The chiral alcohol (2.3 eq.), triphenylphosphine (2.3 eq.), were added in order, diisopropylazodicarboxylate (2.3 eq.) was slowly added and stirred for 16 h at r.t. and then concentrated under reduced pressure. The crude was titurated in ethyl ether and concentrated under reduced pressure, purified by column chromatography.[55]

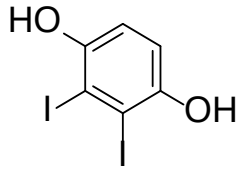
diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate, 2.21



Using the general Mitsunobu procedure 2-iodobenzene-1,3-diol (0.11 g, 0.47 mmol) was dissolved in 2.4 mL distilled anhydrous THF, ethyl-*L*-lactate (0.12 mL, 1.03 mmol), triphenylphosphine (0.28 g, 1.08 mmol), diisopropylazodicarboxylate (0.22 mL, 1.13 mmol, purified by column chromatography yielding transparent yellow oil. (0.14 g, 70%).

Characterisation data was in accordance with the literature[22]

2,3-diiodohydroquinone, 2.22



To a 10 mL r.b. flask was added 1,4-dimethoxy-2,3-diiodobenzene (0.11 g, 0.285 mmol), purged with N_2 and 2.5 mL anhydrous dichloromethane syringed into the flask. The flask was cooled to -78 ˚C and stirred for 30 mins. 1M Boron tribromide in DCM (0.63 mL, 0.63 mmol) was added dropwise with a syringe and then allowed to warm to r.t. and then stirred overnight. The contents were poured carefully on to ice and stirred vigorously, followed by filtering the precipitate and oven drying to give a brown solid (0.08 g, 78%).

^{1}H NMR: (DMSO, 400 MHz) δ: 9.90 (br. s, 2H, 2OH), 6.80 (s, 2H_{ar}, 2CH)

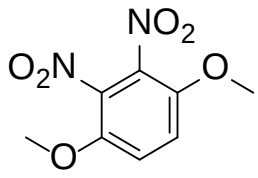
^{13}C NMR: (DMSO, 100 MHz) δ: 150.6 (2CH, s), 114.9 (2CO, s), 99.4 (2CI, s);

HRMS: (DESI-TOF) calculated for $C_6H_4I_2O_2$ $[M-H]^-$ = 360.8228, found 360.8226

FT-IR: v 3201 (br. s), 1583 (w), 1470 (m), 1336 (s), 1189 (s) cm^{-1}

m.p.: 203-205 ˚C, decomposition

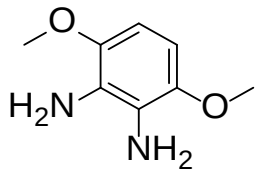
1,4-dimethoxy-2,3-dinitrobenzene, 2.24



According to literature procedure reported by Hammershøj *et al*.[83] Nitric acid (100 mL) was cooled in an icebath for 30 minutes, the 1,4-dimethoxybenzene (10.00 g, 0.07 mmol) was placed in a 250 mL flask and cooled in an icebath. The nitric acid was added slowly to the flask which initially generated yellow-reddish nitrogen dioxide fumes. The flask was sealed and left to stir for 60 minutes in the icebath, then 60 minutes stirring at room temperature, followed by stirring for 60 minutes at 100 ˚C. The crude product was recrystallised from acetic acid, filtered and washed with water, and air-dried to give yellow crystals of 1,4-dimethoxy-2,3-dinitrobenzene (11.91 g, 72%).

Characterisation data was in accordance with the literature[83]

1,4-dimethoxy-2,3-diaminobenzene, 2.25

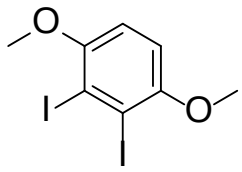


Tin (1.85 g, 15.6 mmol) was flattened and cut into small ribbons, and put in a 25 ml flask, concentrated hydrochloric acid (6 mL) was added and stirred vigorously. The 1,4-dimethoxy-2,3-dinitrobenzene was added and allowed to stir until all the tin had been dissolved. The solution was then filtered, the precipitated was dissolved in water (30 mL), basified to pH10 with 20 % ammonia solution, and extracted with chloroform (3 x 20 mL).

The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, yielding a brown solid (0.29 g, 76%).

Characterisation data was in accordance with the literature[83]

1,4-dimethoxy-2,3-diiodobenzene, 2.26



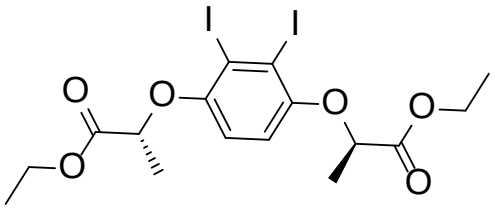
According to literature procedure reported by Hammershøj *et al*.[83] Sulfuric acid (5 mL) was cooled in an icebath and the 1,4-dimethoxy-2,3-diaminobenzene (0.27 g, 0.69 mmol) was added and stirred for 30 minutes at 0 °C. Sulfuric acid (5 mL) was cooled in an icebath and sodium nitrite (0.44 g, 6.44 mmol) was added and stirred at 0 °C for 30 minutes to produce nitrosyl sulfuric acid solution. The 1,4-dimethoxy-2,3—diaminobenzene solution was added dropwise to the nitrosyl sulfuric acid at 0 °C. The red solution was stirred for 30 minutes at 0 °C then ice cold 85 % *o*-phosphoric acid (6.25 mL) was added dropwise. This yellow slurry was added dropwise to a violently stirring solution of potassium iodide (1.20 g, 7.23 mmol) in icewater (30 mL), this red-purple solution was stirred at room temperature for 2 hours and then heated to 40 °C for 1 hour. The product was extracted with DCM (3 x 50 mL), washed with aqueous sodium bisulfite solution (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Yielding a brown solid, which was purified by column chromatography with a 1:1 petrol:ethyl acetate mobile phase to give a beige solid (0.19 g, 71%).

characterisation data was in accordance with the literature[83]

General Triflate S_N2 Substitution Procedure

Burkard and Effenberger procedure,[88] oven-dried r.b. flask was charged with mono or diiodoarene-diol (1 eq.), anhydrous potassium carbonate (2.3 eq.), chiral triflate (2.3 eq.), and purged with nitrogen. Distilled anhydrous acetonitrile was added, and the mixture was stirred overnight at r.t. Mixture was neutralised with 1M HCl (aq), extracted with dichloromethane (3 x 10 mL) and dried over $MgSO_4$ and concentrated, and purified by column chromatography.

Diethyl 2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))(2R,2'R)-dipropionate, 2.27



Using the general triflate S_N2 substitution procedure, 2,3-diiodohydroquinone (0.09 g, 0.26 mmol), anhydrous potassium carbonate (0.08 g, 0.59 mmol), ethyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (triflate) (0.15 g, 0.59 mmol) with acetonitrile, yielding a colourless oil (0.15 g, 46%).

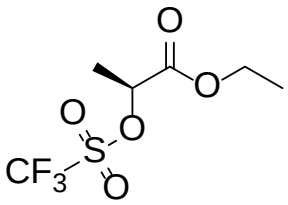
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 6.74 (s, $2H_{ar}$, 2CH), 4.64 (q, *J* = 6.9 Hz, 2H, 2CH), 4.22 (q, *J* = 2.3 Hz, 2H, CH_2), 4.18 (q, *J* = 2.3 Hz, 2H, CH_2), 1.68 (d, *J* = 6.8 Hz, 6H, 2CHC$\underline{H_3}$), 1.25 (t, *J* = 7.0 Hz, 6H, $2CH_2C\underline{H_3}$);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 172.0, 153.5, 114.4, 105.0, 75.9, 61.8, 19.0 (2CH$\underline{C}H_3$), 14.5 ($2CH_2\underline{C}H_3$);

HRMS: (DESI-TOF) calculated for $C_{16}H_{20}I_2O_6$ $[M+Na]^+$ = 584.9241, found 584.9240

FT-IR: v = 3726 (w), 2982 (br. m), 2360 (m), 1733 (s), 1575 (w), 1440 (s), 1375 (m), 1255 (s), 1196 (s), 1128 (s), 1094 (s), 1054 (m) cm^{-1}

ethyl(S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate, 2.29a



According to a literature procedure reported by Enugala *et al*.[126] A solution of ethyl-*L*-lactate (2.3 mL, 20 mmol) in 6 mL anhydrous dichloromethane was added 2,6-lutidine (2.4 mL, 20 mmol) and cooled to -78 ˚C in dry ice/acetone bath. Trifluoromethanesulfonic anhydride (3.7 mL, 22 mmol) was added dropwise and stirred for 40 mins, the solution was warmed to r.t. and stirred for 1 h. The mixture was diluted with 7 mL dichloromethane/hexane (1:1) and filtered through a short silica gel column (3 cm) and concentrated under reduced pressure resulting in a colourless oil (4.44 g, 89%).

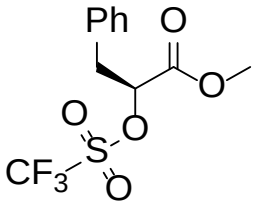
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 5.20 (q, *J* = 7.0 Hz, 1H, CH), 4.30 (q, *J* = 1.9 Hz, 1H, CH), 4.26 (q, *J* = 1.9 Hz, 2H, CH_2), 1.69 (d, *J* = 7.0 Hz, 3H, $CHCH_3$), 1.31 (t, *J* = 7.0 Hz, 3H, (CH_2CH_3);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 167.7 (C=O), 118.8 (q, J_{CF} = 319.4 Hz), CF_3, 118.4 (C=O), 80.5 ($\underline{C}HCH_3$), 63.1 ($\underline{C}H_2CH_3$), 18.3 ($CH\underline{C}H_3$), 14.2 ($CH_2\underline{C}H_3$);

^{19}F NMR: ($CDCl_3$, 370 MHz) δ: -75.4

FT-IR: v = 2990 (br. w), 1755 (m), 1416 (s), 1312 (w), 1196 (s), 1143 (s), 1082 (m), 1018 (m) cm^{-1}

methyl (*S*)-3-phenyl-2-(((trifluoromethyl)sulfonyl)oxy)propanoate, 2.29b



Using a procedure by Enugala *et al*.[126] A solution of (*S*) methyl-2-hydroxy-3-phenylpropanoate (3.61 g, 20 mmol) in 6 mL anhydrous dichloromethane was added 2,6-lutidine (2.4 mL, 20 mmol) and cooled to -78 ˚C in dry ice/acetone bath. Trifluoromethanesulfonic anhydride (3.7 mL, 22 mmol) was added dropwise and stirred for 40 mins, the solution was warmed to r.t. and stirred for 1 h. The mixture was diluted with 7 mL dichloromethane/hexane (3:7) and filtered through a short silica gel column (3 cm) and concentrated under reduced pressure resulting in a light yellow oil (5.92 g, 95%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.40-7.27 (m, $3H_{ar}$, $3CH_{ar}$), 7.25-7.20 (m, $2H_{ar}$, $2CH_{ar}$), 5.27 (app. dd, *J* = 8.7, 4.1 Hz, 1H, CH), 3.83 (s, 3H, CH_3), 3.36 (app. q, *J* = 4.1 Hz, 1H, $PhCH_2$), 3.22 (app. q, *J* = 8.7 Hz, 1H, $PhCH_2$);

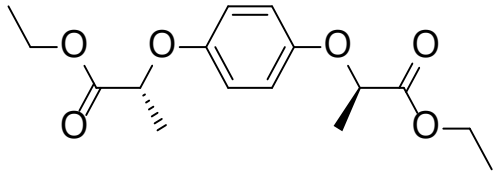
^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 167.4 (C=O), 133.7 ($CH_2\underline{C}C_5H_5$), 129.8 (<u>Ph</u>), 129.2 (<u>Ph</u>), 128.2 ($\underline{C}H_3$), 118.5 (q, J_{CF} = 323.3 Hz, $\underline{C}F_3$), 80.2 (<u>C</u>H), 53.6 ($\underline{C}H_2$), 38.5 ($\underline{C}H_2$);

^{19}F NMR: ($CDCl_3$, 370 MHz) δ: -75.2

HRMS: (DESI-TOF) calculated for $C_{11}H_{11}F_3O_5S$ $[M+H]^+$ = 330.0618, found 330.0612

FT-IR: v 3035 (w), 1763 (m), 1498 (w), 1414 (s), 1281 (m), 1199 (s), 1139 (s), 1082 (w), 1013 (m)

<u>diethyl 2,2'-(1,4-phenylenebis(oxy))(2*R*,2'*R*)-dipropionate, 2.30</u>



Using general triflate S_N2 substitution procedure, 1,4-hydroquinone (0.11 g, 1 mmol), anhydrous potassium carbonate (0.31 g, 2.25 mmol), ethyl (*S*)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (0.57 g, 2.25 mmol) and 4 mL anhydrous acetonitrile was added, yielding a transparent light orange oil (0.15 g, 48%).

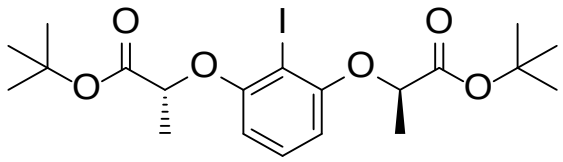
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 6.79 (s, $4H_{ar}$, Ph), 4.63 (q, *J* = 6.8 Hz, 2H, 2CH), 4.19 (q, *J* = 7.1 Hz, 4H, $2CH_2CH_3$), 1.57 (d, *J* = 6.8 Hz, 6H, $2CHCH_3$), 1.23 (t, *J* = 7.1 Hz, 6H, $2CH_2CH_3$);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 172.7 (C=O), 152.7 (Ph), 116.7 (Ph), 73.8 ($2\underline{C}HCH_3$), 61.6 ($2\underline{C}H_2CH_3$), 18.9 ($2CH\underline{C}H_3$), 14.5 ($2CH_2\underline{C}H3$);

HRMS: (DESI-TOF) calculated for $C_{16}H_{22}O_6$ $[M+H]^+$ = 311.1489, found 311.1489

FT-IR: v = 2982 (w), 2342 (w), 1749 (s), 1504 (s), 1446 (w), 1375 (w), 1274 (m), 1191 (s), 1132 (s), 1095 (s), 1050 (s), 1017 (m) cm^{-1}

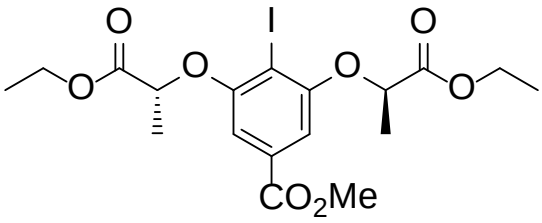
(2*R*,2'*R*)-di-tert-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoate, 2.31



Using the general Mitsunobu procedure. 2-iodobenzene-1,3-diol (1.4 g, 4.24 mmol), 30 mL anhydrous THF, *tert*. butyl-L-lactate (1.43 mL, 9.32mmol), PPh_3 (3.58 g, 9.75 mmol), and DIAD (2.8 mL, 10.18 mmol) was added in order and purified by column chromatography, yielding a yellow oil (1.59 g, 76%).

Characterisation data was in accordance with the literature[135]

diethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropanoate), 2.32



Using general triflate S_N2 substitution procedure, methyl 3,5-dihydroxy-4-iodobenzoate (0.10 g, 0.35 mmol), anhydrous potassium carbonate (0.11 g, 0.79 mmol), ethyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (0.20 g, 0.79 mmol) and 4 mL anhydrous acetonitrile, yielding a colourless oil (0.17 g, 98%).

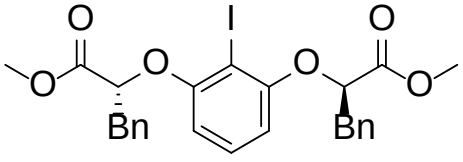
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.02 (s, $2H_{ar}$, Ph), 4.84 (q, *J* = 6.8 Hz, 2H, 2CH), 4.29-4.15 (m, 4H, $2C\underline{H_2}CH_3$), 3.87 (s, 3H, OCH_3), 1.71 (d, *J* = 7.0 Hz, 6H, $2CHC\underline{H_3}$), 1.26 (t, *J* = 7.0 Hz, 6H, $2CH_2C\underline{H_3}$);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 171.5 ($2\underline{C}O_2C_2H_5$), 166.4 ($\underline{C}O_2CH_3$), 158.5 ($2\underline{C}OCH$), 131.9 ($\underline{C}CO_2CH_3$), 107.5 (2Ph), 87.6 (CI), 74.5 ($2\underline{C}H$), 61.8 ($2\underline{C}H_2CH_3$), 52.8 ($O\underline{C}H_3$), 18.8 ($2CH\underline{C}H_3$), 14.5 ($CH_2\underline{C}H_3$);

HRMS: (DESI-TOF) calculated for $C_{18}H_{23}IO_8$ $[M+H]^+$ = 495.0510, found 495.0516;

FT-IR: v = 2985 (w), 2360 (w), 1750 (s), 1575 (m), 1417 (s), 1319 (m), 1240 (s), 1196 (s), 1130 (s), 1105 (s), 1010 (s) cm^{-1}

dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate), 2.33



Using general triflate S_N2 substitution procedure, methyl 2-iodobenzene-1,3-diol (0.50 g, 2.1 mmol), anhydrous potassium carbonate (0.65 g, 4.7 mmol), methyl (*S*)-3-phenyl-2-((trifluoromethyl)sulfonyl)oxy)propanoate (1.47 g, 4.7 mmol) and 50 mL anhydrous acetonitrile, yielding a beige solid (1.16 g, 99%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.42 (d, *J* = 7.4 Hz, $4H_{ar}$, Ph), 7.31 (t, *J* = 7.3 Hz, $4H_{ar}$, Ph), 7.26-7.22 (m, $2H_{ar}$, Ph), 7.04 (t, *J* = 8.3Hz, $1H_{ar}$, Ph), 6.21 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 4.81 (dd, J = 4.5, 8.0 Hz, 2H, 2CH), 3.67 (s, 6H, $2CH_3$), 3.42-3.23 (3.34 (app. dd, *J* = 7.8 14.2 Hz, 2H, 2CHPh), 3.30 (app. dd, *J* = 4.9, 14.2 Hz, 2H, 2CHPh);

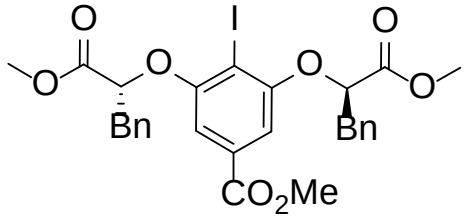
^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 171.4 (2C=O), 158.4 (2<u>C</u>OCH), 136.4 ($2CH_2\underline{C}C_5H_5$), 130.3 (4Ph), 129.6 (1Ph), 128.8 (4Ph), 127.4 (2Ph), 106.2 (2Ph), 79.2 (<u>C</u>I), 79.0 (2O<u>C</u>H), 52.7 (2<u>C</u>H_3), 39.5 (2<u>C</u>H_2);

HRMS: (DESI-TOF) calculated for $C_{26}H_{25}IO_6$ $[M+Na]^+$ = 583.0588, found 583.0607;

FT-IR: v = 3437 (w), 1729 (s), 1589 (m), 1457 (s), 1245 (s) 1097 (s), 999 (s) cm^{-1}

m.p.: 82 – 85 ˚C

<u>dimethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))(2R,2'R)-bis(3-phenylpropanoate), 2.34</u>

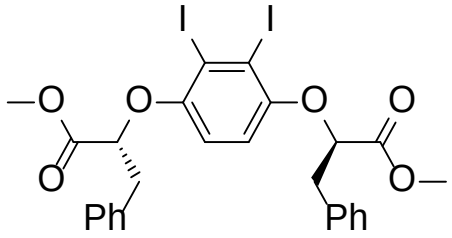


Using general triflate S_N2 substitution procedure, methyl 3,5-dihydroxy-4-iodobenzoate (0.50 g, 1.75 mmol), K_2CO_3 (0.56 g, 3.94 mmol), methyl (*S*)-

3-phenyl-2-((trifluoromethyl)sulfonyl)oxy)propanoate (1.23 g, 3.94 mmol) and 4 mL anhydrous acetonitrile, yielding a white solid (1.07 g, 99%).

Characterisation data in accordance with the literature[90]

dimethyl 2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))(2R,2'R)-bis(3-phenylpropanoate), 2.35



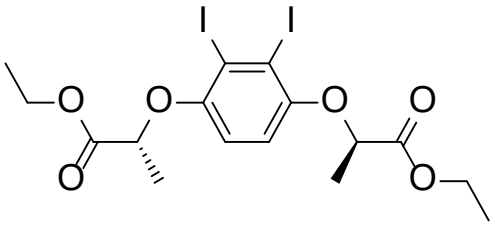
Using general triflate S_N2 substitution procedure, 2,3-diiodohydroquinone (0.15 g, 0.41 mmol), anhydrous potassium carbonate (0.31 g, 2.25 mmol), ethyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (0.57 g, 2.25 mmol) in 4 mL anhydrous acetonitrile, yielding a transparent yellow oil (0.21 g, 74%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (m, $4H_{ar}$, Ph), 7.32-7.24 (m, $6H_{ar}$, Ph), 6.51 (s, $2H_{ar}$, Ph), 4.71 (app. dd, *J* = 7.8, 4.8 Hz, 2H, 2CH), 3.66 (s, 6H, $2CH_3$), 3.29 (app. dq, *J* = 14.0, 5.8 Hz, 4H, $2CH_2$),;

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 171.2 (2<u>C</u>=O), 153.0 (2<u>C</u>OCH), 136.2 ($2CH_2\underline{C}C_5H_5$), 130.1 (Ph), 128.8 (Ph), 127.4 (Ph), 112.6 (Ph), 104.4 (2<u>C</u>H), 80.2 (2<u>C</u>I), 52.7 ($2\underline{C}H_3$), 39.4 ($2\underline{C}H_2$);

FT-IR: v = 2951 (w), 1735 (s), 1578 (m), 1436 (s), 1341 (m), 1285 (m), 1194 (m), 1113 (s), 1044 (w), 1007 (m) cm^{-1}

diethyl 2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))(2R,2'R)-dipropionate, 2.36



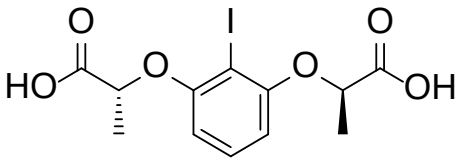
Using general triflate S_N2 substitution procedure, 2,3-diiodohydroquinone (0.15 g, 0.41 mmol), anhydrous potassium carbonate (0.31 g, 2.25 mmol), ethyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (0.57 g, 2.25 mmol) in 4 mL anhydrous acetonitrile, yielding a transparent yellow oil (0.21 g, 74%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (s, $2H_{ar}$, $2CH_{ar}$), 4.66 (q, *J* = 6.7 Hz, 2H, 2CH), 4.22 (q, *J* = 7.2 Hz, 4H, $2CH_2$), 1.70 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 1.27 (t, *J* = 7.1 Hz, 6H, $2CH_3$);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 172.7 (C=O), 152.7 (2<u>C</u>OCH), 116.7 (2O<u>C</u>H_2CH_3), 73.8 (2<u>C</u>I), 61.6 (2<u>C</u>H), 18.9 (2CH<u>C</u>H_3), 14.5 ($2CH_2$<u>C</u>H_3);

FT-IR: v = 2951 (w), 1735 (s), 1578 (m), 1436 (s), 1341 (m), 1285 (m), 1194 (m), 1113 (s), 1044 (w), 1007 (m) cm^{-1}

<u>(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoic acid, 2.37a</u>

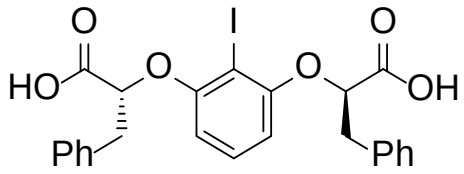


Using a modified procedure by Muniz *et al*.[55] An oven-dried 100 mL r.b. flask was charged with dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(dipropanoate) (0.60 g, 1.38 mmol), was weighed out and dissolved in 25 mL methanol and 50 mL THF, followed by the addition of 6M NaOH (aq) (0.50 mL, 3.03 mmol). The reaction mixture was stirred for 36 h at r.t., then acidified with 3M HCl to pH1 and

extracted with ethyl acetate (3 x 30 mL), washed with water and dried over $MgSO_4$ and concentrated under reduced pressure, and recrystallised, yielding a brown solid (0.44 g, 84%).

Characterisation data in accordance with the literature[55]

(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(3-phenylpropanoic acid), 2.37b



Using a modified procedure by Muniz *et al*.[55] An oven-dried 100 mL r.b. flask was charged with dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) (0.50 g, 0.89 mmol), was weighed out and dissolved in 25 mL methanol and 50 mL THF, followed by the addition of 6M NaOH (aq) (0.32 mL, 1.96 mmol). The reaction mixture was stirred for 36 h at r.t., then acidified with 3M HCl to pH1 and extracted with ethyl acetate (3 x 30 mL), washed with water and dried over $MgSO_4$ and concentrated under reduced pressure and recrystallised, yielding a white solid (0.34 g, 72%).

^{1}H NMR: (CD_3OD, 400 MHz) δ: 7.48 (d, *J* = 7.4 Hz, $4H_{ar}$, Ph), 7.32-7.25 (m, $4H_{ar}$, Ph), 7.24-7.20 (m, $2H_{ar}$, Ph), 7.11 (t, *J* = 8.2 Hz, $1H_{ar}$, Ph), 6.36 (d, *J* = 8.5 Hz, $2H_{ar}$, Ph), 4.88 (dd, *J* = 8.1, 4.1 Hz, 2H, 2CH), 3.34-3.26 (3.32 (app. dd, *J* = 7.8, 14.2 Hz, 2H, CH_2), 3.30 (app. dd, *J* = 4.1, 14.2 Hz, 2H, CH_2);

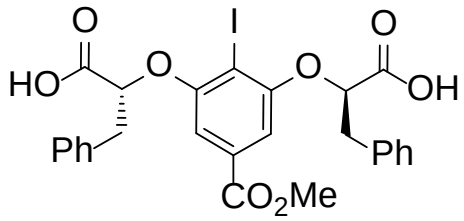
^{13}C NMR: (CD_3OD, 100 MHz) δ: 173.8 (2C=O), 159.6 (2<u>C</u>OCH), 137.9 (2<u>C</u>CH_2), 130.0 (Ph), 129.5 (Ph), 129.2 (Ph), 127.8 (Ph), 106.8 (Ph), 79.7 (CI), 77.5 (2<u>C</u>H), 39.9 (2<u>C</u>H_2);

HRMS: (DESI-TOF) calculated for $C_{26}H_{23}IO_8$ $[M-H]^-$ = 531.0310, found 531.0306;

FT-IR: v = 3027 (w), 1702 (s), 1583 (m), 1458 (s), 1327 (w), 1223 (m), 1192 (s), 1103 (s), 1022 (w), 940 (w) cm^{-1}

m.p.: 127-129 °C (determined by DSC)

(2*R*,2'*R*)-2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))bis(3-phenylpropanoic acid), 2.37c



Using a modified procedure by S. Ahmed *et al* PCT. Appl.201259442. An oven-dried 30 mL r.b. flask was charged with dimethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) (0.12 g, 0.20 mmol), was weighed out and dissolved in 10 mL methanol and 5 mL THF, followed by the addition of 6M NaOH (aq) (0.07 mL, 0.43 mmol). The reaction mixture was stirred for 36 h at r.t., then acidified with 3M HCl to pH1 and extracted with ethyl acetate (3 x 10 mL), washed with water and dried over $MgSO_4$ and concentrated under reduced pressure yielding a beige solid (0.11 g, 92%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 10.88 (br. s, 2H, 2OH), 7.60-7.50 (m, $4H_{ar}$, Ph), 7.37-7.27 (m, $4H_{ar}$, Ph), 7.26-7.19 (m, $2H_{ar}$, Ph), 7.06 (s, $2H_{ar}$, Ph), 5.16-5.03 (dd, *J* = 4.4, 8.0 Hz, 2H, 2CH), 3.77 (s, 3H, CH_3), 3.40 (dd, *J* = 4.2, 14.2 Hz, 2H, $2CH_2$), 3.33 (dd, *J* = 7.9, 14.2 Hz,;

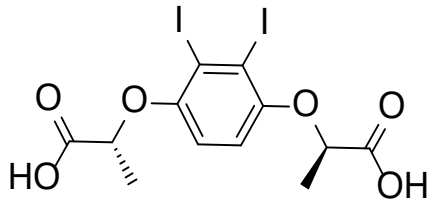
^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 172.1 (C=O), 159.1 (2COCH), 137.5 ($2CCH_2$), 130.9 (Ph), 129.1 (Ph), 127.7 (Ph), 107.0 (Ph), 85.6 (2CH), 79.0 (CI), 68.1 (CH_3), 39.5 ($2CH_2$);

HRMS: (DESI-TOF) calculated for $C_{26}H_{23}IO_8$ $[M+H]^+$ = 591.0510, found 591.0500;

FT-IR: v = 3030 (br. w), 2360 (w), 1711 (s), 1574 (m), 1497 (w), 1419 (s), 1321 (w), 1231 (s), 1192 (m), 1115 (s), 1020 (w) cm^{-1}

m.p.: 127-129 °C (determined by DSC)

(2*R*,2'*R*)-2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))dipropionic acid, 2.37d



Using a modified procedure by Muniz *et al*.[55] An oven-dried 25 mL r.b. flask was charged with diethyl 2,2'-((2,3-iodo-1,4-phenylene)bis(oxy))(2*R*,2'*R*)- dipropanoate (0.40 g, 0.71 mmol), was weighed out and dissolved in 7 mL methanol and 7 mL THF, followed by the addition of 3M NaOH (aq) (4.1 mL, 2.85 mmol). The reaction mixture was stirred for 36 h at r.t., then acidified with 3M HCl to pH1 and extracted with ethyl acetate (3 x 10 mL), washed with water and dried over $MgSO_4$ and concentrated under reduced pressure and recrystallised, yielding a brown solid (0.35 g, 99%).

^{1}H NMR: ($(CD_3)_2CO$, 400 MHz) δ: 6.94 (s, $2H_{ar}$, Ph), 4.84 (q, *J* = 6.8 Hz, 2H, 2CH), 1.64 (d, *J* = 6.8 Hz, 6H, $2CH_3$);

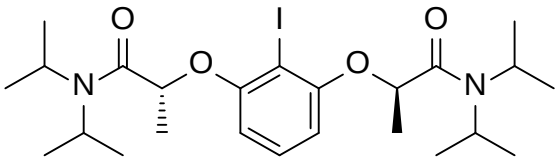
^{13}C NMR: ($(CD_3)_2CO$, 100 MHz) δ: 172.7 (2C=O), 153.8 (2COCH), 114.3 (Ph), 104.1 (2CH), 75.2 (CI), 18.9 ($2CH_3$);

General Iodoarene Bislacatamidation Procedure

Using the procedure from the thesis of S.T. Kamouka.[127] Oven-dried r.b. flask was charged with iodoarene dicarboxylic acid (1 eq.), dissolved in

anhydrous dichloromethane, 1 drop of dimethylformamide catalyst was added and purged with nitrogen. Oxalyl chloride (8 eq.) was added, and the mixture was stirred overnight at r.t. under nitrogen. The mixture was concentrated under reduced pressure, assuming 100% conversion to the di-acyl chloride. Di acyl chloride (1 eq.) was dissolved in anhydrous dichloromethane and cooled to 0 ˚C and diisopropylamine (2.2 eq.) was added dropwise, after 30 mins triethylamine (2.4 eq.) was added. The solution was allowed to warm to r.t. and stirred overnight. The solution was poured into 1M HCl (aq) to neutralise the mixture and extracted with dichloromethane (3 x 10 mL) and dried over $MgSO_4$ and washed with brine, concentrated under reduced pressure and purified by column chromatography,

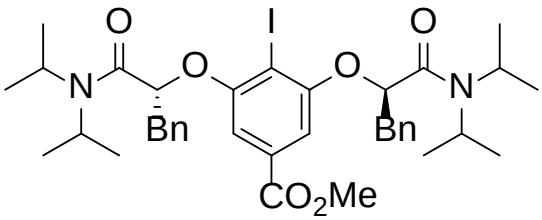
(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(N,N-diisopropylpropanamide), 1.82



Using the general bislacatamidation procedure, (2*R*,2'*R*)-2,2'-((2 -diiodo-1,3-phenylene)bis(oxy))dipropionic acid (0.10 g, 0.26 mmol), 3 mL anhydrous dichloromethane, 1 drop of DMF and oxalyl chloride (0.18 mL, 2.10 mmol) was added. The iodoarene di-acyl chloride dissolved in 8 mL of anhydrous DCM and diisopropylamine (0.22 mL, 1.56 mmol), then triethylamine (0.33 mL, 2.4 mmol). Product was purified by column chromatography, yielding a beige solid (0.26 g, 76%).

Characterisation data was in accordance with the literature[64]

methyl 3,5-bis(((R)-1-(diisopropylamino)-1-oxo-3-phenylpropan-2-yl)oxy)-4-iodobenzoate, 2.39



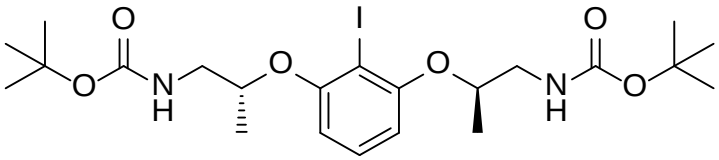
Using the procedure by F. Kayamba *et al*.[128] Propylphosphonic acid cyclic anhydride (in 50% DMF, 2.48 mL, 4.18 mmol) was dissolved in 5mL anhydrous dichloromethane and cooled to 0 ˚C and triethylamine (1.16 mL, 8.35 mmol) and (2*R*,2'*R*)-2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))bis(3-phenylpropanoic acid) (0.20 g, 0.35 mmol), were added. The reaction mixture was stirred at 0 ˚C for 30 mins and diisopropylamine (0.1 mL, 0.70 mmol), was added. The reaction was stirred overnight at r.t. The reaction was quenched with water and extracted with ethyl acetate (3 x 20 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure yielding a colourless oil (0.14 g, 56%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.50-7.48 (m, 5H_{ar}, Ph), 7.48-7.42 (m, 5H_{ar}, Ph), 6.86 (s, 2H_{ar}, Ph), 4.95 (dd, *J* = 5.0, 11.6 Hz,2H, 2CH_2), 4.90 (dd, *J* = 5.0, 6.7 Hz, 2H, 2CH_2), 3.83 (s, 3H CO_2CH_3), 3.36-3.30 (m, 6H, 6CH), 1.41-1.37 (m, 6H, 2CH_3), 1.36-1.32 (m, 6H, 2CH_3), 1.28-1.22 (m, 6H, 2CH_3), 0.99-0.93 (m, 6H, 2CH_3);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 170.9 (2N$\underline{C}$=O), 166.3 ($\underline{C}O_2CH_3$), 158.3 (2$\underline{C}$OCH), 136.2 (Ph), 131.9 (Ph), 130.2 (Ph), 128.8 (Ph), 127.5 (2N2$\underline{C}$H), 106.7 (CH), 79.0 ($\underline{C}$I), 52.8 (CH(2$\underline{C}H_3$)), 48.5 (CH(2$\underline{C}H_3$)), 39.3 (2$\underline{C}H_2$), 20.7 ($CO_2\underline{C}H_3$);

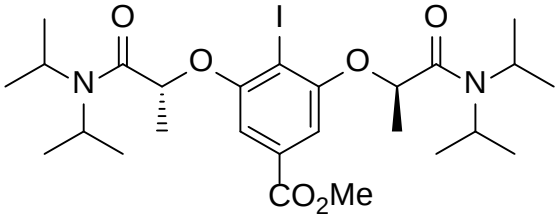
HRMS: (DESI-TOF) calculated for $C_{38}H_{49}IN_2O_6$ $[M+H]^+$ = 757.2708, found 757.2704;

((2*R*,2'*R*) di-tert-butyl –((2-iodo-1,3-phenylene)bis(oxy))bis(propane-2,1-diyl))dicarbamate, 2.40



Using the general Mitsunobu procedure, 2-iodobenzene-1,3-diol (0.94 g, 4 mmol), (*R*)-*tert*. butyl-2-hydroxypropyl carbamate (1.78 g, 10 mmol), PPh_3 (2.62 g, 10 mmol), in 15 mL dry THF, followed by the dropwise addition of DIAD (1.92 mL, 10 mmol), purified by column chromatography, yielding a colourless oil (1.47 g, 67%).

Characterisation data was in accordance with the literature[59]methyl 3,5-bi®(R)-1-(diisopropylamino)-1-oxopropan-2-yl)oxy)-4-iodobenzoate, 2.41

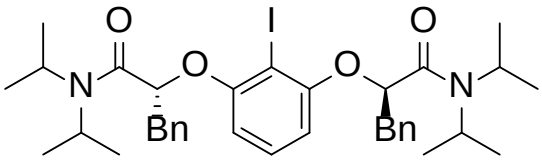


Using the general bislacatamidation procedure,'(2*R*,2'')-2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))dipropanoic acid (0.10 g, 0.26 mmol), 3 mL anhydrous DCM, 1 drop DMF and oxalyl chloride (0.18 mL, 2.10 mmol) was added. The diacyl chloride was dissolved in 4 mL of anhydrous DCM and diisopropylamine (0.22 mL, 1.56 mmol) was added dropwise, after 30 mins triethylamine (0.33 mL, 2.4 mmol), purified by column chromatography, yielding a beige solid (0.26 g, 56%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.02 (s, $2H_{ar}$), 4.82 (q, *J* = 6.7 Hz, 2H), 4.38-4.23 (m, 2H), 3.87 (s, 3H), 3.43-3.27 (m, 2H), 1.55 (d, *J* = 6.7 Hz,

6H), 1.42 (*J* = 6.7 Hz, 6H), 1.35 (*J* = 6.7 Hz, 6H), 1.19 (*J* = 6.7 Hz, 6H), 1.02 (*J* = 6.7 Hz, 6H);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 169.9, 166.4, 158.0, 130.3, 106.3, 78.9, 78.3, 48.0, 46.8, 21.3, 21.0, 20.9, 20.2, 18.3;'**(2*R*,2'')-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(*N*,*N*-diisopropyl-3-phenylpropanamide), 2.42**



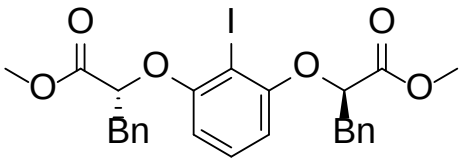
Using the general bislacatamidation procedure,'(2*R*,2'')-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(3-phenylpropanoic acid) (0.10 g, 0.19 mmol), 4 mL anhydrous DCM, 1 drop of DMF and oxalyl chloride (0.14 mL, 1.60 mmol) was added. The diacyl chloride was dissolved in 2 mL of anhydrous dichloromethane and cooled to 0 ˚C and diisopropylamine (0.07 mL, 0.48 mmol) added dropwise, after 30 mins triethylamine (0.10 mL, 0.7 mmol), purified by column chromatography, yielding a beige solid (0.06 g, 48%).

^{1}H NMR: ($CDCl_3$, 600 MHz) δ: 7.43 (d, *J* = 7.6 Hz, $4H_{ar}$, Ph), 7.28 (app. t, *J* = 7.6 Hz, $4H_{ar}$, Ph), 7.24-7.19 (m, $2H_{ar}$, Ph), 7.04 (t, *J* = 8.0 Hz, $1H_{ar}$, Ph), 6.45 (d, *J* = 8.5 Hz, $2H_{ar}$, Ph), 4.85 (dd, *J* = 4.5, 11.0, 2H, $2CH_2$), 4.60 (dd, *J* = 4.5, 7.0 Hz, 2H, $2CH_2$), 4.46 -4.30 (m, 2H, 2CH), 3.31-3.24 (m, 4H, 4NCH), 1.40 (d, *J* = 6.7 Hz, 6H, $2CH_3$), 1.26 (d, *J* = 6.7 Hz, 6H, $2CH_3$), 1.11 (d, *J* = 6.7 Hz, 6H, $2CH_3$), 0.78 (d, *J* = 6.7 Hz, 6H, $2CH_3$);

^{13}C NMR: ($CDCl_3$, 150 MHz) δ: 168.9 (2N<u>C</u>=O), 158.2 (2<u>C</u>OCH), 137.4 (Ph), 130.3 (Ph), 128.8 (Ph), 128.7 (Ph), 127.2 (2N4<u>C</u>H(8CH_3), 83.0 (<u>C</u>I), 48.2 (<u>C</u>H(2<u>C</u>H_2), 47.0 (CH(2<u>C</u>H_2), 39.2 (2<u>C</u>H), 21.3 (2<u>C</u>H_3), 21.0 (2<u>C</u>H_3), 20.8 (2<u>C</u>H_3), 20.2 (2<u>C</u>H_3);

HRMS: (DESI-TOF) calculated for $C_{36}H_{47}IN_2O_4$ $[M+H]^+$ = 699.2653, found 699.2645;

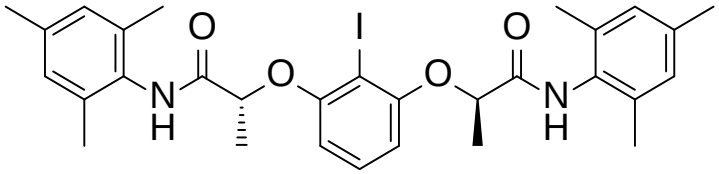
FT-IR: v 2965 (w), 1632 (s), 1455 (s), 1340 (m), 1247 (s), 1136 (w), 1089 (s), 1036 (m) cm^{-1}



^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.42 (d, *J* = 7.4 Hz, $4H_{ar}$, Ph), 7.31 (t, *J* = 7.3 Hz, $4H_{ar}$, Ph), 7.26-7.22 (m, $2H_{ar}$, Ph), 7.04 (t, *J* = 8.3Hz, $1H_{ar}$, Ph), 6.21 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 4.81 (dd, J = 4.5, 8.0 Hz, 2H, 2CH), 3.67 (s, 6H, $2CH_3$), 3.42-3.23 (3.34 (app. dd, *J* = 7.8 14.2 Hz, 2H, 2CHPh), 3.30 (app. dd, *J* = 4.9, 14.2 Hz, 2H, 2CHPh);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 171.4 (2C=O), 158.4 (2<u>C</u>OCH), 136.4 ($2CH_2\underline{C}C_5H_5$), 130.3 (4Ph), 129.6 (1Ph), 128.8 (4Ph), 127.4 (2Ph), 106.2 (2Ph), 79.2 (<u>C</u>I), 79.0 (2O<u>C</u>H), 52.7 (2<u>C</u>H_3), 39.5 (2<u>C</u>H_2);

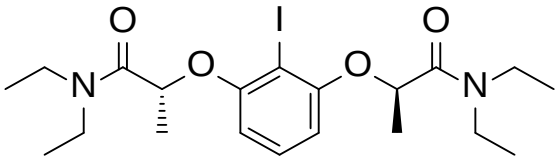
<u>(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(N-mesitylpropanamide), 1.50</u>



Using the general bislacatamidation procedure, (2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoic acid (0.50 g, 1.3 mmol), 15 mL anhydrous DCM, 5 drop of DMF and oxalyl chloride (0.9 mL, 10.5 mmol) was added. The diacyl chloride dissolved in 15 mL dry DCM and cooled to -78 ˚C and 2,4,6-trimethylaniline (0.5 mL, 2.85 mmol) was added dropwise, purified by column chromatography yielding a beige solid (0.38 g, 48%).

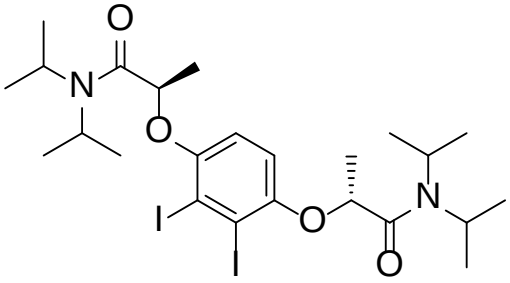
Characterisation data was in accordance with the literature[22]

(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(N,N-diethylpropanamide), 1.51



Using the general bislacatamidation procedure, (2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropanoic acid (0.25 g, 0.65 mmol), 5 mL anhydrous DCM, 1 drop of DMF and oxalyl chloride (0.45 mL, 5.25 mmol) was added. The diacyl chloride was dissolved in 8 mL DCM and diethylamine (0.17 mL, 1.56 mmol) added dropwise, followed by 0.33 mL triethylamine and purified by column chromatography yielding a cream solid (0.13 g, 42%).

Characterisation data was in accordance with the literature[54](2*R*,2'*R*)-2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))bis(N,N-diisopropylpropanamide), 2.43



Using the general bislacatamidation procedure, (2*R*,2'*R*)-2,2'-((2,3-diiodo-1,4-phenylene)bis(oxy))dipropanoic acid (0.10 g, 0.2 mmol), 2 mL anhydrous DCM, 1 drop of DMF and oxalyl chloride (0.14 mL, 1.6 mmol) was added stirred. Diacyl chloride dissolved in 2 mL of anhydrous DCM and diisopropylamine (0.1 mL, 0.5 mmol) added dropwise, triethylamine (0.10 mL, 0.7 mmol), purified by column chromatography, yielding a beige solid (0.06 g, 42%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 6.84 (s, $2H_{ar}$, Ph), 4.75 (q, *J* = 6.8 Hz, 2H, 2CH), 4.55-4.38 (m, 2H, NCH($2CH_3$)), 3.42-3.21 (m, 2H, NCH($2CH_3$)), 1.66 (d, *J* = 6.9 Hz, 6H, 2OCHCH_3), 1.40 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 1.29 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 1.18 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 0.94 (d, *J* = 6.5 Hz, 6H, $2CH_3$),

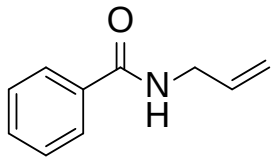
^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 169.8 (2NC=O), 152.6(2COCH), 112.9 (Ph), 103.5 (Ph), 78.6 (CI), 48.0 ($CHCH_3$), 46.8 ($CHCH_3$), 21.3 ($4NCH_2CH_3$), 20.9 ($CHCH_3$), 20.3 ($2CHCH_3$), 18.4 ($4CH_3$);

HRMS: (DESI-TOF) calculated for $C_{24}H_{39}I_2N_2O_4$ $[M+H]^+$ = 673.0994, found 673.0975;

FT-IR: v = 2967 (w), 1620 (s), 1570 (w), 1438 (s), 1375 (m), 1344 (m), 1252 (s), 1194 (m), 1125 (m), 1088 (s), 1029 (s) cm^{-1};

m.p.: 118 – 120 ˚C (by DSC);

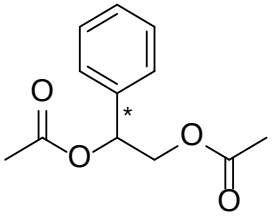
***N*-Allylbenzamide, 2.45**



According to a literature procedure reported by Alhalib, Kamouka and Moran.[64] In a 150 ml flask was added allylamine (2.6 mL, 35.2 mmol) dissolved in DCM (40 mL) cooled to 0 ˚C. Benzoyl chloride (4.48 mL, 38.8 mmol) and triethylamine (12.0 mL, 77.4 mmol) were added and the mixture was stirred overnight under a nitrogen atmosphere. 1 M sodium hydroxide solution (40 ml) was added and the mixture extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure giving a transparent, light yellow oil (3.00 g, 53%).

Characterisation data was in accordance with the literature[64]

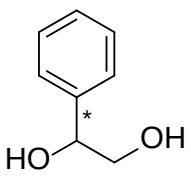
1-phenylethane-1,2-diyl diacetate, 2.47



According to a literature procedure reported by Muniz *et al*.[55] To a 10 mL r.b. flask was added ((*R*)(2-iodo-6,2-dimethyl)-diphenylmethyl-trifluoromethanesulfonamide (0.008 g, 0.02 mmol) and trifluoromethanesulfonic acid (0.01 mL, 0.01 mmol) in 1 mL acetic acid and 39% peracetic acid in acetic acid (0.0845 g, 0.4 mmol), the reaction mixture was stirred for 2 h at r.t. Then a solution of styrene (0.02 g, 0.2 mmol) in 1.5 mL acetic acid was added slowly via a syringe pump over 3 h, after the addition the reaction mixture was allowed to stir for 1 h at r.t. Water, brine, and dichloromethane were added, the organic layer separated and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in 1 mL DCM and acetic anhydride (0.05 g, 0.5 mmol), pyridine (0.04 g, 0.5 mmol), and 4-*N*,*N*-dimethylpyridine (0.007 g, 0.05 mmol) was added. After stirring for 5 h at r.t., aqueous 3M HCl and H_2O were added and the aqueous phase was extracted with DCM (3 x 10 mL) and dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purified by column chromatography, giving a colourless oil (0.03 g, 75%).

Characterisation data was in accordance with the literature[55]

1-phenylethane-1,2-diol, 2.48



According to a lierature procedure reported by Muniz *et al*.[55] To a 10 mL r.b. flask was added phenylethane-1,2-diyl diacetate (0.06g, 0.25 mmol) dissolved in 2 mL dry methanol and anhydrous potassium carbonate (0.05 g, 3.77 mmol) followed by stirring for 12 h at r.t. The methanol was evaporated under reduced pressure after acidification with 3M HCl to pH1. After extraction with DCM (3 x 10 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica, yielding a colourless solid (0.03 g, 86%).

Characterisation data was in accordance with the literature[55]

Chiral Separation Conditions:

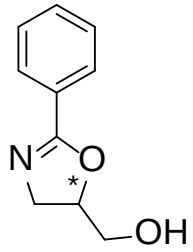
instrument: Agilent HPLC 1260;

column: Chiralpak OD-3; solvent: 95:5 hexane:IPA;

flow: 0.7 mL/min, temperature: 25 ˚C;

MWD @ 254 nm, R_t: 26.3 : 28.4 mins.

(2-phenyl-4,5-dihydrooxazol-5-yl)methanol, 2.49



According to a literature procedure reported by Alhalib, Kamouka and Moran.[64] In a 10 mL round bottom flask *N*-allylbenzamide (0.05 g, 0.31 mmol) was added followed by acetonitrile (1mL). Then Selectfluor™ fluorinating agent (0.17 g, 0.46 mmol) and trifluoroacetic acid (38 µL, 0.47 mmol) were added and stirred for 10-20 minutes. Finally, the 2-iodophenyl-1,5,7-trimethyl-2,4-dioxo-3-oxabicyclo[3.3.1.] nonane-7-

carboxylate precatalyst (0.03 g, 0.062 mmol) was added and the flask was stoppered and stirred overnight. The following day, 2M NaOH aqueous solution (10 mL) was added and the mixture extracted with DCM (3 x 20 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated under vacuum to give a light yellow oil. The product was purified by column chromatography to give a white solid (>90% yield by NMR analysis).

Characterisation data was in accordance with the literature[64]

Chiral Separation Conditions:

instrument: Agilent HPLC 1260;

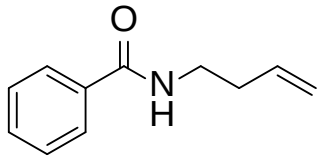
column: Chiralpak IB;

solvent gradient: 100:0 to 80:20 hexane:IPA over 35 mins;

flow: 1.0 mL/min, temperature: 25 ˚C;

MWD @ 210 nm, R_t: 24.2 : 26.2 mins.

***N*-(but-3-en-1-yl)benzamide, 2.50**

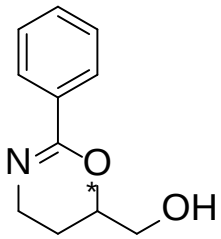


From the PhD thesis of S. Kamouka.[127] 3-butenylamine hydrochloride (1.08 g, 10 mmol) was added to a oven dried 50 mL r.b. flask, followed by 20 mL DCM and triethylamine (3.1 mL, 22 mmol) then cooled in an icebath. Benzoyl chloride (1.30 mL, 11 mmol) was added dropwise and after the addition, the reaction mixture was returned to r.t. and stirred overnight. 1M aq. NaOH (30 mL) was added and the mixture extracted with DCM (3 x 30 mL), the organic layers were combined and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude

was purified by column chromatography giving a colourless oil (1.55 g, 89%).

Characterisation data was in accordance with the literature[64]

(2-phenyl-4,5-dihydro-6H-1,3-oxazin-6-yl)methanol, 2.51



In a 10 mL round bottom flask *N*-(but-3-en-1-yl)benzamide (0.05 g, 0.29 mmol) was added followed by acetonitrile (2mL). Then Selectfluor™ (0.21 g, 0.58 mmol) and trifluoroacetic acid (45 µL, 0.58 mmol) were added and stirred for 10-20 minutes. Finally, methyl-3,5-bis((1-diisopropylamino)-1-oxo-3-phenylpropan-2-yl)oxy)-4-iodobenzoate precatalyst (0.02 g, 0.029 mmol) was added and the flask was stoppered and stirred overnight. The following day, 2M NaOH aqueous solution (10 mL) was added and the mixture extracted with DCM (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated under vacuum to give a colourless oil. The product was purified by column chromatography to give a colourless oil (0.02 g, 41%).

Characterisation data was in accordance with the literature[64]Chiral Separation Conditions:

instrument: Agilent HPLC 1260;

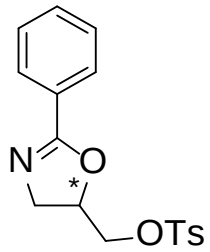
column: Chiralpak IA;

solvent gradient: 100:0 to 80:20 hexane/EtOH over 25 mins;

flow: 1.0 mL/min, temperature: 25 ˚C;

MWD @ 210 nm, R_t: 26.2 : 27.6 mins.

(2-phenyl-5-3-oxazol-5-(4H)-yl)methyl-4-methylbenzenesulfonate, 2.52

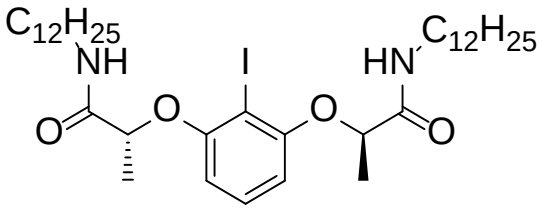


In a 10 mL round bottom flask *N*-allylbenzamide (0.05 g, 0.33 mmol) was added, followed by acetonitrile (2mL). Then *m*CPBA (0.17, 1.00 mmol) were added and stirred for 10-20 minutes and *p*-TsOH.H_2O (0.19 g, 1.00 mmol) was divided into 3 portions and added every 15 minutes. Finally, the iodoarene precatalyst (10 mol%, 0.033 mmol) was added and the flask was stoppered and stirred overnight. The following day, 2M NaOH aqueous solution (10 mL) was added and the mixture extracted with dichloromethane (3 x 20 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated under vacuum to give a light yellow oil. The product was purified by column chromatography to give a white solid (up to 62% yield by NMR analysis).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.87-7.73 (m, $5H_{ar}$, Ph), 7.52-7.34 (m, $4H_{ar}$, Ph), 4.97-4.81 (m, 1H, OCH), 4.24-4.05 (m, 4H, $2CH_2$), 3.78 (dd, *J* =15.0, 7.0 Hz, 1H, OCH), 2.4 (s, 3H, CH_3);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 164.5 (N=C), 141.5 ($\underline{C}CH_3$), 132.6 (O_3SC), 129.7 (Ph), 128.5 (Ph), 127.9 (Ph), 127.7 (Ph), 126.8 (Ph), 126.5 (Ph), 80.5 (O$\underline{C}$H), 64.7(SO$\underline{C}H_2$), 56.7 (N$\underline{C}H_2$), 21.3 ($\underline{C}H_3$);

(2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(N-dodecylpropanamide), 2.53

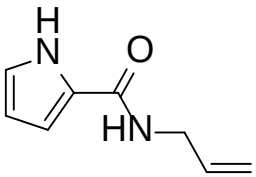


Using the general amidation procedure, (2*R*,2'*R*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid (0.25 g, 0.65 mmol), 5 mL anhydrous DCM, 1 drop of DMF and oxalyl chloride (0.45 mL, 5.25 mmol) was added. The diacyl chloride was dissolved in 8 mL DCM and dodecylamine (0.30 g, 1.56 mmol) was added, followed by 0.33 mL triethylamine, purified by column chromatography yielding a cream solid (0.31 g, 68%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.3 (s, $2H_{ar}$, Ph), 6.85 (t, *J* = 5.3 Hz, $1H_{ar}$, Ph), 6.49 (d, *J* = 7.9 Hz, 2H, 2NH), 4.78 (q, *J* = 6.8 Hz, 2H, 2CH), 3.37-3.26 (m, 4H, $2CH_2$), 1.64 (d, *J* = 6.5 Hz, 6H, $2CH_3$), 1.25 (s, 40H, $11CH_2$), 0.88 (t, *J* = 6.7 Hz, 6H, $2CH_3$);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 169.9 (2NC=O), 158.1 (2COCH), 130.2 (Ph), 106.8 (2CH), 79.7 (CI), 76.2 ($2NCH_2$), 41.2 (CH), 40.5 (CH), 29.4 ($2CH_2$), 29.3 ($2CH_2$), 27.1 ($2CH_2$), 22,6 ($2CH_2$), 16.1 ($2OCHCH_3$), 14.3 ($2(CH_2)_{11}CH_3$;

***N*-allyl-1*H*-pyrrole-2-carboxamide, 2.55**

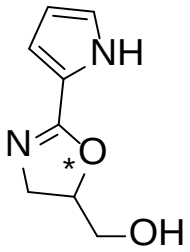


Pyrrole-2-carboxylic acid (1.37 g, 12.5 mmol) dissolved in oxalyl chloride (6 mL, 69.6 mmol) and heated to 50 ˚C for 1 hour under a nitrogen atmosphere. The residual oxalyl chloride was evaporated under reduced pressure to yield 1H-pyrrole-2-carbonyl chloride as a pink solid, it was used without further purification *in situ*. A solution of allylamine (0.75 mL), triethylamine (2.80 mL, 20 mmol), and a catalytic amount of 4-DMAP (0.06

g, 0.5 mmol) in DCM (10 mL) were cooled in an icebath. To it was added dropwise 1*H*-yyrrole-2-carbonyl chloride (1.30 g, 10 mmol) dissolved in DCM (10 mL), after the addition, the reaction was allowed to warm to rt. After 12 hours, the reaction was diluted with an equal amount of water and extracted with DCM (3 x 20 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow solid. It was recrystallized from MeOH to obtain the pure product as a brown solid after collection of 3 crops of *N*-allyl-1H-pyrrole-2-carboxamide crystals (0.77 g, 52%).[129,130]

Characterisation data was in accordance with the literature[129,130]

(2-(1H-pyrrol-2-yl)-5λ³-oxazol-5(4H)-yl)methanol, 2.58



N-allyl-1*H*-pyrrole-2-carboxamide (0.05 g, 0.33 mmol) dissolved in 2 mL HFIP, in a oven dried 10 mL r.b. flask and 4-iodotoluene catalyst (0.04 g, 0.16 mmol) was added, followed by a third of the *m*CPBA (0.058 g, 0.33 mmol) and all of the *p*-TsOH·H_2O (0.19 g, 1 mmol). The mixture was stirred for 4 hours, at room temperature and another third of *m*CPBA (0.058 g, 0.33 mmol) was added and stirred for a further 4 hours at room temperature, followed by adding the final third of *m*CPBA (0.058 g, 0.33 mmol), then finally stirred for another 4 hours at room temperature. 8 mL of 1M NaOH (aq) was added to the mixture and extracted with dichloromethane (3 x 10 mL) and then concentrated under reduced pressure. The crude was purified by column chromatography to yield a brown solid (0.02 g, 20%).[91]

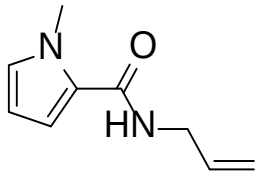
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 9.99 (br. s, 1H, OH), 6.90 (dd, *J* = 2.31, 1.42 Hz, $1H_{ar}$, Py), 6.74 (dd, *J* = 3.7, 1.3 Hz, $1H_{ar}$, Py), 6.23 (dd, *J* = 3.48, 2.82 Hz, $1H_{ar}$, Py), 4.83-4.73 (m, 1H, OCH), 4.01 (dd, *J* = 14.1, 9.8 Hz, 1H, OCH_2), 3.85 (dd, *J* = 12.3, 3.2 Hz, 1H, OCH_2), 3.77 (app. dd, *J* = 12.3, 7.5 Hz, 1H, NCH_2), 3.69 (dd, *J* = 12.3, 5.7 Hz, 1H, NCH_2), 2.40 (br. s, 1H, NH);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 159.3 (N=C), 122.7 (Py), 120.0 (Py), 113.4 (Py), 110.1 (Py), 80.5 (OCH), 64.3 ($HOCH_2$), 55.7 (NCH_2);

FT-IR: v 3128 (br. m), 2922 (w), 1650 (s), 1605 (m), 1558 (w), 1433 (m), 1380 (w), 1227 (w), 1130 (m), 1066 (m), 994 (s) cm^{-1};

m.p.: decomposition at 80 °C (determined by DSC);

***N*-Allyl-1-methyl-1H-pyrrole-2-carboxamide, 2.60**

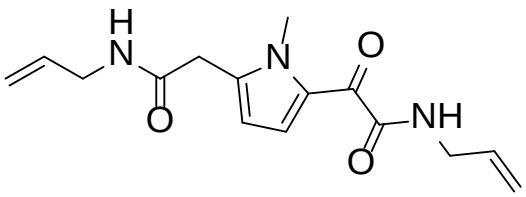


1-Methyl-1H-pyrrole-2-carboxylic acid (0.39 g, 3.13 mmol) is dissolved in oxalyl chloride (1.5 mL, 17.53 mmol) and heated to 50 °C for 1 hour under a nitrogen atmosphere. The residual oxalyl chloride was evaporated under reduced pressure to give 1-methyl-1H-pyrrole-2-carbonyl chloride and used *in situ* without further purification. A solution of allylamine (0.24 mL, 3.13 mmol), triethylamine (0.95 mL, 9.39 mmol), and a catalytic amount of 4-DMAP (0.21 g, 0.17 mmol) in DCM (10 mL) were cooled in an icebath. To it was added the 1-methyl-1*H*-pyrrole-2-carbonyl chloride (0.45 g, 3.13 mmol) dissolved in DCM (10 mL), dropwise. The reaction was allowed to warm to room temperature, after 12 hours, the reaction was diluted with an equal amount of water and extracted with DCM (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, and

concentrated under reduced pressure. Column chromatography using 5:1 petrol:ethyl acetate ratio, producing a colourless oil (0.27 g, 52%).[129,130]

Characterisation data was in accordance with the literature[141]

<u>*N*-Allyl-2-(5-(2-(allylamino)-2-oxoethyl)-1-methyl-1H-pyrrol-2-yl)-2-oxoacetamide, 2.61</u>



2-(1-methyl-1H-pyrrol-2-yl)-2-acetic acid (0.30 g, 2.2 mmol) dissolved in oxalyl chloride (1.04 mL, 5.6 mmol) and heated to 50 ˚C for 12 hours under nitrogen. The residual oxalyl chloride was evaporated under reduced pressure to give 2-(5-(2-chloro-2-oxoethyl)-1-methyl-1*H*-pyrrol-2-yl)-2-oxoacetyl chloride and used immediately without further purification. A solution of allylamine (0.07 mL, 0.95mmol), triethylamine (0.27 mL, 1.9 mmol), and a catalytic amount of 4-DMAP (0.01 g, 0.05 mmol) in DCM (1 mL) was cooled in an ice bath. To it was added the 2-(5-(2-chloro-2-oxoethyl)-1-methyl-1*H*-pyrrol-2-yl)-2-oxoacetyl chloride (0.15 g, 0.8 mmol) dissolved in DCM (2 mL), dropwise. After the addition the reaction was allowed to warm to rt, after 22 hours, the reaction was diluted with an equal amount of water and extracted with DCM (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure, affording a yellow solid (0.07 g, 35%).[131]

^{1}H NMR: ($CDCl_3$, 500 MHz) δ: 7.95 (d, *J*= 4.2 Hz, $1H_{ar}$, Py), 7.37 (br, s, 1H, NH), 6.13 (d, *J*= 4.2 Hz, $1H_{ar}$, Py), 5.92-5.82 (m, 1H, C<u>H</u>=C<u>H_2</u>), 5.81-5.70 (m, 1H, C<u>H</u>=C<u>H_2</u>), 5.58 (br, s, 1H, NH), 5.24 (dd, *J*= 17.3, 1.3 Hz, 1H, CH=C<u>H_2</u>), 5.18 (dd, *J*= 10.3, 1.3 Hz, 1H, CH=C<u>H_2</u>), 5.10 (dd, *J*= 5.4, 1.3

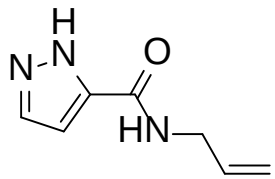
Hz, 1H, CH=C$\underline{H}_2$), 5.07 (dd, *J*= 12.3, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 3.97 (tt, *J*= 5.9,1.5 Hz, 2H, CH_2), 3.87 (s, 3 H, CH_3), 3.84 (tt, *J*= 5.9, 1.5 Hz, 2H, CH_2),

^{13}C NMR: ($CDCl_3$, 125 MHz) δ: 175.8 ($\underline{C}$=OCON), 167.9 (NH$\underline{C}$=O), 162.6 (CO$\underline{C}$=ON), 134.0 ($\underline{C}$H=CH_2), 133.7 (CO$\underline{C}$), 129.3 ($\underline{C}$H=$\underline{C}H_2$), 126.8 N$\underline{C}CH_2$), 117.3 (CH=$\underline{C}H_2$), 117.1 (Py), 111.9 (Py), 95.5 (CH=$\underline{C}H_2$), 42.1 (NCH_2), 35.6 (NCH_3), 34.0 (CO$\underline{C}H_2$);

HRMS: (DESI-TOF) calculated for $C_{15}H1_9N_3O_3$ $[M+H]^+$ = 290.1499, found 290.1502

FT-IR: v = 3344 (m), 3276 (m), 2179 (w), 1680 (s), 1608 (s), 1538 (m), 1489 (s), 1452 (s), 1338 (m), 1246 (m), 1184 (s), 989 (m), 922 (s) cm^{-1}

<u>*N*-allyl-1*H*-pyrazole-3-carboxamide, 2.62</u>



1H-Pyrazole-3-carboxylic acid (0.50 g, 4.5 mmol) dissolved in thionyl chloride (8 mL, 112.5 mmol) was heated to reflux for 2.5 h under a nitrogen atmosphere. The residual thionyl chloride was evaporated under reduced pressure to yield *1H*-pyrazole-3-carbonyl chloride as a pink solid, it was used without further purification *in situ*. A solution of allylamine (0.60 mL, 4.5 mmol), triethylamine (1.25 mL, 9.0 mmol), and a catalytic amount of 4-DMAP (0.03 g, 0.23 mmol), in anhydrous DCM (5 mL) was cooled to 0 °C. To it was added dropwise 1*H*-Pyrazole-3-carbonyl chloride (0.59 g, 4.5 mmol) dissolved in anhydrous DCM (5 mL), the reaction was allowed to warm to rt. After 12 hours, the reaction was diluted with an equal amount of water and extracted with DCM (3 x 20 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product. Crude was purified by

column chromatography to yield a white solid of *N*-allyl-1*H*-pyrazole-3-carboxamide (0.18 g, 27%).[129,132]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 10.52 (br. S, 1H, CONH), 7.60 (d, *J* = 2.4 Hz, $1H_{ar}$, Py), 6.96 (br. S, 1H, NNH), 6.87 (d, *J* = 2.4 Hz, $1H_{ar}$, Py), 6.04-5.83 (m, 1H, C<u>H</u>=CH_2), 5.27 (dd, *J* = 7.1, 1.4 Hz, 1H, CH=C<u>H_2</u>), 5.17 (dd, *J*= 10.2, 1.4 Hz, 1H, CH=C<u>H_2</u>), 4.08 (app. d, *J* = 5.6, 2H, NHC<u>H_2</u>);

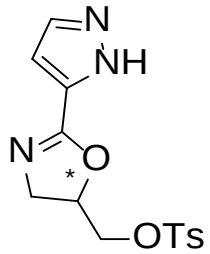
^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 161.9 (C=O), 134.4 (N=<u>C</u>H<u>C</u>H), 131.2 ((<u>C</u>H=<u>C</u>H_2), 128.6 (NNH<u>C</u>C=O), 116.9 (CH=<u>C</u>H_2), 106.5 (N=CH<u>C</u>H), 42.0 (CH_2);

HRMS: (DESI-TOF) calculated for $C_7H_{10}N_3O$ $[M+H]^+$: 152.0818, found 152.0818;

FT-IR: v 3290 (br. M), 2917 (w), 1634 (s), 1556 (s), 1421 (m), 1313 (m), 1220 (m), 1056 (m) cm^{-1};

m.p.: 141-143 °C (determined by DSC);

<u>(2-(1H-pyrazol-5-yl)-5λ^3-oxazol-5(4*H*)-yl)methyl 4-methylbenzenesulfonate, 2.62a</u>



N-allyl-1*H*-pyrazole-3-carboxamide (0.05 g, 0.33 mmol) dissolved in 2 mL HFIP, in a oven-dried 10 mL r.b. flask and 4-iodotoluene catalyst (0.014 g, 0.07 mmol) was added, followed by a third of the *m*CPBA (0.058 g, 0.33 mmol) and all of the *p*-TsOH.H_2O (0.19 g, 1 mmol). The mixture was stirred for 4 hours, at room temperature and another third of *m*CPBA (0.058 g, 0.33 mmol) was added and stirred for a further 4 hours at room

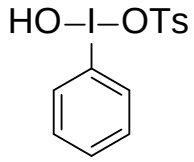
temperature, followed by adding the final third of *m*CPBA (0.058 g, 0.33 mmol), then finally stirred for 4 hours at room temperature. 8 mL of 1M NaOH (aq) was added to the mixture and extracted with dichloromethane (3 x10 mL) and then concentrated under reduced pressure. The crude was purified by column chromatography to yield a cream solid (0.05 g, 50%).[91]

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 7.75 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.66 (d, *J* = 2.2 Hz, $1H_{ar}$, Py), 7.28 (d, *J* = 9.6 Hz, $2H_{ar}$, Ph), 6.72 (d, *J* = 2.2 Hz, $1H_{ar}$, Py), 5.01-4.83 (m, 1H OCH), 4.27-4.06 (m, 2H, SO_3CH_2), 3.88 (dd, *J* = 15.0, 4.2 Hz, 1H, NCH_2), 3.83 (dd, *J* = 15.0, 7.2 Hz, 1H, NCH_2), 2.40 (s, 3H, CH_3);

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 158.7 (N=C), 145.7 ($\underline{C}CH_3$), 137.5 (Py), 133.6 (N=C$\underline{C}$), 132.7 (SO_3Ph), 130.4 (Ph), 128.3 (Ph), 128.2 (Ph), 107.3 (Py), 70.0 (OCH), 66.2 (SO_3CH_2), 56.8 (NCH_2), 22.0 (CH_3);

m.p.: decomposition at 120 ˚C (determined by DSC);

Koser's Reagent (HTIB), 1.14



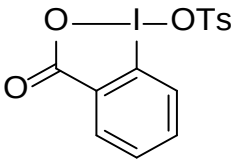
Using a literature procedure by Koser, iodobenzene diacetate (20.0 g, 62.0 mmol) was dissolved in 100 mL dry MeCN, the solution was stirred and *p*-TsOH·H_2O (13.0 g, 68.3 mmol) was added, stirred at rt, overnight, and then filtered and used without further purification, yielding a white powder (23.8 g, 98%)[95].

Characterisation data was in accordance with the literature[94,95]

Electron Deficient Koser's Derivative General Procedure

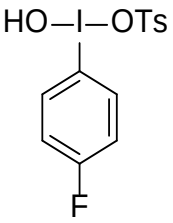
Using the procedure by Merrit, the iodoarene (1eq.) was dissolved in DCM/TFE (1:1), and *m*CPBA (1 eq.), followed by *p*-TsOH.H_2O (1eq.). The reaction mixture was stirred for 30 mins at rt, then concentrated under reduced pressure. Et_2O (50 mL) was added and stirred to cause the product to triturate out, then filtered and air dried.[102]

3-oxo-1λ^3-benzo[d][1,2]iodaoxol-1(3H)-yl 4-methylbenzenesulfonate, 2.68



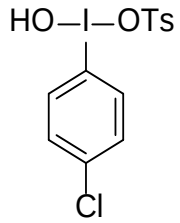
Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielded an off-white solid (0.55 g, 63%).

(4-fluorophenyl)(hydroxy)-l3-iodaneyl 4-methylbenzenesulfonate, 2.69



Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielded an off-white solid (1.10 g, 67%).

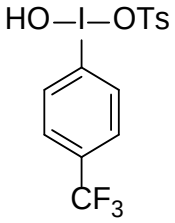
(4-chlorophenyl)(hydroxy)-l3-iodaneyl 4-methylbenzenesulfonate, 2.70



Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielded a off-white solid (1.13 g, 67%).

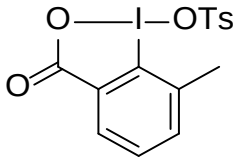
Hydroxy(4-(trifluoromethyl)phenyl)-λ^3-iodaneyl 4-methylbenzenesulfonate, 2.71

Using the electron-deficient Koser's derivative general procedure, used without further purification, yielding a white solid (1.02 g, 54%).



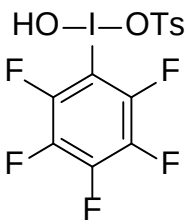
Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielding a white solid (0.55 g, 63.2%).

7-methyl-3-oxo-1λ^3-benzo[d][1,2]iodaoxol-1(3*H*)-yl 4-methylbenzenesulfonate, 2.72



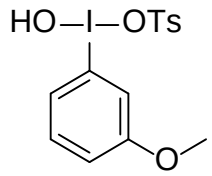
Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielding a white solid (0.65 g, 38%).

Hydroxy(perfluorophenyl)- λ^3-iodaneyl 4-methylbenzenesulfonate, 2.73



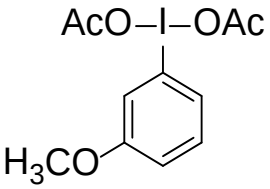
Using the electron-deficient Koser's derivative general procedure, used without further purification or characterisation, yielding a white solid (0.54 g, 28%).

Hydroxy(3-methoxyphenyl)-λ^3-iodanediyl 4-methylbenzenesulfonate, 2.74



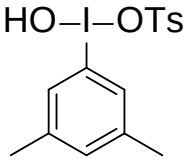
(3-methoxyphenyl)- λ^3-iodanediyl diacetate (0.60 g, 1.70 mmol) was added to p-TsOH.H_2O (0.32 g, 1.70 mmol) in dry MeCN (3 mL) and stirred at rt, overnight under N_2. 10 mL Et_2O:EtOAc (2:1) was added and a white solid precipitated out, which was filtered out and air dried and used without further purification and characterisation (0.60 g, 84%).[104]

(3-methoxyphenyl)- λ^3-iodanediyl diacetate, 2.74a



3-iodoanisole (0.9 mL, 7.5 mmol) was charged into a 10 mL oven-dried rb flask and cooled to -10 °C, peroxyacetic acid in acetic acid (2.7 mL, 16.5 mmol) was added dropwise and the reaction mixture was allowed to warm to rt, causing a colour change to a yellow solution. After stirring for an hour, 5 mL of water was added and the product was extracted with (3 x 10 mL) DCM, dried over $MgSO_4$, and concentrated under reduced pressure. The oil was triturated with Et_2O and the white solid was filtered and air-dried and used without further purification and characterisation (1.02 g, 39%).[103]

***m*-xylyl substituted Koser's Derivative, 2.75**



39% peroxyacetic acid in acetic acid was added to iodo-1,3-dimethylbenzene at 0 ˚C, the reaction was stirred at 0 ˚C for 4 h, followed by the addition of 1 mL distilled water. The white diacetate solid was filtered, washed with Et_2O, and air-dried (2.43 g, 87%). The diacetate intermediate (0.70 g, 2.00 mmol) was dissolved in dry MeCN and poured into a hot (~80 ˚C) solution of *p*-TsOH.H_2O (0.42g, 2.2 mmol). The solution was maintained at 80 ˚C for 15 mins, then stirred overnight at -20 ˚C. The solid precipitate was filtered, then triturated with Et_2O to give a pale yellow solid (0.69 g, 82%).[103,133]

Or, following a modified one-step procedure reported by Yamamoto and Togo, to a mixture of *p*-TsOH.H_2O (2.10 g, 11.0 mmol) and *m*CPBA (1.90 g, 11.0 mmol) dissolved in dry DCM (10 mL) under nitrogen, was added iodo-3,5-dimethylbenzene (1.44 mL g, 10.0 mmol) by syringe.[105] The mixture was stirred at room temperature for 2 hours and then was concentrated under reduced pressure and Et_2O (10 mL) was added. The product precipitated out after 10 minutes and adhered to the flask wall, the solvent wash was decanted out. The product was washed again with Et_2O (10 mL) and the solvent wash decanted out again. The solid was scraped off the sides of the flask wall and air-dried, isolated as a pale yellow solid (3.88 g, 92%).

^{1}H NMR: (400 MHz, MeOD) δ 7.98 (s, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.47 (s, 1H), 7.22 (d, *J* = 7.7 Hz, 2H), 4.89 (s, 1H), 2.42 (s, 6H*),* 2.36 (s, 3H*)*;

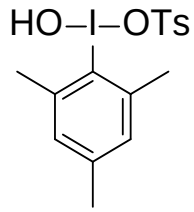
^{13}C NMR: (100 MHz, MeOD) δ 143.5, 143.2, 141.8, 136.4, 134.5, 126.9, 121.6, 21.3, 21.2;

FT-IR: v 2916 (w), 2362 (w), 1741 (s), 1598 (w), 1285 (m), 1145 (s), 1094 (s), 963 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{15}H_{17}IO_4S$ $[M+H]^+$: not found, decomposition at 150 ˚C**;**

m.p.: decomposition 150 ˚C (determined by DSC)

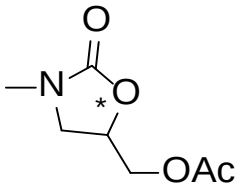
hydroxy(mesityl)- λ³-iodaneyl 4-methylbenzenesulfonate, 2.77



To an oven-dried rb flask was added iodine (2.31 g, 9.0 mmol) in 60 mL DCM, to the stirred solution was added mesitylene (2.5 mL, 18.0 mmol), followed by *m*CPBA (6.11 g, 27 mmol) and *p*-TsOH.H_2O (3.40 g, 18 mmol), stirred at 80 ˚C for 3 h, before concentrating under reduced pressure. 75 mL Et_2O was added to the oil and cooled to -20 ˚C and stirred for 30 mins, the precipitate was filtered out and washed twice with Et_2O and air dried, a white solid (4.92 g, 63%).

Characterisation data was in accordance with the literature[142]

(3-methyl-2-oxo-5λ³-oxazolidin-5-yl)methyl acetate, 2.81

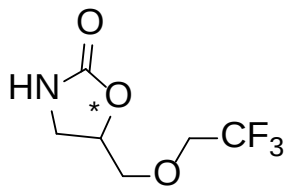


PIDA (0.19 g, 0.52 mmol) and *N*-allylmethylcarbamate (0.057 g, 0.44 mmol), AcOH (0.05 mL, 0.7 mmol) were dissolved in 6 mL DCM, under nitrogen, stirred at 0 ˚C, for 30 mins. BF_3.Oet_2 (0.07 mL, 0.52 mmol) was added dropwise and stirred at 0 ˚C for 1 h, then allowed to rt and stirred

overnight. The reaction was quenched with distilled water and extracted with DCM and dried over $MgSO_4$ and concentrated under reduced pressure, purified by column chromatography, yielding a cream solid (0.007 g, 10%).[107]

Characterisation data was in accordance with the literature[143]

5-((2,2,2-trifluoroethoxy)methyl)-5λ³-oxazolidin-2-one, 2.82



The *tert*-butyl allylcarbamate (0.03 g, 0.16 mmol), iodoarene (0.36 µL, 0.32 mmol), $LiClO_4$ (0.05 g, 0.46 mmol), 2.5 mL TFE were charged into an IKA ElectroSyn 2.0, 10 mL cell, fitted with a glassy carbon working electrode and a platinum counter electrode, at a constant current of 4 mA and electric charge of 5 F per mol, for a reaction time of 5 hours and 21 mins. Yielding up to 34% product by NMR with internal standard.

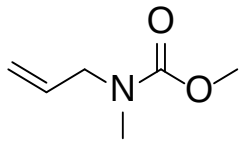
^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.85-4.77 (m, 1H, CH), 4.31 (dd, *J* = 12.0, 3.6 Hz, 1H, CHC$\underline{H_2}$O), 4.27 (dd, *J* = 12.0, 6.1 Hz, 1H, CHC$\underline{H_2}$O), 3.86 (dd, *J* = 14.1, 6.8 Hz, 2H, CH_2), 3.74 (dd, *J* = 14.1, 3.4 Hz, 2H, CH_2);

General carbamoylation procedure

Using the general carbamate procedure by Kozmin,[110] Amine (1 eq.) is dissolved in (10 mL) dry DCM, was slowly added to 25 mL rb flask of methyl chloroformate (1.2 eq.) at 0 °C, under nitrogen, the reaction mixture was warmed to rt, and stirred overnight. The mixture was washed with (5 mL) 1M HCl (aq), (5 mL) saturated $NaHCO_3$, and then (10 mL) brine. The

organic phase was extracted (3 x 10 mL) DCM and dried over $MgSO_4$ and concentrated under reduced, crude was purified by column chromatography.

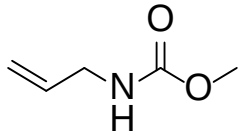
methyl allyl (methyl) carbamate, 2.64



Using the general carbamoylation procedure.[110] *N*-allyl methylamine (0.55 mL, 5.76 mmol) in 10 mL dry DCM, methyl chloroformate (0.54 mL, 6.91 mmol), to give a transparent, light yellow oil, (0.22 g, 85%).

Characterisation data was in accordance with the literature[144]

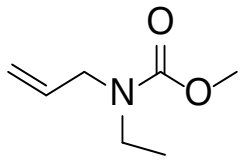
methyl allyl carbamate, 2.83



Using the general carbamoylation procedure.[110] Allylamine (1.4 mL, 18.7 mmol) in 13 mL dry DCM, methyl chloroformate (0.7 mL, 9.1 mmol), to give a transparent, light yellow oil, (1.03 g, 98%).

Characterisation data was in accordance with the literature[144]

methyl allyl(ethyl)carbamate, 3.06



Prepared using a modified procedure reported by Akinleye and Porel.[112] A solution of allylamine (13.0 mL, 175 mmol), K_2CO_3 (29.0 g, 210 mmol) in 50 mL DCM was stirred and bromoethane (6.5 mL, 87.5 mmol) was

added dropwise over 30 mins at rt, then stirred overnight. The mixture was filtered through celite and washed with water, then extracted with DCM and purified by column chromatography. Using the general carbamoylation procedure, *N*-ethyl-*N*-allylamine (7.45 g, 87.5 mmol) in 75 mL dry DCM, methyl chloroformate (15.6 mL, 175 mmol), to give a transparent, light yellow oil, (1.59 g, 84%).

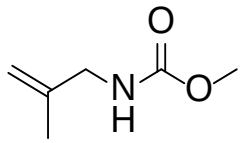
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.87-5.65 (m, 1H, CH_2=C<u>H</u>CH_2), 5.11 (d, *J* = 10.9 Hz, 2H, CHC<u>H_2</u>N), 3.96-3.74 (m, 2H, CH_2=CH), 3.68 (s, 3H, OCH_3), 3.38-3.11 (m, 2H, CH_3C<u>H_2</u>), 1.08 (t, *J* = 6.9 Hz, 3H, CH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.8 (C=O), 134.3 CH_2=<u>C</u>H, 116.7 (<u>C</u>H_2=CH), 52.7 (OCH_3), 49.3 (N<u>C</u>H_2=CH), 41.7 (N<u>C</u>H_2CH_3), 13.6 (NCH_2<u>C</u>H_3);

FT-IR: v 2977 (w), 1697 (s), 1475 (m), 1251 (m), 1163 (m), 1078 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_7H_{13}NO_2$ $[M+H]^+$: 144.1019; found 144.1024;

<u>methyl (2-methylallyl)carbamate, 2.84</u>



Using the general carbamoylation procedure.[110] 2-methyl allylamine.HCl (0.95 mL, 8.80 mmol) in 10 mL dry DCM, Et_3N (2.5 mL, 18.1 mmol), methyl chloroformate (0.85 mL, 9.68 mmol) were added, to give a transparent, light yellow oil, (1.13 g, 99%).

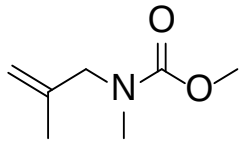
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.46 (br. S, 1H, NH), 4.69 (app. d, *J* = 6.3 Hz, 1H, CH_2=C), 4.64 (app. d, *J* = 6.3 Hz, 1H, CH_2=C), 3.53 (s, 2H, NCH_2), 3.49 (s, 3H, OCH_3), 1.56 (s, 3H, CCH_3);

^{13}C NMR: (125 MHz, $CDCl_3$) δ 157.3 (C=O), 142.3 ($\underline{C}CH_3$), 110.3 ($\underline{C}H_2$=C), 51.9 (OCH_3), 46.5 (NCH_2), 20.0 ($C\underline{C}H_3$);

FT-IR: v 3341 (m, br), 2979 (m, br), 1700 (s), 1522 (s), 1257 (s), 1234 (s), 986 (s), 896 (s), 731 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_6H_{11}NO_2$ $[M+H]^+$: 130.0863; found 130.0867;

methyl methyl(2-methylallyl)carbamate, 3.04



Using Jeschke's *N*-alkylation procedure,[111] Hexamethyldisilane (1.03 mL, 9.0 mmol) was dissolved in freshly distilled THF (20 mL) under a nitrogen atmosphere and cooled to 0 °C. *n*-Butyllithum in hexanes (2.5 M, 3.8 mL, 9.0 mmol) was added dropwise and the mixture was stirred at 0 °C for 20 mins. To this mixture, methyl (2-methylallyl)carbamate, **2.84** (0.58 g, 4.5 mmol) dissolved in freshly distilled THF (5 mL), cooled to 0 °C, was added by cannula. After 10 mins, iodomethane (0.44 mL, 9.0 mmol) was added dropwise and the reaction mixture was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), separated, and washed with water (6 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by flash

chromatography product was isolated as a mixture of two rotamers in a ~1:1 ratio as a transparent yellow oil (0.11 g, 53%).

Major rotamer

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.83 (d, *J* = 6.2 Hz, 1H, CH_2=C), 4.75 (d, *J* = 6.2 Hz, 1H, CH_2=C), 3.82 (s, 2H, NCH_2), 3.68 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 1.65 (s, 3H, C<u>C</u>H_3*)*.

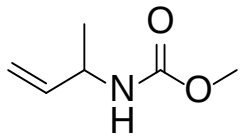
Minor rotamer

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.83 (d, *J* = 6.2 Hz, 1H, CH_2=C), 4.75 (d, *J* = 6.2 Hz, 1H, CH_2=C), 3.74 (s, 2H, NCH_2), 3.68 (s, 3H OCH_3), 2.84 (s, 3H, NCH_3), 1.65 (s, 3H, CCH_3*)*.

^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.4 (C=O), 141.2 (CH_2=<u>C</u>CH_3), 112.1 (<u>C</u>H_2=<u>C</u>CH_3), 54.9 (OCH_3), 53.0 (NCH_2), 34.0 (NCH_3), 20.1 (C<u>C</u>H3);

FT-IR: v 3328 (m, br), 2918 (m, br), 2360 (s), 2342 (s), 1755 (m), 1653 (m), 1456 (w), 1363 (w), 1259 (w), 1177 (m) 922 (m) cm^{-1};

<u>methyl but-3-en-2-ylcarbamate, 2.85</u>



Using the general carbamoylation procedure.[110] But-3-en-2-amine.HCl (0.73 g, 6.75 mmol) in 15 mL dry DCM, methyl chloroformate (0.50 mL, 5.65 mmol), Et_3N (1.90 mL, 13.55 mmol) were added together, to give a colourless oil, (0.45 g, 51%).

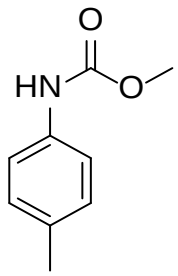
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.91-5.69 (m, 1H, CH_2=C<u>H</u>), 5.14 (dd, *J* = 17.2, 1.3 Hz*,* 1H, C<u>H</u>$_2$=C<u>H</u>), 5.05 (dd, *J* = 10.3, 1.3 Hz, 1H, C<u>H</u>$_2$=C<u>H</u>), 4.70 (m, 1H, C<u>H</u>C<u>H</u>$_3$), 4.26 (br. s, 1H, NH), 3.65 (s, 3H, OC<u>H</u>$_3$*)*, 3.22 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.6 (C=O), 140.1 (<u>C</u>H=CH_2), 114.3 (CH=<u>C</u>H_2), 52.4 (OCH_3), 49.0 (<u>C</u>H<u>C</u>H_3), 21.0 (CH<u>C</u>H_3);

FT-IR: v 3316 (m, br), 2975 (m, br), 1691 (s), 1525 (s), 1453 (m), 1331 (w), 1243 (s), 1192 (m), 1083 (m), 1058(m) 992 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_6H_{12}NO_2$ $[M+H]^+$: 130.0863; found 130.0862;

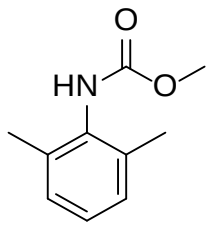
<u>methyl (4-methylphenyl)carbamate, 2.86</u>



Using the general carbamoylation procedure.[110] *p*-Toluidine (2.74 g, 25.6 mmol) in 50 mL dry DCM, methyl chloroformate (3.04 mL, 34.1 mmol) were added, to give a white solid, (4.05 g, 96%).

Characterisation data was in accordance with the literature[145]

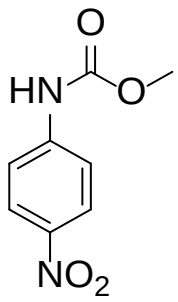
<u>methyl (2,6-dimethylphenyl)carbamate, 2.87</u>



Using the general carbamoylation procedure, 2,6-dimethylaniline (1.05 mL, 8.53 mmol) in 25 mL dry DCM, methyl chloroformate (1.52 mL, 17.1 mmol), to give a white solid, (1.69 g, 55%).

Characterisation data was in accordance with the literature[146]

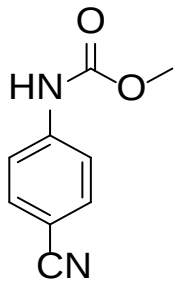
methyl (4-nitrophenyl)carbamate, 2.88



Using the general carbamoylation procedure, 4-nitrolaniline (3.32 g, 24.1 mmol), pyridine (2.58 mL, 32.1 mmol) in 100 mL dry THF, methyl chloroformate (2.86 mL, 32.1 mmol), to give yellow needles, (3.95 g, 84%).

Characterisation data was in accordance with the literature[145]

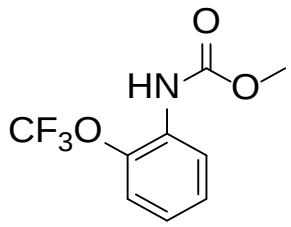
methyl (4-cyanophenyl)carbamate, 2.89



Using the general carbamoylation procedure.[110] 4-Aminobenzonitrile (1.42 g, 12.0 mmol), pyridine (1.29 mL, 16.1 mmol) in 60 mL dry THF, methyl chloroformate (1.43 mL, 16.1 mmol), to give yellow solid, (2.08 g, 98%).

Characterisation data was in accordance with the literature[147]

methyl (2-(trifluoromethoxy)phenyl)carbamate, 2.90



Using the general carbamoylation procedure, 2-trifluoromethoxyaniline (2.16 g, 12.1 mmol), in 20 mL dry DCM, methyl chloroformate (1.45 mL, 16.3 mmol), to give cream solid, (1.68 g, 63%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, $1H_{ar}$, Ph), 7.24-7.07 (s, $2H_{ar}$, Ph), 6.95 (t, *J* = 8.2 Hz, $1H_{ar}$, Ph), 6.90 (br. s, 1H, NH), 3.70 (s, 3H, OCH_3);

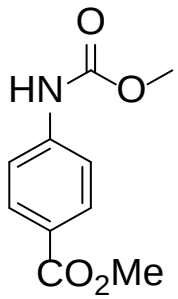
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.9 (C=O), 138.1 (CF_3OC), 131.1 (Ph), 127.9 (Ph), 123.6 (Ph), 120.7 (Ph), 120.6 (q, J_{CF} = 259.1 Hz, OCF_3), 52.9 (OCH_3);

FT-IR: v 3303 (m, br), 2363 (w), 1720 (m), 1611 (m), 1534 (s), 1456 (m), 1315 (m), 1237 (s) 1170 (s), 1043 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_9H_8F_3NO_2$ $[M+H]^+$: 236.0529; found 236.0531;

m.p.: 55-57 °C (determined by DSC);

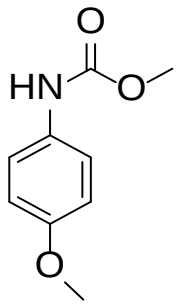
methyl 4-((methoxycarbonyl)amino)benzoate, 2.91



Using the general carbamoylation procedure.[110] Methyl 4-benzoate (3.64 g, 12.0 mmol), Et_3N (2.24 mL, 16.1 mmol) in 40 mL dry DCM, methyl chloroformate (2.86 mL, 16.1 mmol) were added, to give white solid, (1.54 g, 62%).

Characterisation data was in accordance with the literature[146]

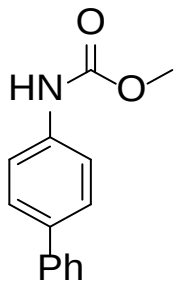
methyl (4-methoxyphenyl)carbamate, 2.92



Using the general carbamoylation procedure.[110] 4-Anisidine (1.48 g, 12.0 mmol), Et_3N (1.7 mL, 12.0 mmol) in 40 mL dry DCM, methyl chloroformate (1.40 mL, 16.0 mmol) were added, to give pale brown solid, (2.02 g, 93%).

Characterisation data was in accordance with the literature[148]

methyl [1,1'-biphenyl]-4-ylcarbamate, 2.93



Using the general carbamoylation procedure, 4-aminobiphenyl (0.80 g, 4.7 mmol), Et_3N (0.66 mL, 12.0 mmol) in 20 mL dry DCM, methyl chloroformate (0.56 mL, 6.3 mmol) were added, to give beige solid, (0.88 g, 82%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.5 Hz, $2H_{ar}$, Ph), 7.55 (d, *J* = 6.7 Hz, $2H_{ar}$, Ph), 7.46 (d, *J* = 9.2 Hz, $2H_{ar}$, Ph), 7.42 (d, *J* = 7.9 Hz, $2H_{ar}$, Ph), 7.33 (tt, *J* = 7.4, 1.4 Hz, $2H_{ar}$, Ph), 6.69 (br. s, 1H, NH), 3.81 (s, 3H, CH_3);

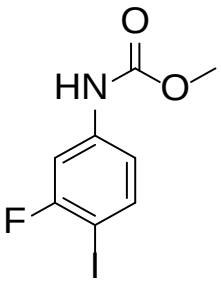
^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.4 (C=O) 140.9 (CPh), 137.5 (CPh), 136.7 (NPh), 129.1 (Ph), 128.1 (Ph), 127.4 (Ph), 127.2 (Ph), 119.3 (Ph), 52.8 (OCH_3);

FT-IR: v 3324 (m, br), 2946 (w), 2359 (w), 1705 (s), 1594 (m), 1540 (s), 1447 (m), 1406 (m), 1319 (s), 1289 (w), 1236 (s), 1189 (s), 1079 (s), 961 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019; found 228.1026;

m.p.: 126-128 ˚C.

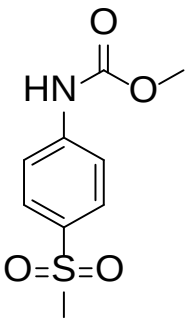
methyl (3-fluoro-4-iodophenyl)carbamate, 2.94



A modified procedure by Bachmann was used.[134] 4-Iodo-3-fluoroaniline (1.19 g, 5.0 mmol) in 10 mL DCM was added rapidly to a solution of $NaHCO_3$ (0.44 g, 5.25 mmol) and tetrabutylammonium bromide (0.16 g, 0.5 mmol) in 10 mL water, the resulting solution was stirred vigorously and methyl chloroformate (0.67 mL, 7.5 mmol) was added over 30 mins, the mixture was stirred for 4.5 h, at rt. The organic phase was separated and washed twice with 20 mL of water, combined aqueous phases were washed twice with 20 mL DCM. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, yielding brown solid (1.37 g, 93%).

Characterisation data was in accordance with the literature[149]

methyl (4-(methylsulfonyl)phenyl)carbamate, 2.95



Using the general carbamoylation procedure.[110] 4-(Methylsulfonyl)aniline (1.71 g, 10.0 mmol), Et_3N (1.4 mL, 10.0 mmol) in 40 mL dry DCM, methyl chloroformate (1.2 mL, 13.0 mmol) were added, to give off white solid, (0.75 g, 33%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, $2H_{ar}$, Ph), 7.59 (d, *J* = 8.8 Hz, $2H_{ar}$, Ph), 6.94 (br. S, 1H, NH), 3.81 (s, 3H, SO_2CH_3), 3.04 (s, 3H, OCH_3);

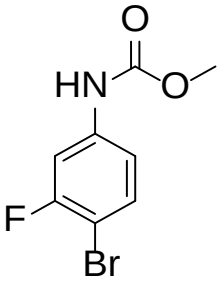
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.8 (C=O), 143.3 (NPh), 134.9 (SO_2Ph), 129.3 (Ph), 118.6 (Ph), 53.2 (OCH_3), 45.1 (SO_2CH_3);

FT-IR: v 3327 (br. M), 2358 (w), 1732 (m), 1597 (m), 1529 (m), 1404 (m), 1279 (s), 1219 (s), 1140 (s), 1088 (s), 1052 (s), 971 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_9H_{12}NO_4S$ $[M+H]^+$: 230.0482; found 218.0482;

m.p.: 184-186 ˚C

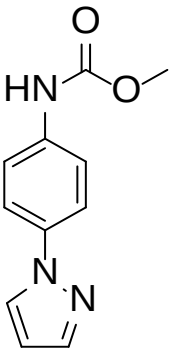
<u>methyl (3-fluoro-4-bromophenyl)carbamate, 2.96</u>



A procedure by Bachmann was used.[134] 4-Bromo-3-fluoroaniline (2.00 g, 10.5 mmol) in 20 mL DCM was added rapidly to a solution of $NaHCO_3$ (0.92 g, 11.1 mmol) in 20 mL water, the resulting solution was stirred vigorously and methyl chloroformate (1.21 mL, 15.8 mmol) was added over 30 mins, the mixture was stirred for 4.5 h, at rt. The organic phase was separated and washed twice with 20 mL of water, combined aqueous phases were washed twice with 20 mL DCM. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, yielding brown solid (2.01 g, 77%).

Characterisation data was in accordance with the literature[134]**methyl (4-(*1H*-pyrazol-1-yl)phenyl)carbamate, 2.97**

Using the general carbamoylation procedure.[110] 4-(1*H*-pyrazol-1-yl)aniline (0.80 g, 5.0 mmol), Et_3N (0.70 mL, 5.0 mmol) in 20 mL dry DCM, methyl chloroformate (0. 6 mL, 5.0 mmol), to give off white solid, (0.53 g, 49%).



^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.4 Hz, $1H_{ar}$, Py), 7.70 (d, *J* = 1.7 Hz, $1H_{ar}$, Py), 7.62 (d, *J* = 8.9 Hz, $2H_{ar}$, Ph), 7.47 (d, *J* = 8.9 Hz, $2H_{ar}$, Ph), 6.73 (br. S, 1H, NH), 6.45 (t, *J* = 2.1 Hz, $1H_{ar}$, Py), 3.79 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.0 (C=O), 140.9 (NN=CH), 136.0 (NNPh), 126.7 (NNCH), 120.1 (Ph), 119.5 (Ph), 107.5 (NNCHCH), 52.5 (OCH_3);

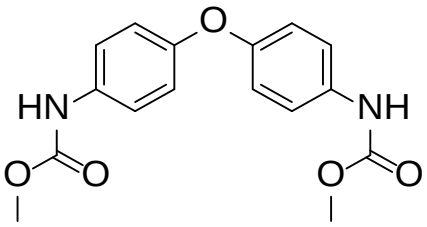
FT-IR: v 3232 (br. W), 2951 (w), 1716 (s), 1645 (m), 1548 (s), 1525 (s), 1443 (m), 1413 (s), 1321 (s), 1261 (w), 1231 (w), 1210 (s), 1136 (s), 1061 (s), 1035 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_9 H_{11} NO_3$ $[M+H]^+$: 218.0924; found 218.0924;

m.p.: 143-145 ˚C (determined by DSC);

dimethyl (oxybis(4,1-phenylene))dicarbamate, 2.98

Using the general carbamoylation procedure.[110] 4,4-Oxydianiline (1.00 g, 5.0 mmol), Et_3N (1.4 mL, 10.0 mmol) in 40 mL dry DCM, methyl chloroformate (1.2 mL, 13.0 mmol), to give beige solid (0.87 g, 55%).



^{1}H NMR: (400 MHz, $(CD_3)_2CO$) δ 8.63 (br. S, 2H, 2NH), 7.54 (d, *J* = 9.1 Hz, $4H_{ar}$, Ph), 6.94 (d, *J* = 9.1 Hz, $4H_{ar}$, Ph), 3.69 (s, 6H, $2OCH_3$);

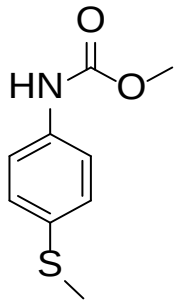
^{13}C NMR: (100 MHz, $(CD_3)_2CO$) δ 155.0 (O2C), 153.7 (2C=O), 135.6 (2NHC), 120.7 (Ph) , 119.7 (Ph), 52.1 ($2OCH_3$);

FT-IR: v 3264 (br. M), 1712 (m), 1684 (m), 1600 (m), 1548 (s), 1498 (s), 1435 (w), 1311 (m), 1239 (s), 1211 (s), 1101 (w), 1073 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{16}H_{16}N_2O_5$ $[M+H]^+$: 317.1132; found 317.1127;

m.p.: 179-181 ˚C (determined by DSC);

methyl (4-(methylthio)phenyl)carbamate, 2.99



Using the general carbamoylation procedure.[110] 4-(Methylthio)aniline (1.24 mL, 10.0 mmol), Et_3N (1.4 mL, 10.0 mmol) in 40 mL dry DCM, methyl chloroformate (1.2 mL, 13.0 mmol), to give beige solid (1.96 g, 99%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, $2H_{ar}$, Ph), 7.20 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 6.96 (br. s, 1H, NH), 3.74 (s, 3H, (OCH_3)), 2.43 (s, 3H, SCH_3);

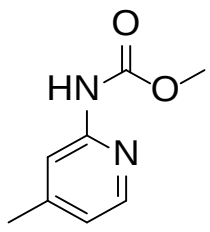
^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.5 (C=O), 136.0 (SPh), 132.7 (NPh), 128.6 (Ph), 119.8 (Ph), 52.6 (OCH_3), 17.1 (SCH_3);

FT-IR: v 3334 (br. M), 2949 (w), 2362 (w), 1703 (m), 1592 (s), 1531 (s), 1493 (m), 1426 (m), 1324 (m), 1226 (s), 1095 (s), 1067 (s), 1014 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_9H_{11}NO_2S$ $[M+H]^+$: 198.0582; found 198.0583;

m.p.: 90-92 ˚C (determined by DSC), beige solid

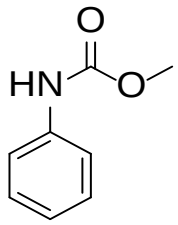
methyl (4-methylpyridin-2-yl)carbamate, 3.00



Using the general carbamoylation procedure.[110] 2-Amino-4-methylpyridine (1.79 g, 16.6 mmol), Et_3N (3.10 mL, 22.1 mmol) in 25 mL dry DCM, methyl chloroformate (2.0 mL, 22.1 mmol), to give transparent orange oil (0.85 g, 46%).

Characterisation data was in accordance with the literature[150]

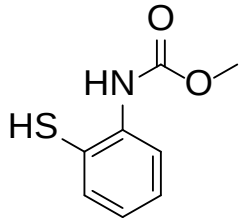
methyl phenylcarbamate, 3.01



Using the general carbamoylation procedure.[110] Aniline (1.12 mL, 12.0 mmol), Et_3N (2.24 mL, 16.0 mmol) in 40 mL dry DCM, methyl chloroformate (1.43 mL, 16.0 mmol) were added, to give brown solid (1.71 g, 94%).

Characterisation data was in accordance with the literature[152]–

methyl (2-mercaptophenyl)carbamate, 3.02



Using the general carbamoylation procedure.[110] 2-Aminothiophenol (1.70 g, 13.6 mmol), in 20 mL dry DCM, methyl chloroformate (1.61 mL, 18.1 mmol), to give brown solid (1.06 g, 43%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, $1H_{ar}$, Ph), 7.55 (br. s, 1H, NH), 7.39 (t, *J* = 7.8 Hz, $1H_{ar}$, Ph), 7.23 (dd, *J* = 7.8, 1.4 Hz, $1H_{ar}$, Ph), 6.91 (t, *J* = 7.8 Hz, $1H_{ar}$, Ph), 3.72 (s, 3H, OCH_3);

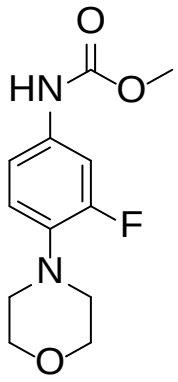
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.8 (C=O), 140.3 (NPh), 136.8 (Ph), 135.3 (Ph), 129.6 (Ph), 119.2 (Ph), 111.8 (SPh), 52.8 (OCH_3);

FT-IR: v 3379 (m), 1738 (s), 1578 (m), 1509 (s), 1439 (s), 1309 (m), 1212 (s), 1077 (m), 1034 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_8H_9NO_2S$ $[M-H_2+H]^+$: 182.0267; found 182.0281;

m.p.: 113 – 115 ˚C (determined by DSC);

methyl (3-fluoro-4-morpholinophenyl)carbamate, 3.03



Using the general carbamoylation procedure.[110] 2-Fluoro-4-morpholin-aniline (2.00 g, 10.2 mmol), Et_3N (2.84 mL, 20.4 mmol) in 20 mL dry DCM, methyl chloroformate (1.82 mL, 20.4 mmol), to give light pink solid (1.06 g, 87%).

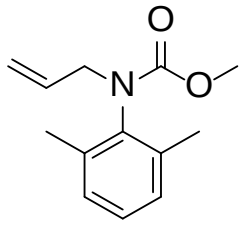
Characterisation data was in accordance with the literature[151]

General Allylation Procedure

Based on the *N*-allylation method reported by Murphy.[113] NaH (60% in mineral oil, 1.3 eq.) was placed into a flask and purged with N_2. Dry petroleum ether (5 mL) was added and stirred. After 10 mins, the petroleum ether and mineral oil layer were removed using a long needle

and positive nitrogen pressure and replaced with freshly distilled THF (2 mL). A separate flask was charged with carbamate (1 eq.) and this was dissolved in freshly distilled THF (2 mL) under N_2 at rt. The carbamate solution was added dropwise via cannula to the NaH solution and the mixture was stirred for 20 minutes. Allyl bromide (1.1 eq.) was added dropwise, followed by DMF (0.5 mL) to aid solubility, then the mixture was stirred overnight at room temperature. The THF was evaporated and the crude product was partitioned between water and DCM (3 x 20 mL) and separated. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography.

methyl allyl(2,6-dimethylphenyl)carbamate, 3.07



Isolated as a white solid (0.43 g, 99%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.17-7.01 (m, $3H_{ar}$, Ph), 6.06-5.88 (m, 1H, CH_2=C<u>H</u>), 5.17-5.02 (m, 2H, C<u>H_2</u>=CH), 4.13 (d, *J* = 6.8 Hz, 2H, NCH_2), 3.63 (s, 3H, OCH_3*),* 2.20 (s, 6H, $2CH_3$);

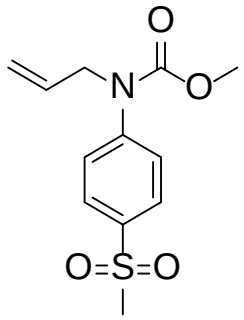
^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.3 (C=O), 139.4 (Ph), 133.4 (CH_2=<u>C</u>H), 128.6 (Ph), 127.8 (Ph), 118.6 (<u>C</u>H_2=CH), 53.2 (OCH_3), 53.1 (NCH_2), 18.6 (Ph(<u>C</u>H_3)$_2$);

FT-IR: v 2952 (m, br), 1693 (s), 1591 (w), 1446 (s), 1373 (s), 1289 (s), 1227 (m), 1164 (s) 1009 (s), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1332; found 220.1337;

m.p.: 45-47 °C;

methyl allyl(4-(methylsulfonyl)phenyl)carbamate, 3.08



Isolated as a yellow oil (0.18 g, 96%).

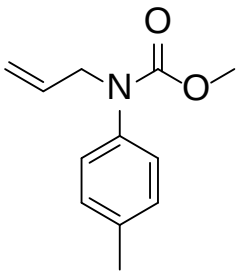
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, $2H_{ar}$, Ph), 7.48 (d, *J* = 8.8 Hz, $2H_{ar}$, Ph), 6.00-5.81 (m, 1H CH_2=C<u>H</u>), 5.24-5.12 (5.21 (dd, *J* = 4.5, 0.6, 0.5 Hz, 1H, C<u>H_2</u>=CH), 5.16 (dd, *J* = 1.5, 0.6, 0.5 Hz, 1H, C<u>H_2</u>=CH), 4.34 (d, *J* = 5.6 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.07 (s, 3H, SO_2CH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.6 (C=O), 147.6 (NPh), 137.6 (SPh), 133.5 (CH_2=<u>C</u>H), 128.6 (Ph), 126.4 (Ph), 117.8 (<u>C</u>H_2=CH), 53.7 (OCH_3), 53.1 (NCH_2), 45.0 (SO_2<u>C</u>H_3);

FT-IR: v 3649 (w), 2956 (w), 2359 (w), 1704 (s), 1593 (m), 1496 (w), 1447 (m), 1374 (m), 1296 (s), 1228 (s), 1193 (w), 1143 (s), 1090 (m), 1046 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_4S$ $[M+H]^+$: 270.0795; found 270.0821;

methyl allyl(*p*-tolyl)carbamate, 3.09



Isolated as a colourless oil (0.18 g, 40%).

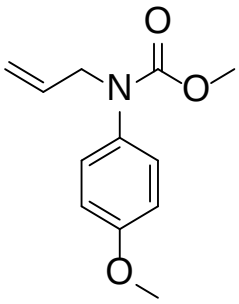
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.4 Hz, $2H_{ar}$, Ph), 7.09 (d, *J* = 8.0 Hz, $2H_{ar}$, Ph), 6.00-5.81 (m, 1H, CH_2=C<u>H</u>), 5.15 (dd, 1H, *J* = 8.0, 1.3 Hz, C<u>H$_2$</u>=CH), 5.12 (ddt, *J* = 8.0, 1.2 Hz, 1H, C<u>H$_2$</u>=CH), 4.24 (d, *J* = 5.8 Hz, 2H, NCH_2), 3.69 (s, 3H, OCH_3), 2.34 (s, 3H, $PhCH_3$);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.4 (C=O), 140.0 (NPh), 136.7 (<u>C</u>CH_3), 134.1 (CH_2=<u>C</u>H), 130.0 (Ph), 127.2 (Ph), 117.4 (<u>C</u>H_2=CH), 53.8 (OCH_3), 53.3 (N<u>C</u>H_2), 21.3 (Ph<u>C</u>H_3);

FT-IR: v 2955 (m, br), 1701 (s), 1514 (s), 1446 (s), 1376 (s), 1231 (s), 1191 (s), 1148 (m) 1013 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176; found 206.1176;

<u>methyl allyl(4-methoxyphenyl)carbamate, 3.10</u>



Isolated as a yellow oil (0.36 g, 76%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 6.85 (d, *J* = 9.2 Hz, $2H_{ar}$, Ph), 5.98-5.79 (m, 1H, CH_2=C<u>H</u>), 5.18-5.03 (5.13 (dd, *J* =

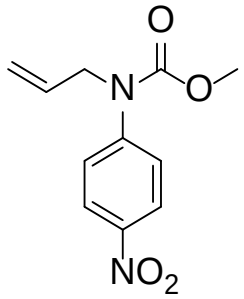
3.0, 1.4 Hz, 1H, C$\underline{H}_2$=CH), 5.08 (dd, *J* = 2.8, 1.4 Hz, 1H, C$\underline{H}_2$=CH)), 4.19 (d, *J* = 6.0 Hz, 2H, CH_2), 3.77 (s, 3H, PhOCH_3)), 3.66 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 158.3 ($CH_3O\underline{Ph}$), 156.4 (C=O), 135.2 (NPh), 133.9 (CH_2=$\underline{C}$H), 128.5 (Ph), 117.5 ($\underline{C}H_2$=CH), 114.3 (Ph), 55.5 (PhO$\underline{C}H_3$), 53.8 (OCH_3), 53.1 (NCH_2);

FT-IR: v 2954 (w), 1698 (s), 1609 (w), 1510 (s), 1446 (m), 1378 (m), 1279 (m), 1246 (s), 1227 (s), 1181 (m), 1146 (m), 1032 (m), 1005 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1125 found 222.1121;

<u>methyl allyl(4-nitrophenyl)carbamate, 3.11</u>



Isolated as a yellow oil (0.18 g, 36%).

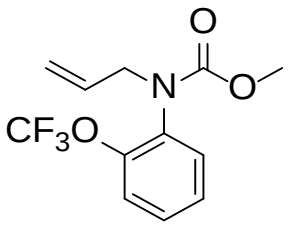
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15 (ddd, *J* = 9.0, 2.3, 0.3 Hz, $2H_{ar}$, Ph), 7.44 (ddd, *J* = 9.0, 2.1, 0.3 Hz, $2H_{ar}$, Ph), 5.97-5.81 (m, 1H, CH_2=C$\underline{H}$), 5.18 (dd, *J* = 6.4, 1.3 Hz, 1H, C$\underline{H}_2$=CH), 5.15 (dd, *J* = 13.0, 1.3 Hz, 1H, C$\underline{H}_2$=CH), 4.34 (d, *J* = 5.4 Hz, 2H, NCH_2), 3.75 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.3 (C=O), 148.4 (O_2NPh), 145.0 (NPh), 133.4 (CH_2=$\underline{C}$H), 125.7 (Ph), 124.5 (Ph), 117.6 ($\underline{C}H_2$=CH), 53.7 (OCH_3), 52.8 (NCH_2);

FT-IR: v 3083 (w), 2955 (w), 2357 (w), 1709 (s), 1593 (s), 1514 (s), 1446 (s), 1375 (m), 1334 (s), 1221 (s), 1192 (s), 1147 (s), 1110 (s), 1064 (m), 993 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{11}H_{13}N_2O_4$ $[M+H]^+$: 237.0870 found 237.0866;

methyl allyl(2-(trifluoromethoxy)phenyl)carbamate, 3.12



Isolated as a colourless oil (0.68 g, 57%).

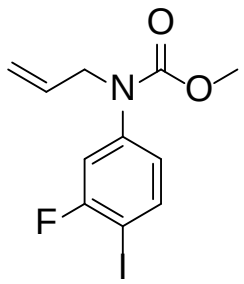
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, $2H_{ar}$, Ph), 7.29-7.23 (m, $2H_{ar}$, Ph), 6.00-5.80 (m, 1H, CH_2=C<u>H</u>), 5.12 (dd, *J* = 5.9, 1.4 Hz, 1H, C<u>H_2</u>=CH), 5.10 (dd, *J* = 2.6, 1.4 Hz,1H , C<u>H_2</u>=CH), 4.47 (br s, 1H, NCH_2*),* 3.96 (br. s, 1H, NCH_2), 3.64 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.9 (C=O), 145.6 (CF_3OPh), 133.8 (CH_2=<u>C</u>H) , 133.3 (NPh), 130.5 (Ph) , 128.8 (Ph) , 120.6 (q, J_{CF} = 256.8 Hz, OCF_3), 118.1 (Ph), 53.3 (OCH_3), 53.1 (N<u>C</u>H_2);

FT-IR: v 2957 (w), 1710 (s), 1501 (m), 1446 (m), 1378 (m), 1347 (w), 1249 (s), 1151 (s) 1013 (m), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{13}F_3NO_2$ $[M+H]^+$: 276.0842; found 276.0843;

methyl allyl(3-fluoro-4-iodophenyl)carbamate, 3.13



Isolated as a colourless oil (0.18 g, 78%).

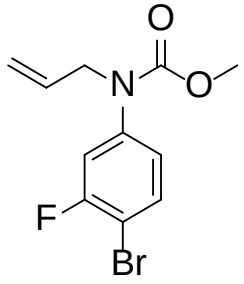
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.68 (dd, J_{HF} = 8.5, 1.2 Hz, $1H_{ar}$, Ph), 7.01 (d, J_{HH} = 8.8 Hz, $1H_{ar}$, Ph), 6.84 (d, J_{HH} = 7.8 Hz, $1H_{ar}$, Ph), 5.94-5.80 (m, 1H, CH_2=C<u>H</u>), 5.17 (dd, J_{HH} = 10.1, 1.1 Hz, 1H, C<u>H_2</u>=CH), 5.15 (dd, J_{HH} = 16.9, 1.1 Hz, 1H, <u>CH_2</u>=CH)), 4.25 (d, J_{HH} = 5.6 Hz, 2H, NCH_2), 3.72 (s, 3H, OCH_3);

^{13}C NMR: (150 MHz, $CDCl_3$) δ 161.3 (d, J_{CF} = 246.0 Hz, CF), 155.7 (C=O), 144.3 (d, *J* = 9.0 Hz, NPh), 139.3 (d, *J* = 2.7 Hz, Ph), 133.6 (CH_2=<u>C</u>H), 123.9 (Ph), 117.9 (<u>C</u>H_2=CH), 114.5 (d, *J* = 24.5 Hz, Ph), 78.2 (d, *J* = 27.0 Hz, CI), 53.6 (OCH_3), 53.3 (NCH_2);

FT-IR: v 3357 (w), 2326 (w), 1700 (s), 1598 (s), 1455 (s), 1382 (m), 1249 (m), 1172 (w), 1021 (s), 938 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{11}H_{12}FINO_2$ $[M+H]^+$: 335.9891; found 335.9891;

<u>methyl allyl(3-fluoro-4-bromophenyl)carbamate. 3.14</u>



Isolated as a colourless oil (0.37 g, 80%).

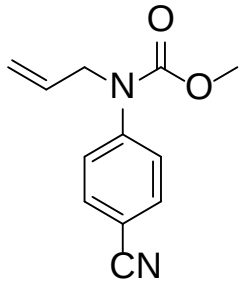
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.49 (dd, J_{HF} = 8.5, 0.6 Hz, $1H_{ar}$), 7.07 (dd, J_{HH} = 9.9, 1.7 Hz, $1H_{ar}$), 6.94 (dd, J_{HH} = 8.6, 1.4 Hz, $1H_{ar}$), 5.97-5.79 (m, 1H, CH_2=C<u>H</u>), 5.18 (dd, J_{HH} = 10.0, 1.4 Hz, 1H, C<u>H_2</u>=CH), 5.15 (dd, J_{HH} = 17.0, 1.4 Hz, 1H, C<u>H_2</u>=CH)), 4.25 (app. dt, J_{HH} = 5.7, 1.3 Hz, 2H, NCH_2), 3.73 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 160.3 (d, J_{CF} = 249.0 Hz,CF), 155.7 (C=O) , 143.1 (NPh), 133.5 (CH_2=<u>C</u>H) , 123.5 (Ph), 118.0 (<u>C</u>H_2=CH), 115.1 (d, *J* = 26 Hz, CBr), 106.8 (d, *J* = 22 Hz, Ph), 53.6 (OCH_3), 53.3 (NCH_2);

FT-IR: v 2953 (w), 1705 (s), 1578 (m), 1483 (s), 1375 (s), 1303 (m), 1237 (s), 1188 (s), 1052(m), 1024 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{11}H_{12}BrFNO_2$ $[M+H]^+$: 288.0030; found 288.0028;

<u>methyl allyl(4-cyanophenyl)carbamate, 3.15</u>



Isolated as a white solid (0.56 g, 60%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.62 (app. d, *J* = 8.7 Hz, $2H_{ar}$, Ph), 7.39 (app. d, *J* = 8.5 Hz, $2H_{ar}$, Ph), 5.98-5.81 (m, 1H, CH_2=C<u>H</u>), 5.19 (dd, *J* = 9.1, 1.3 Hz, 1H, C<u>H_2</u>=CH), 5.16 (dd, *J* = 15.7, 1.3 Hz, 1H, C<u>H_2</u>=CH), 4.31 (d, *J* = 5.4 Hz, 2H, NCH_2), 3.76 (s, 3H, OCH_3));

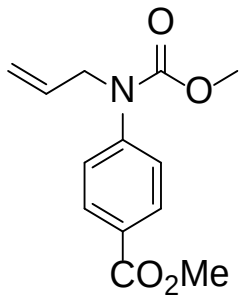
^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.5 (C=O), 146.7 (NPh), 133.5 (CH_2=<u>C</u>H), 133.1 (CNPh), 126.4 (Ph), 118.9 (Ph), 117.8 (<u>C</u>H_2=CH), 109.5 (CN), 53.7 (OCH_3), 53.0 (NCH_2);

FT-IR: v 2956 (w), 2927 (w), 2226 (w), 1705 (s), 1605 (m), 1507 (m), 1447 (m), 1373 (m), 1319 (w), 1225 (s), 1181 (w), 1151 (m), 1012 (w), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0972 found 217.0981;

m.p.: 74-76 °C;

methyl 4-(allyl(methoxycarbonyl)amino)benzoate, 3.16



Isolated as a colourless oil (yield: 0.53 g, 70%).

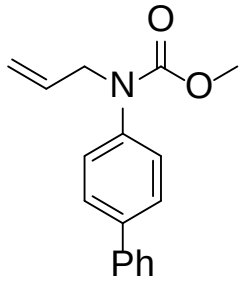
^{1}NMR: (400 MHz, $CDCl_3$) δ 8.00 (app. d, *J* = 8.6 Hz, $2H_{ar}$, Ph), 7.32 (app. d, *J* = 8.6 Hz, $2H_{ar}$, Ph), 5.97-5.81 (m, 1H, CH_2=C<u>H</u>), 5.17 (dd, *J* = 16.3, 1.2 Hz, 1H, C<u>H_2</u>=CH), 5.14 (dd, *J* = 10.6, 1.2 Hz, 1H, C<u>H_2</u>=CH), 4.31 (d, *J* = 5.5 Hz, 2H, NCH_2), 3.90 (s, 3H, $PhCO_2C$<u>H_3</u>), 3.73 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.8 (PhC=O), 155.8 (C=O), 146.7 (NPh), 133.8 (CH_2=<u>C</u>H), 130.6 (<u>Ph</u>C=O), 127.9 (Ph), 126.0 (Ph), 117.6 (<u>C</u>H_2=CH), 53.5 ($PhCO_2$<u>C</u>H_3), 53.2 (OCH_3), 52.5 (NCH_2);

FT-IR: v 2954 (w), 1705 (s), 1605 (m), 1512 (m), 1435 (m), 1375 (m), 1376 (s), 1273 (s), 1226 (s), 1188 (m), 1148 (m), 1104 (m), 1065 (w), 1015 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1074 found 250.1080;

methyl [1,1'-biphenyl]-4-yl(allyl)carbamate, 3.17



Isolated as a cream solid (0.37 g, 64%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.5 Hz, $2H_{ar}$, Ph), 7.56 (d, *J* = 6.7 Hz, $2H_{ar}$, Ph), 7.45 (d, *J* = 7.3 Hz, $1H_{ar}$, Ph), 7.43 (d, *J* = 7.8 Hz, $1H_{ar}$, Ph), 7.35 (tt, *J* = 7.3, 2.0 Hz, $1H_{ar}$, Ph), 7.30 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 6.02-5.87 (m, 1H, CH_2=C<u>H</u>), 5.24-5.13 (5.20 (dd, *J* = 11.7, 1.5 Hz, 1H, C<u>H$_2$</u>=CH), 5.17 (dd, *J* = 4.9, 1.5 Hz, 1H, C<u>H$_2$</u>=CH)), 4.31 (d, *J* = 5.8 Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3);

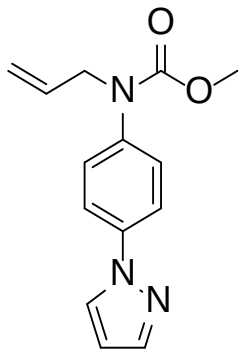
^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.2 (C=O), 141.6 (NPh), 140.6 (<u>Ph</u>Ph), 139.6 (Ph<u>Ph</u>), 134.0 (CH_2=<u>C</u>H), 129.1 (Ph), 127.8 (Ph), 127.7 (Ph), 127.3 (Ph), 117.4 (<u>C</u>H_2=CH), 53.6 (OCH_3), 53.3 (NCH_2);

FT-IR: v 3324 (m, br), 2958 (w), 1704 (s), 1604 (m), 1522 (m), 1445 (s), 1372 (s), 1319 (w), 1190 (s), 1146 (s), 1118 (w), 1026 (w), 1003 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1332; found 268.1339;

m.p.: 47-50 ˚C;

<u>methyl (4-(1H-pyrazol-1-yl)phenyl)(allyl)carbamate, 3.18</u>



Isolated as a yellow oil (0.40 g, 73%).

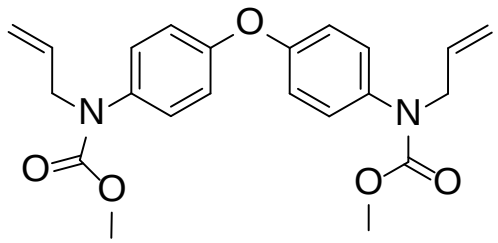
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.4 Hz, 1H_{ar}, Py), 7.69 (d, *J* = 1.4 Hz, 1H_{ar}, Py), 7.64 (ddd, *J* = 8.8, 2.9, 2.0 Hz, 2H_{ar}, Ph), 7.28 (d, *J* = 8.5, Hz, 2H_{ar}, Ph), 6.43 (t, *J* = 2.2 Hz, 1H_{ar}, Py), 6.00-5.76 (m, 1H, CH_2=C<u>H</u>), 5.19-5.06 (5.15 (dd, *J* = 1.7, 1.5, 1.3 Hz, 1H_{ar}, C<u>H_2</u>=CH), 5.11 (dd, *J* = 2.7, 1.4, 1.3 Hz, 1H_{ar}, C<u>H_2</u>=CH)), 4.26 (d, *J* = 5.8 Hz, 2H, NCH_2), 3.70 (s, 3H, OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.1 (C=O), 141.7 (NPh), 140.4 (NN=<u>C</u>H), 138.6 (NNPh), 133.8 (CH_2=<u>C</u>H), 128.1 (Ph), 127.0 (NNCH), 119.8 (Ph) 117.7 (<u>C</u>H_2=CH), 108.0 (NNCHCH), 53.5 (OCH_3), 53.2 (NCH_2);

FT-IR: v 2954 (w), 1698 (s), 1609 (w), 1523 (s), 1449 (m), 1375 (m), 1252 (m), 1148 (m), 1121 (w), 1088 (s), 1045 (w), 935 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{14}H_{16}N_3O_2$ $[M+H]^+$: 258.1237; found 258.1236

<u>dimethyl (oxybis(4,1-phenylene))bis(allylcarbamate), 3.19</u>



Using the relevant dicarbamate (1.0 equiv), 60% NaH (2.6 equiv), allyl bromide (2.6 equiv).

Isolated as a transparent yellow oil (0.34 g, 87%).

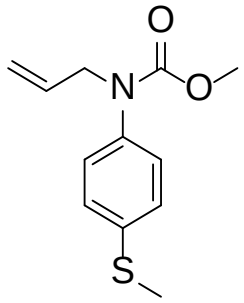
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24-7.09 (m, 4H_{ar}, Ph), 6.96 (d, *J* = 8.9 Hz, 4H_{ar}, Ph), 5.97-5.82 (m, 2H, 2CH_2=C<u>H</u>), 5.18-5.13 (m, 2H, 2C<u>H_2</u>=CH), 5.13-5.10 (m, 2H, 2C<u>H_2</u>=CH), 4.22 (d, *J* = 5.9 Hz, 4H, 2NCH_2), 3.69 (s, 6H, 2OCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.3 (2PhOPh), 155.5 (2C=O), 137.6 (2NPh), 133.9 (2CH_2=<u>C</u>H), 128.6 (Ph), 119.4 (Ph), 117.6 (2<u>C</u>H_2=CH), 53.7 (2OCH_3), 53.3 (2NCH_2);

FT-IR: v 2954 (w), 1698 (s), 1498 (s), 1447 (m), 1377 (m), 1273 (m), 1217 (s), 1146 (m), 1052 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{22}H_{24}N_2O_5$ $[M+H]^+$: 397.1758; found 397.1751;

<u>methyl allyl(4-(methylthio)phenyl)carbamate, 3.20</u>



Isolated as a colourless oil (0.25 g, 48%).

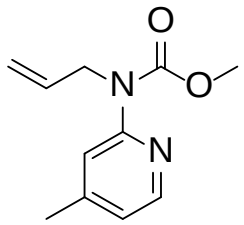
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H_{ar}, Ph), 7.19 (d, *J* = 8.2 Hz, 2H_{ar}, Ph), 5.95-5.80 (m, 1H, CH_2=C<u>H</u>), 5.17-5.06 (5.14 (dd, *J* = 2.9, 1.6, 1.4 Hz, 1H_{ar}, C<u>H_2</u>=CH), 5.11 (dd, *J* = 3.1, 1.6, 1.4 Hz, 1H_{ar}, C<u>H_2</u>=CH)), 4.22 (d, *J* = 5.9 Hz, 2H, NCH_2), 3.68 (s, 3H, OCH_3), 2.46 (s, 3H, SCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.1 (C=O), 139.4 (NPh), 136.9 (SPh), 133.9 (CH_2=<u>C</u>H), 127.5 (Ph), 127.2 (Ph), 117.5 (<u>C</u>H_2=CH), 53.5 (OCH_3), 53.2 (NCH_2), 16.2 (SCH_3);

FT-IR: v 3649 (w), 2952 (w), 1698 (s), 1593 (w), 1494 (s), 1445 (s), 1374 (s), 1260 (m), 1229 (s), 1147 (m), 1094 (m), 1009 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_2S$ $[M+H]^+$: 238.0896; found 238.0892

methyl allyl(4-methylpyridin-2-yl)carbamate, 3.21



Isolated as an orange oil (0.34 g, 55%).

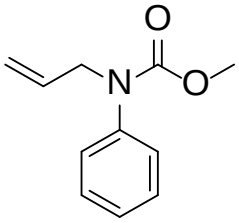
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 5.0, 0.3 Hz, $1H_{ar}$, Ph), 7.41 (app. dd, *J* = 1.7, 0.3 Hz, $1H_{ar}$, Ph), 6.84 (app. dd, *J* = 5.0, 1.7 Hz, $1H_{ar}$, Ph), 5.96-5.81 (m, 1H, CH_2=C<u>H</u>), 5.11 (dd, *J* = 17.1, 1.3 Hz, 1H, C<u>H_2</u>=CH), 5.05 (dd, *J* = 10.3, 1.3 Hz, 1H, C<u>H_2</u>=CH)), 4.55 (d, *J* = 5.4 Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 2.31 (s, 3H, $PhCH_3$);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.9 (NCN), 154.3 (C=O), 148.8 (<u>Ph</u>CH_3), 147.7 (Ph), 134.5 (CH_2=<u>C</u>H), 121.6 (Ph), 120.5 (Ph), 116.4 (<u>C</u>H_2=CH), 53.2 (OCH_3), 49.5 (NCH_2), 21.4 (Ph<u>C</u>H_3);

FT-IR: v 2955 (w), 1710 (s), 1603 (s), 1562 (w), 1444 (m), 1404 (m), 1376 (s), 1275 (m), 1235 (s), 1193 (m), 1144 (s), 1069 (m), 994 (m), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128 found 207.1131;

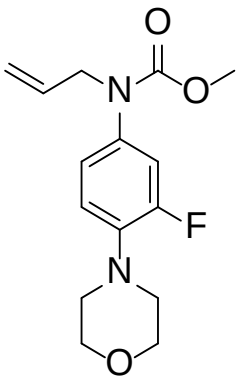
methyl allyl(phenyl)carbamate, 3.22



Using the relevant carbamate (1.0 equiv), 60% NaH (4.5 equiv), allyl bromide (1.3 equiv). Isolated as a colourless oil (0.20 g, 59%).

Characterisation data was in accordance with the literature[153]

methyl allyl(3-fluoro-4-morpholinophenyl)carbamate, 3.23



Isolated as a pink solid (0.27 g, 58%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00-6.80 (m, $3H_{ar}$, Ph), 6.94 (d, J_{HF} = 9.2 Hz, F), 5.98-5.76 (m, 1H, CH_2=C<u>H</u>), 5.17-5.10 (5.16 (app. s, 1H, C<u>H$_2$</u>=C<u>H</u>), 5.12 (app. d, J = 6.4 Hz, 1H) C<u>H$_2$</u>=C<u>H</u>), 4.21 (d, J = 5.3 Hz, 2H, NCH_2), 3.90-3.82 (m, 4H, ($2CH_2$)), 3.70 (s, 3H, OCH_3), 3.14-2.99 (m, 4H, $2CH_2$);

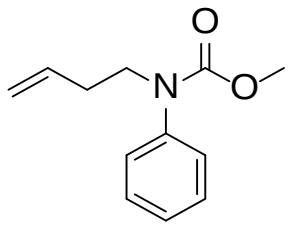
^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.2 (d, J_{CF} = 247.3 Hz), 154.1 (C=O), 138.7 (NPh), 136.9 ((CH_2)$_2$N<u>Ph</u>)133.9 (CH_2=<u>CH</u>), 123.0 (Ph), 118.6 (Ph), 117.7 (<u>C</u>H_2=C<u>H</u>), 115.6 (Ph), 67.3 (<u>C</u>H_2O<u>C</u>H_2), 53.6 (OCH_3), 53.4 (C=ON<u>C</u>H_2), 51.2 (<u>C</u>H_2N<u>C</u>H_2);

FT-IR: v 2957 (w), 1702 (s), 1512 (s), 1448 (s), 1376 (m), 1302 (m), 1247 (s), 1182 (m), 1115 (s), 1031 (w), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{15}H_{19}FN_2O_3$ $[M+H]^+$: 295.1452 found 295.1455;

m.p.: 51-53 °C.

methyl but-3-en-1-yl(phenyl)carbamate, 3.52



Prepared using a modified version of a procedure by Uhlig and Li.[118]Methyl chloroformate (0.5 mL, 5.70 mmol) was dissolved in dry 1,2-dichloroethane (10 mL). This solution was added dropwise over 30 mins to a vigorously stirred biphasic mixture of *N*-(but-3-en-1-yl)aniline, **3.51** (0.77 g, 5.23 mmol), water (5 mL), Na_2CO_3 (0.33 g, 3.1 mmol) and 1,2-dichloroethane (30 mL). The reaction mixture was stirred at 40 °C for 3 hours, then water (40 mL) and 1,2-dichloroethane (20 mL) were added. The separated organic layer was washed with HCl (1 M, 20 mL), water (2 x 20 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography, to yield a light orange oil (1.07 g, 99%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 (dddd, *J* = 7.4, 1.8, 0.9, 0.6 Hz, $2H_{ar}$, Ph), 7.19 (dd, *J* = 7.3, 0.9 Hz, $1H_{ar}$, Ph), 7.12 (d, *J* = 7.8 Hz, $2H_{ar}$, Ph), 5.75-5.51 (m, 1H, CH_2=C<u>H</u>), 4.92 (dd, *J* = 10.0, 1.0 Hz, 1H, C<u>H_2</u>=C<u>H</u>), 4.89 (dd, *J* = 7.0, 2.0 Hz, 1H, C<u>H_2</u>=C<u>H</u>), 3.60 (app. t, *J* = 7.4 Hz, 2H, NCH_2), 3.52 (s, 3H, OCH_3), 2.16 (app. q, *J* = 7.3 Hz, 2H, CHC<u>H_2</u>CH_2);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.2 (C=O), 141.9 (NPh), 135.3 (CH_2=<u>CH</u>), 129.2 (Ph), 127.7 (Ph), 126.9 (Ph), 117.0 (<u>C</u>H_2=C<u>H</u>), 53.0 (OCH_3), 49.9 (N<u>C</u>H_2CH_2), 32.9 (NCH_2<u>C</u>H_2);

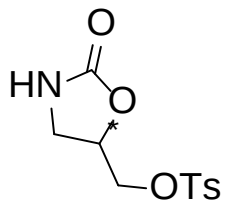
FT-IR: v 3370 (w), 2955 (br. W), 2918 (br. W), 1710 (s), 1597 (m), 1497 (m), 1445 (s), 1383 (s), 1294 (s), 1192 (m), 1149 (s), 1022 (m), 915 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176; found 206.1180;

General Cyclisation Procedure of Carbamates

1 equiv. of the relevant *N*-allylcarbamate and along with 2 equiv. (3,5-dimethylphenyl)(hydroxy)-λ^3-iodaneyl 4-methylbenzenesulfonate was weighed out and placed in a sealed flask. 2 mL of 1,1,1,3,3,3-hexafluoroisopropanol was syringed in to the flask. The flask was heated at 50 °C, for 16 hours and then the HFIP was evaporated and the mixture was diluted in ethyl acetate and pumped through a 2 cm plug of silica. The crude product was purified by column chromatography, giving the desired oxazolidinone product.

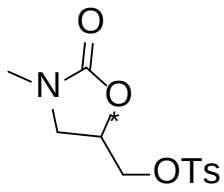
(2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 2.67



Yielding white solid, (0.05 g, up to 97%)

Characterisation data was in accordance with the literature[139]

(3-methyl-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 2.65



Using 2 eq. (3,5-dimethylphenyl)(hydroxy)-λ^3-iodaneyl 4-methylbenzenesulfonate, **2.75** gives yields of 42%. Employing 5 eq. Koser's reagent, **1.14** gives higher yields, cream solid (0.10 g, 67%).

Characterisation data was in accordance with the literature[124]

Chiral Separation Conditions:

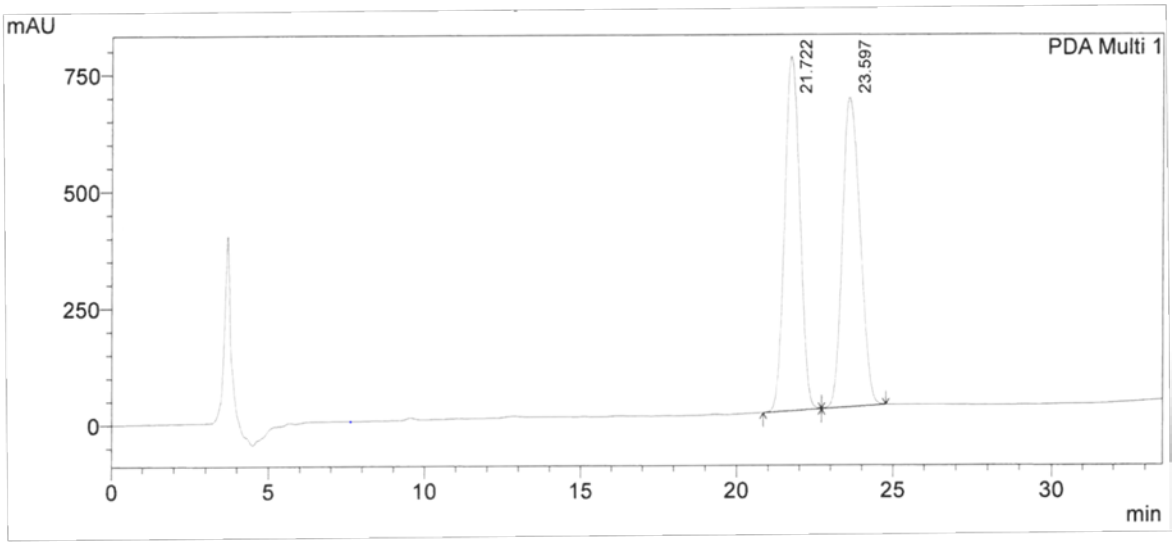
instrument: Shimadzu HPLC LC-40;

column: Chiralpak IF, 3µ, 250 x 4.6 mm;

Isocratic: 70% water + 30& MeCN;

flow: 1.0 mL/min, temperature: 25 ˚C;

MWD @ 254 nm, R_t: 22.1 : 23.5 mins.

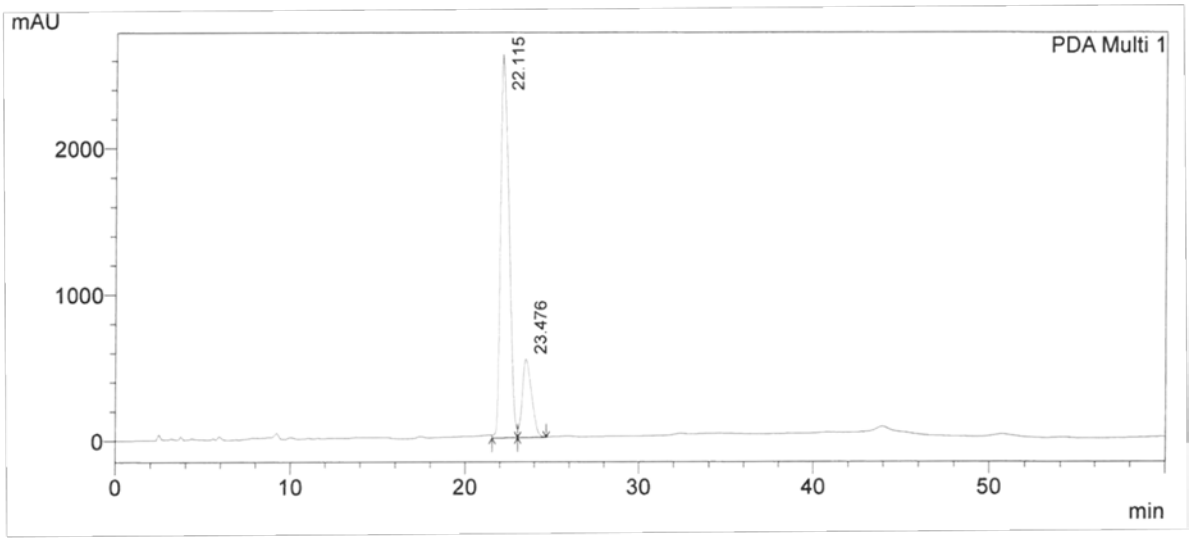


PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.722	25949066	759101	50.001	53.395
2	23.597	25948322	662573	49.999	46.605
Total		51897387	1421674	100.000	100.000

Figure 26: Racemic Product Peak Retention Times



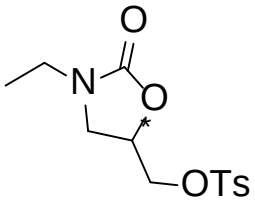
PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.115	88483377	2624275	81.324	82.988
2	23.476	20320278	537966	18.676	17.012
Total		108803656	3162240	100.000	100.000

Figure 27: Enantiomer Retention Times and Peak Area Integrations

(3-ethyl-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.26



Isolated as an orange oil (0.05 g, 81%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.37 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 4.71-4.62 (m, 1H, CH), 4.15 (d, *J* =, 4.3 Hz, 1H,

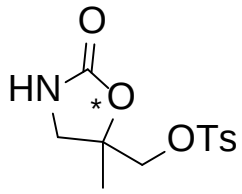
OTsC$\underline{H_2}$), 4.26 (d, *J* = 4.3 Hz, 1H, OTsC$\underline{H_2}$), 3.63 (app. t, *J* = 9.0 Hz, 1H NC$\underline{H_2}$CH), 3.40 (dd, *J* = 8.9, 5.9 Hz, 1H, NC$\underline{H_2}$CH), 3.28 (q, *J* = 7.3 Hz, 2H, NC$\underline{H_2}$CH$_3$), 2.45 (s, 3H, PhCH$_3$), 1.13 (t, *J* = 7,3 Hz, 3H, CH$_2$C$\underline{H_3}$);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.9 (C=O), 145.9 ($\underline{Ph}CH_3$), 132.4 ($\underline{Ph}S$), 130.4 (Ph), 128.3 (Ph), 69.8 ($CH_2\underline{C}HCH_2$), 69.0 ($\underline{TsOC}H_2$), 45.7 ($N\underline{C}H_2CH$), 39.1 ($CH_3\underline{C}H_2N$), 22.0 ($\underline{PhC}H_3$), 12.7 ($\underline{C}H_3CH_2N$);

FT-IR: v 2980 (m, br), 1743 (s), 1450 (m), 1358 (s), 1173 (s), 1095 (m), 956 (s), 813 (m, br.) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{13}H_{18}NO_5S$ $[M+H]^+$: 300.0900; found 300.0900;

(5-methyl-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.27



Isolated as a white solid (0.020 g, 36%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H$_{ar}$, Ph), 7.37 (d, *J* = 8.2 Hz, 2H$_{ar}$, Ph), 5.72 (br s, 1H, NH), 4.02 (d, *J* = 10.3 Hz, 1H, OTsC$\underline{H_2}$), 3.96 (d, *J* = 10.3 Hz, 1H, NC$\underline{H_2}$C), 3.59 (d, *J* = 9.0 Hz, 1H, NC$\underline{H_2}$C), 3.29 (d, J = 9.0 Hz, 1H, NC$\underline{H_2}$C), 2.46 (s, 3H, PhCH$_3$), 1.45 (s, 3H, CCH$_3$);

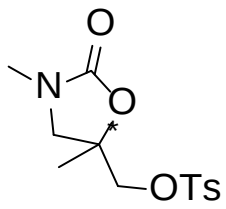
^{13}C NMR: (100 MHz, $CDCl_3$) δ 158.8 (C=O), 145.9 ($\underline{Ph}CH_3$), 132.4 ($\underline{Ph}S$), 130.5 (Ph), 128.4 (Ph), 80.1 ($\underline{C}CH_3$), 72.1 ($C\underline{H_2}OTs$), 48.5 ($N\underline{C}H_2$), 23.3 (CCH_3), 22.1 ($Ph\underline{C}H_3$);

FT-IR: v 3259 (m, br), 2921 (w), 1750 (s), 1708 (s), 1495 (w), 1348 (s), 1310 (s), 1189 (s), 1094 (s) 1002 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_5S$ $[M+H]^+$: 286.0744; found 286.0751;

m.p.: 151-153 °C

(3,5-dimethyl-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.28



Using 5 equiv Koser's reagent instead of 2 equiv **2.75**

Isolated as an orange oil (0.11 g, 74%).

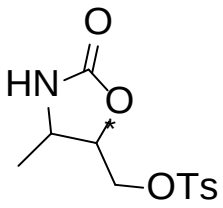
^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 7.37 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 3.97 (d, *J* = 10.2 Hz, 1H, OTsC$\underline{H_2}$), 3.93 (d, *J* = 10.2 Hz, 1H, OTsC$\underline{H_2}$), 3.54 (d, *J* = 9.0 Hz, 1H, NC$\underline{H_2}$C), 3.23 (d, *J* = 9.0 Hz, 1H, NC$\underline{H_2}$C), 2.85 (s, 3H, NCH_3), 2.46 (s, 3H, $PhCH_3$), 1.42 (s, 3H, CCH_3);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.1 (C=O), 145.9 ($\underline{Ph}CH_3$), 132.4 ($\underline{Ph}S$), 130.5 (Ph), 128.4 (Ph), 76.4 ($\underline{C}CH_3$), 72.2 ($C\underline{H_2}OTs$), 54.6 ($N\underline{C}H_2$), 31.3 ($N\underline{C}H_3$), 23.4 (CCH_3), 22.1 ($Ph\underline{C}H_3$);

FT-IR: ν 2980 (m, br), 1743 (s), 1450 (m), 1358 (s), 1173 (s), 1095 (m), 956 (s), 813 (m, br.) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{13}H_{18}NO_5S$ $[M+H]^+$: 300.0900; found 300.0916;

(4-methyl-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.29



Isolated as an orange oil (0.020 g, 44%, 1.4:1 dr)

Major diastereomer

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.37 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 5.70 (br s, 1H, NH), 4.27 (q, *J* = 5.0 Hz, 2H, $CHCH_2$), 4.15 (dd, *J* = 7.8, 4.6 Hz, 1H, $OTsCH_2$), 4.12 (dd, *J* = 7.8, 5.1 Hz, 1H, $OTsCH_2$), 3.80 (dq, J = 6.0, 0.70 Hz, 1H, $CHCH_3$), 2.46 (s, 3H, $PhCH_3$), 1.30 (d, *J* = 6.2 Hz, 3H, $CHCH_3$);

^{13}C NMR: (150 MHz, $CDCl_3$) δ 158.1 (C=O), 145.9 ($PhCH_3$), 132.4 (PhS), 130.5 (Ph), 128.4 (Ph), 80.1 ($CHCH_3$), 68.3 (CH_2OTs), 50.4 (NHCH), 22.1 ($CHCH_3$), 21.3 ($PhCH_3$);

Minor diastereomer

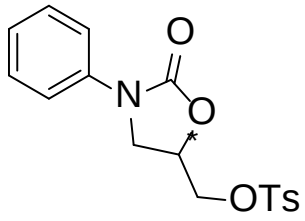
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.37 (d, *J* = 8.2 Hz, $2H_{ar}$, Ph), 5.44 (br s, 1H, NH), 4.73 (q, *J* = 7.0 Hz, 1H, $CHCH_2$), 4.22 (dd, *J* = 10.8, 6.1 Hz, 1H, $OTsCH_2$), 4.17 (dd, *J* = 10.8, 5.9 Hz, 1H, $OTsCH_2$), 4.08 (dq, J = 7.0, 0.70 Hz, 1H, $CHCH_3$), 2.46 (s, 3H, $PhCH_3$), 1.21 (d, *J* = 6.6 Hz, 3H, $CHCH_3$);

^{13}C NMR: (150 MHz, $CDCl_3$) δ 158.1 (C=O), 145.9 ($PhCH_3$), 132.3 (PhS), 130.5 (Ph), 128.4 (Ph), 75.8 ($CHCH_3$), 66.2 (CH_2OTs), 50.1 (NHCH), 22.1 ($CHCH_3$), 16.0 ($PhCH_3$);

FT-IR: v 3287 (m, br), 1741 (s), 1597 (m), 1356 (s), 1232 (m), 1173 (s), 1094 (m), 973 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{12}H_{16}NO_5S$ $[M+H]^+$: 286.0744; found 286.0750;

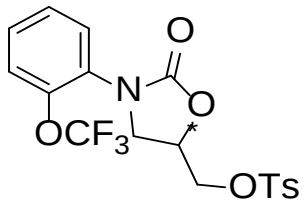
(2-oxo-3-phenyloxazolidin-5-yl) methyl 4-methylbenzenesulfonate, 3.30



Using 2 eq. (3,5-dimethylphenyl)(hydroxy)-λ^3-iodaneyl 4-methylbenzenesulfonate gives lower yields of 16%. Employing 5 eq. Koser's reagent in the reaction instead, gives higher yields. Isolated as a grey solid (0.03 g, 61%).

Characterisation data was in accordance with the literature[140]

(2-oxo-3-(2-trifluoromethoxy)phenyl)-5λ^3-oxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.31



Isolated as an orange-brown oil (0.090 g, 99%).

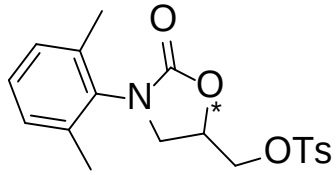
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, $2H_{ar}$, Ph), 7.45-7.41 (m, $1H_{ar}$, Ph), 7.38-7.29 (m, $5H_{ar}$ Ph), 4.89-4.82 (m, 1H, $CH_2C\underline{H}CH_2$), 4.24 (dd, *J* = 11.1, 4.3 Hz, 1H, OTsC$\underline{H}_2$), 4.22 (dd, *J* = 11.1, 4.2 Hz, 1H, OTsC$\underline{H}_2$), 4.09 (app. t, *J* = 9.0 Hz, 1H, NC$\underline{H}_2$), 3.78 (dd, *J* = 9.1, 5.6 Hz, 1H, NC$\underline{H}_2$), 2.44 (s, 3H, $PhCH_3$);

^{13}C NMR: (150 MHz, $CDCl_3$) δ 155.4 (C=O), 145.9 (Ph<u>O</u>CF_3), 144.8 (<u>Ph</u>CH_3), 132.3 (<u>Ph</u>S), 130.4 (Ph), 129.8 (Ph), 129.3 (Ph), 128.9 (Ph), 128.3 (Ph), 128.0 (Ph), 121.5 (Ph), 120.6 (q, J_{CF} = 258.4 Hz, (OCF)) 70.8 (<u>C</u>H), 68.8 (<u>C</u>H_2OTs), 48.6 (NCH_2), 22.0 (Ph<u>C</u>H_3);

FT-IR: v 1758 (s), 1598 (w), 1505 (m), 1456 (w), 1415 (m), 1362 (m), 1248 (s), 1210 (s), 1172 (s) 1094 (s), 963 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{18}H_{17}F_3NO_6S$ $[M+H]^+$: 432.0723; found 432.0734;

<u>(3-(2,6-dimethylphenyl)-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.32</u>



Isolated as a cream solid (0.070 g, 97%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, $2H_{ar}$, Ph), 7.39 (d, J = 8.1 Hz, $2H_{ar}$, Ph), 7.16 (dd, J = 8.3, 6.7 Hz, $1H_{ar}$, Ph), 7.09 (app. d, J = 7.5 Hz, $2H_{ar}$, Ph), 4.97-4.85 (m, 1H, CH_2<u>C</u>HCH_2), 4.29 (dd, J = 11.0, 4.1 Hz, 1H, OTsC<u>H_2</u>), 4.24 (dd, J = 11.0, 3.6 Hz, 1H, OTsC<u>H_2</u>), 3.90 (app. t, J = 9.2 Hz, 1H, NC<u>H_2</u>), 3.73 (dd, J = 9.3, 5.8 Hz, 1H, NC<u>H_2</u>), 2.47 (s, 3H, TolCH_3), 2.25 (s, 3H, PhCH_3), 2.20 (s, 3H, PhCH_3);

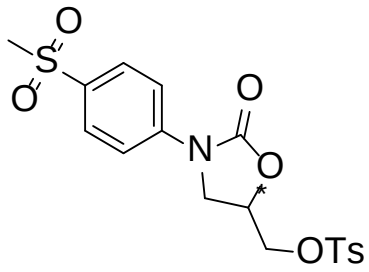
^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.5 (C=O), 146.0 (<u>Ph</u>CH_3), 137.4 (2<u>Ph</u>CH_3), 136.9 (PhS), 133.7 (Ph), 132.3 (Ph), 130.5 (Ph), 129.24 (Ph), 129.2 (Ph), 129.1 (Ph), 128.4 (Ph), 70.4 (CH), 68.8 (<u>C</u>H_2OTs), 47.5 (NCH_2), 22.0 (Tol<u>C</u>H_3), 18.0 (<u>C</u>H_3)$_2$Ph;

FT-IR: v 2957 (w), 1746 (s), 1472 (m), 1416 (m), 1360 (s), 1347 (w), 1189 (s), 1086 (m) 962 (m), cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{19}H_{22}NO_5S$ $[M+H]^+$: 376.1213; found 376.1222;

m.p.: 127-129 °C;

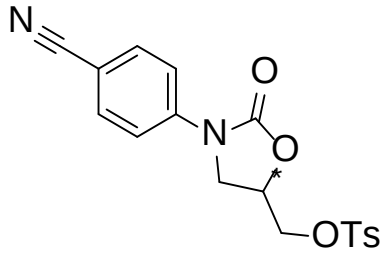
(3-(4-(methylsulfonyl)phenyl)-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.33



Isolated as a cream solid (0.050 g, 55%). M.p. 167-169 °C.

Characterisation data was in accordance with the literature[140]

(3-(4-cyanophenyl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.34



Isolated as a cream solid (0.070 g, 87%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4, Hz, $2H_{ar}$, Ph), 7.70-7.60 (m, $4H_{ar}$, Ph), 7.36 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 4.93-4.83 (m, 1H, $CH_2C\underline{H}CH_2$), 4.30 (dd, *J* = 11.2, 3.9 Hz, 1H, OTsC$\underline{H}_2$), 4.26 (dd, *J* = 11.2, 4.4 Hz, 1H, OTsC$\underline{H}_2$)), 4.14 (app. t, *J* = 9.2 Hz, 1H, NC$\underline{H}_2$), 3.97 (dd, *J* = 9.2, 6.0 Hz, 1H, NC$\underline{H}_2$), 2.46 (s, 3H, $PhCH_3$);

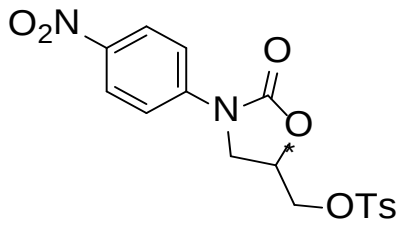
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.5 (C=O), 146.2 (PhCH_3), 141.8 (CN), 133.6 (NPh), 132.2 (PhS), 130.5 (Ph), 128.4 (Ph), 118.9 (Ph), 118.3 (Ph), 107.8 (CH), 69.8 (CN), 68.3 (CH_2OTs), 46.6 (NCH_2), 22.1 PhCH_3);

FT-IR: v 2224 (w), 1754 (s), 1605 (m), 1513 (m), 1480 (w), 1427 (m), 1366 (m), 1216 (m), 1175(s), 1139 (m), 1018 (w), 982 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{18}H_{17}N_2O_5S$ $[M+H]^+$: 373.0853; found 373.0862;

m.p.: 135 – 137 ˚C;

3-(4-cyanophenyl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.35



Isolated as a yellow solid (0.060 g, 70%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.3 Hz, $2H_{ar}$, Ph), 7.77 (d, *J* = 8.3 Hz, $4H_{ar}$, Ph), 7.68 (d, *J* = 9.3 Hz, $2H_{ar}$, Ph), 7.36 (d, *J* = 7.9 Hz, $2H_{ar}$, Ph), 4.93-4.83 (m, 1H, CH_2CHCH_2), 4.30 (dd, *J* = 11.2, 3.8 Hz, 1H, OTsCH_2), 4.26 (dd, *J* = 11.2, 4.4 Hz, 1H, OTsCH_2), 4.19 (app. t, *J* = 9.1 Hz, 1H, NCH_2), 4.01 (dd, *J* = 9.2, 5.9 Hz, 1H, NCH_2), 2.46 (s, 3H, $PhCH_3$);

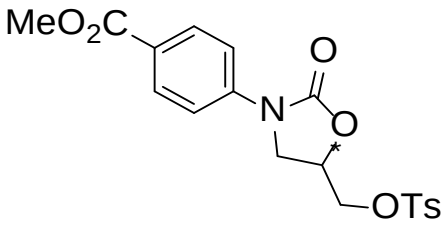
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.4 (C=O), 146.2 (PhNO_2), 144.0 ((PhCH_3), 143.5 (NPh), 132.2 (PhS), 130.6 (Ph), 128.4 (Ph), 125.4 (Ph), 117.9 (Ph), 69.9 (CH), 68.3 (OTsCH_2), 46.8 (NCH_2), 22.1 (PhCH_3);

FT-IR: v 2981 (w), 2357 (m), 1751 (m), 1597 (m), 1503 (s), 1404 (m), 1363 (m), 1326 (s), 1190(s), 1132 (s), 1048 (w), 974 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{17}H_{17}N_2O_7S$ $[M+H]^+$: 393.0751; found 394.0762;

m.p.: 142 – 144 ˚C.

4-(2-oxo-5-((tosyloxy)methyl)-5λ^3-oxazolidin-3-yl)benzoate, 3.36



Isolated as a beige solid (0.070 g, 87%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.9 Hz, $2H_{ar}$, Ph), 7.78 (d, *J* = 8.4 Hz, $2H_{ar}$, Ph), 7.58 (d, *J* = 8.9 Hz, $2H_{ar}$, Ph), 7.36 (d, *J* = 8.1 Hz, $2H_{ar}$, Ph), 4.93-4.81 (m, 1H, CH_2CHCH_2), 4.30 (dd, *J* = 11.2, 4.1 Hz, 1H, $OTsCH_2$), 4.26 (dd, *J* = 11.2, 4.6 Hz, 1H, $OTsCH_2$), 4.15 (app. t, *J* = 9.1 Hz, 1H, NCH_2), 3.96 (dd, *J* = 9.1, 6.0 Hz, 1H, NCH_2), 3.92 (s, 3H, CO_2CH_3), 2.45 (s, 3H, $PhCH_3$);

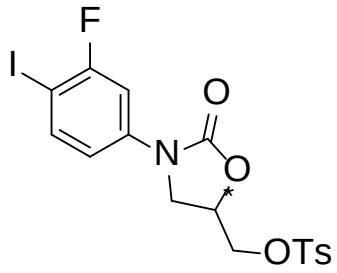
^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.8 (PhC=O), 153.7 (C=O), 146.1 ($PhCH_3$), 142.0 (NPh), 132.3 (PhS), 131.2 (Ph), 130.5 (Ph), 128.4 (Ph), 126.0 (Ph), 117.6 (Ph), 69.7 (CH), 68.5 ($OTsCH_2$), 52.5 (OCH_3), 46.8 (NCH_2), 22.1 ($PhCH_3$);

FT-IR: v 2952 (m), 1744 (s), 1708 (s), 1611 (m), 1515 (m), 1438 (m), 1428 (m), 1360 (s), 1288 (s), 1189(s), 1173 (s), 994 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{19}H_{20}NO_7S$ $[M+H]^+$: 406.0955; found 406.0961;

m.p.: 138 – 140 ˚C.

(3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl)methyl4methylbenzenesulfonate, 3.37



Isolated as a cream solid (0.080 g, 84%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, J_{HH} = 8.3 Hz, 2H_{ar}, Ph), 7.70 (dd, J_{HF} = 8.6, 1.5 Hz, 1H_{ar}, Ph), 7.40 (dd, J_{HH} = 10.2, 2.5 Hz, 1H_{ar}, Ph), 7.36 (d, J_{HH} = 8.3 Hz, 2H_{ar}, Ph), 6.99 (dd, J_{HH} = 8.7, 2.5 Hz, 2H_{ar}, Ph), 4.93-4.77 (m, 1H, $CH_2C\underline{H}CH_2$), 4.30 (dd, J_{HH} = 11.1, 3.9 Hz, 1H, OTsC$\underline{H}_2$), 4.26 (dd, J_{HH} = 11.1, 4.5 Hz, 1H, OTsC$\underline{H}_2$), 4.15 (app. t, J_{HH} = 9.1 Hz, 1H, NC$\underline{H}_2$), 3.87 (dd, J_{HH} = 9.1, 5.9 Hz, 1H, NC$\underline{H}_2$), 2.46 (s, 3H, $PhCH_3$);

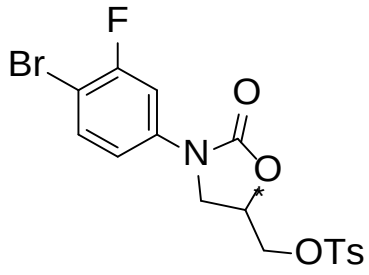
^{13}C NMR: (100 MHz, $CDCl_3$) δ 161.0 (s) (CF), 153.5 (C=O), 146.1 ($\underline{Ph}CH_3$), 139.7 (NPh),, 132.3 (PhS), 130.5 (Ph), 128.3 (Ph), 115.4 (Ph), 106.5 (Ph), 75.1 (CI), 69.7 (CH), 68.4 (OTsC$\underline{H}_2$), 46.8 (NCH_2), 22.1 ($PhCH_3$);

FT-IR: v 2929 (br. W), 2364 (w), 1759 (s), 1650 (w), 1599 (s), 1454 (m), 1412 (m), 1362 (s), 1228 (m), 1176 (s), 1095 (w), 992 (m) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{17}H_{16}FINO_5S$ $[M+H]^+$: 491.9973; found 491.9783;

m.p.: 128 – 131 ˚C.

(3-(3-fluoro-4-bromophenyl)-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.38



Isolated as a white solid (0.15 g, 85%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, J_{HH} = 8.3 Hz, $2H_{ar}$ Ph), 7.51 (dd, J_{HF} = 8.6, 1.0 Hz, $1H_{ar}$, Ph), 7.46 (dd, J_{HH} = 10.7, 2.6 Hz, $1H_{ar}$, Ph), 7.35 (d, J_{HH} = 8.1 Hz, $2H_{ar}$, Ph), 7.08 (dd, J_{HH} = 8.8, 2.7 Hz, $1H_{ar}$, Ph), 4.90-4.77 (m, 1H, $CH_2C\underline{H}CH_2$), 4.28 (dd, J_{HH} = 11.5, 3.9 Hz, 1H, OTsC$\underline{H}_2$), 4.25 (dd, J_{HH} = 11.5, 4.3 Hz, 1H, OTsC$\underline{H}_2$), 4.07 (app. t, J_{HH} = 9.1 Hz, 1H, NC$\underline{H}_2$), 3.87 (dd, J_{HH} = 9.1, 5.9 Hz, 1H, NC$\underline{H}_2$), 2.45 (s, 3H, $PhCH_3$);

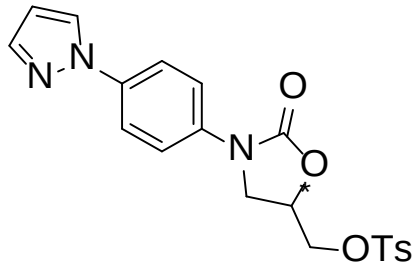
^{13}C NMR: (100 MHz, $CDCl_3$) δ 160.7 (s) (CF), 153.6 (C=O), 146.1 ($\underline{Ph}CH_3$), 138.8 (NPh), 133.9 (PhS), 132.2 (Ph), 130.5 (Ph), 128.3 (Ph), 114.8 (Ph), 107.2 (Ph), 77.3 (Cl), 69.7 (CH), 68.5 (OTsC$\underline{H}_2$), 46.8 (NCH_2), 22.1 (Ph$\underline{C}H_3$);

FT-IR: v 2924 (br. W), 2358 (w), 1750 (s), 1610 (w), 1495 (m), 1354 (s), 1233 (s), 1189 (s), 1122 (m), 1092 (m), 988 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{17}H_{16}FbrNO_5S$ $[M+H]^+$: 443.9911; found 443.9912;

m.p.: 143 – 146 ˚C;

(3-(4-(1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.39



Isolated as a beige solid (0.060 g, 67%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.4 Hz, $1H_{ar}$, Py), 7.80 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.73 (d, *J* = 1.6 Hz, $1H_{ar}$, Py), 7.71 (d, *J* = 9.1 Hz, $2H_{ar}$, Ph), 7.58 (d, *J* = 9.1 Hz, $2H_{ar}$, Ph), 7.36 (d, *J* = 8.2 Hz, $2H_{ar}$, Ph), 6.48 (t, *J* = 2.0 Hz, $1H_{ar}$, Py), 4.90-4.80 (m, 1H, CH_2CHCH_2), 4.30 (dd, *J* = 11.0, 4.2 Hz, 1H, OTsCH_2), 4.27 (dd, *J* = 11.0, 4.8 Hz, 1H, OTsCH_2), 4.15 (app. t, *J* = 9.0 Hz, 1H, NCH_2), 3.95 (dd, *J* = 9.1, 6.0 Hz, 1H, NCH_2), 2.45 (s, 3H, $PhCH_3$);

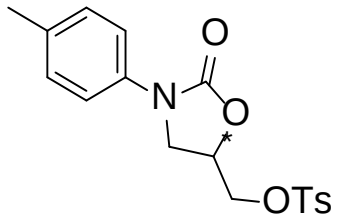
^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.0 (C=O), 146.1 (PhCH_3),, 141.5 (NN=CH), 136.9 (CH_3Ph), 136.3 ($CHCH_2$NPh), 132.3 (PhS), 130.5 (Ph), 128.4 (Ph), 127.1 (Ph), 120.2 (Ph), 119.5 (Ph), 108.1 (Ph), 69.7 (CH), 68.6 (OTsCH_2), 47.1 (NCH_2), 22.1 ($PhCH_3$);

FT-IR: v 2357 (w), 1737 (s), 1529 (s), 1449 (w), 1394 (m), 1364 (m), 1228 (m), 1180 (s), 1140 (m), 1093 (m), 989 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{20}H_{20}N_3O_5S$ $[M+H]^+$: 414.1118; found 414.1119;

m.p.: 153-155 ˚C.

(2-oxo-3-(p-tolyl)-5λ^3-oxazolidin-5-yl)methyl-4-methylbenzenesulfonate, 3.40



Isolated as a white solid (0.060 g, 85%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, $2H_{ar}$, Ph), 7.35 (dd, *J* = 8.5, 2.2 Hz, $4H_{ar}$, Ph), 7.17 (d, *J* = 8.4 Hz, $2H_{ar}$, Ph), 4.89-4.75 (m, 1H, CH_2CHCH_2), 4.25 (dd, *J* = 10.8, 4.1 Hz, 1H, OTsCH_2), 4.22 (dd, *J* = 10.8,

4.9 Hz, 1H, OTsC$\underline{H}_2$), 4.08 (app. t, *J* = 9.1 Hz, 1H, NC$\underline{H}_2$), 3.87 (dd, *J* = 9.2, 6.0 Hz, 1H, NC$\underline{H}_2$), 2.45 (s, 3H, TolCH_3), 2.23 (s, 3H, PhCH_3);

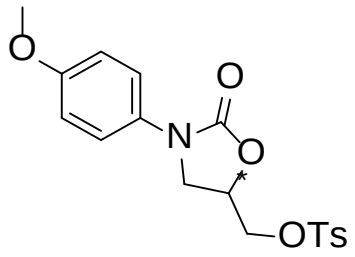
^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.2 (C=O), 146.0 (Tol$\underline{C}H_3$), 135.5 (Ph$\underline{C}H_3$), 134.6 (PhS), 132.4 (Ph), 130.5 (Ph), 130.0 (Ph), 128.4 (Ph), 118.9 (Ph), 69.5 (CH), 68.7 (OTsC$\underline{H}_2$), 47.3 (NCH_2), 22.1 (Tol$\underline{C}H_3$), 21.1 (Ph$\underline{C}H_3$);

FT-IR: v 2922 (m, br), 1746 (s), 1518 (m), 1485 (w), 1422 (m), 1358 (s), 1225 (m), 1190 (s), 1121 (m) 984 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{18}H_{20}NO_5S$ $[M+H]^+$: 362.1057; found 362.1056;

m.p.: 119-121 °C;

(3-(4-methoxyphenyl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.41



Isolated as a white solid (0.060 g, 75%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H_{ar}, Ph), 7.41-7.32 (m, 4H_{ar}, Ph), 6.90 (d, *J* = 9.2 Hz, 2H_{ar}, Ph), 4.87-4.74 (m, 1H, $CH_2C\underline{H}CH_2$), 4.25 (dd, *J* = 2.7, 1.0 Hz, 1H, OTsC$\underline{H}_2$), 4.23 (dd, *J* = 3.6, 1.0 Hz, 1H, OTsC$\underline{H}_2$), 4.15 (app. t, *J* = 9.0 Hz, 1H, NC$\underline{H}_2$), 3.87 (dd, *J* = 9.1, 6.0 Hz, 1H, NC$\underline{H}_2$), 3.80 (s, 3H, OCH_3), 2.46 (s, 3H, PhCH_3);

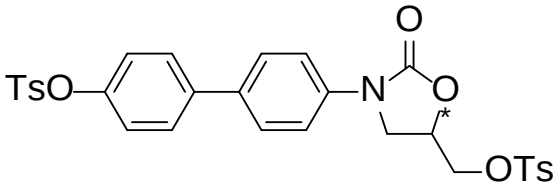
^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.0 (OPh), 154.4 (C=O), 146.0 (Ph$\underline{C}H_3$), 132.3 (PhS), 131.1 (Ph), 130.5 (Ph), 128.4 (Ph), 121.0 (Ph), 114.7 (Ph), 69.5 (CH), 68.7 (OTsC$\underline{H}_2$), 55.9 (O$\underline{C}H_3$), 47.7 (NCH_2), 22.1 (Ph$\underline{C}H_3$);

FT-IR: v 1742 (s), 1515 (m), 1406 (w), 1358 (m), 1228 (m), 1189 (s), 1092 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{18}H_{20}NO_6S$ $[M+H]^+$: 378.1006; found 378.1000;

m.p.: 133-135 ˚C;

(2-oxo-3-(4'-(tosyloxy)-[1,1'-biphenyl]-4-yl)-5λ³-oxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.42

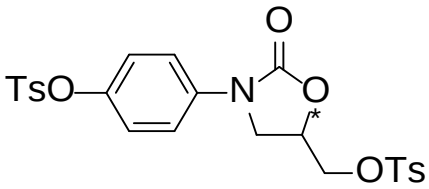


Isolated as an orange oil (0.02 g, 16%).

FT-IR: v 2924 (w), 2180 (s), 1749 (s), 1652 (w), 1606 (m), 1496 (m), 1417 (m), 1362 (s), 1176 (s), 1094 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{30}H_{27}NO_8S_2$ $[M+H]^+$: 594.1241; found 594.1254;

(2-oxo-3-(4-(tosyloxy)phenyl)-5λ³-oxazolidin-5-yl)methyl 4-methylbenzenesulfonate, 3.43



Isolated as a off white solid (0.03 g, 26%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.69 (d, *J* = 8.3 Hz, $2H_{ar}$, Ph), 7.41 (d, *J* = 9.1 Hz, $2H_{ar}$, Ph), 7.34 (dd, *J* = 10.4, 8.3 Hz, $4H_{ar}$, Ph), 6.97 (d, *J* = 9.1 Hz, $2H_{ar}$, Ph), 4.89-4.75 (m, 1H, CH_2CHCH_2),

4.26 (dd, *J* = 4.2, 1.5 Hz, 1H, OTsC$\underline{H}_2$), 4.21 (dd, *J* = 4.2, 2.0 Hz, 1H, OTsC$\underline{H}_2$), 4.15 (app. t, *J* = 9.0 Hz, 1H, NC$\underline{H}_2$), 3.89 (dd, *J* = 9.1, 6.0 Hz, 1H, NC$\underline{H}_2$), 2.45 (s, 6H, 2TolCH_3);

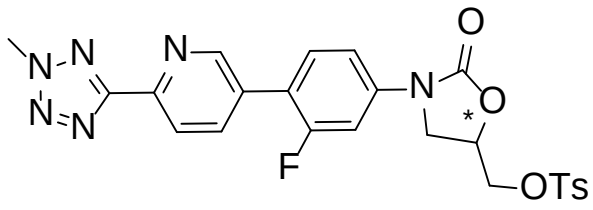
^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.9 (C=O), 146.1 (TolSO$_3\underline{Ph}$), 145.9 (PhCH_3), 136.9 (NPh), 132.4 (PhS), 132.2 (Ph), 130.5 (Ph), 130.2 (Ph), 128.9 (Ph), 128.4 (Ph), 123.5 (Ph), 119.4 (Ph), 69.6 (CH), 68.5 (OTsC$\underline{H}_2$), 47.0 (NCH_2), 22.1 (Ph$\underline{C}H_3$);

FT-IR: v 3069 (w), 1743 (s), 1508 (s), 1404 (m), 1344 (s), 1224 (m), 1178 (s), 1091 (s), 990 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{24}H_{23}NO_8S_2$ $[M+H]^+$: 518.0937; found 518.0941;

m.p.: 160-162 ˚C;

(3-(3-fluoro-4-(6-(2-methyl-2H-tetrazol-5-yl)-5λ^3-oxazolidin-3-yl)phenyl)-2-oxo-5λ^3-oxazolidin-5-yl)methyl4-methylbenzenesulfonate, 3.48



An oven-dried rb flask was charged with iodoarene oxazolidinone **3.38** (0.039g, 0.09 mmol), 5-(4-bromo-2-fluorophenyl)-2-(2-methyl-2H-tetrazol-5-yl)pyridine (0.030 g, 0.14 mmol), K_2CO_3 (0.034 g, 0.25 mmol), $PdCl_2$(dppf.CH_2Cl_2) (0.009 g, 0.012 mmol). The solids were degassed with N_2, before the addition of 5 mL dioxane/water (7:1). The reaction mixture was degassed with N_2 again, before heating at 80 ˚C, overnight. The reaction mixture was cooled to rt, diluted with 100 mL DCM and washed with water (3 x 20 mL). The organics were dried over $MgSO_4$, filtered and

concentrated under reduced pressure, purified by column chromatography, to give a white solid (0.02 g, 47%)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.93 (s, 1H_{ar}, Ph), 8.32 (d, *J* = 8.0 Hz, 1H_{ar}, Ph), 8.06 (d, *J* = 6.6 Hz, 1H_{ar}, Ph), 7.81 (d, *J* = 8.4 Hz, 2H_{ar}, Ph), 7.60-7.49 (m, 2H_{ar}, Ph), 7.37 (d, *J* = 7.4 Hz, 2H_{ar}, Ph), 7.34 (d, *J* = 8.4 Hz, 1H_{ar}, Ph), 4.92-4.85 (m, 1H, $CH_2C\underline{H}CH_2$), 4.48 (s, 3H, NCH_3), 4.32 (dd, *J* = 11.2, 4.1 Hz, 1H, OTsC$\underline{H}_2$), 4.28 (dd, *J* = 11.2, 4.4 Hz, 1H, OTsC$\underline{H}_2$), 4.17 (app. t, *J* = 9.0 Hz, 1H, NC$\underline{H}_2$), 4.12 (dd, *J* = 8.8, 2.0 Hz, 1H, NC$\underline{H}_2$), 3.98 (dd, *J* = 8.8, 2.0 Hz, 1H, CH), 2.46 (s, 3H, $PhCH_3$);

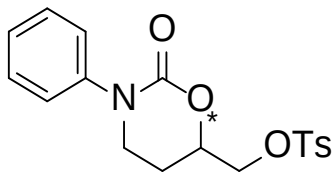
13C NMR: (150 MHz, $CDCl_3$) δ 160.5 (d, J_{CF} = 249 Hz,CF), 153.6 (C=O), 150.3 (d, *J* = 3.5 Hz, N=C), 146.0 (d, *J* = 25 Hz, NPh), 139.9 (d, *J* = 11 Hz, $\underline{Ph}CH_3$), 137.5 (d, *J* = 3.8 Hz, Ph), 132.5 (d, *J* = 1.5 Hz, PhPh), 131.0 (d, *J* = 4.4 Hz, PhS), 130.6 (Ph), 128.4 (Ph), 121.0 (d, *J* = 14 Hz, Ph), 114.3 (d, *J* = 3.3 Hz, Ph), 106.9 (d, *J* = 29 Hz) (Ph), 69.8 (CH), 68.5 (OTsC$\underline{H}_2$), 46.9 (NCH_2), 41.7 (NCH_3), 23.0 ($PhCH_3$);

FT-IR: v 2924 (br w), 1746 (s), 1625 (m), 1513 (m), 1407 (s), 1363 (s), 1176 (s), 1095 (m), 996 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{24}H_{22}FN_6O_5S$ $[M+H]^+$: 525.1351; found 525.1355;

m.p.: 186 – 188 ˚C;

(2-oxo-3-phenyl-1,3-oxazinan-6-yl)methyl-4-methylbenzenesulfonate, 3.50



Isolated as a white solid (30 mg, 46%).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, $2H_{ar}$, Ph), 7.43 (m, $4H_{ar}$, Ph), 7.28 (d, *J* = 7.8 Hz, $2H_{ar}$, Ph), 4.70-4.60 (m, 1H, CH_2CHCH_2), 4.25 (dd, *J* = 11.0, 4.5 Hz, 1H, $OTsCH_2$), 4.18 (dd, *J* = 11.0, 5.1 Hz, 1H, $OTsCH_2$), 3.78 (dd, *J* = 11.4, 4.5 Hz, 1H, NCH_2), 3.70 (dd, *J* = 11.4, 4.0 Hz, 1H, NCH_2), 2.46 (s, 3H, $PhCH_3$), 2.27-2.14 (m, 2H, NCH_2CH_2);

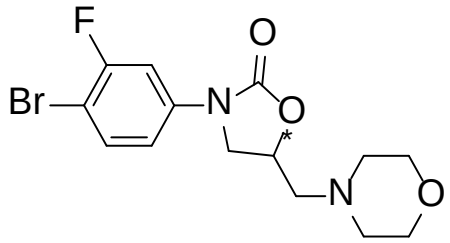
^{13}C NMR: (150 MHz, $CDCl_3$) δ 154.3 (C=O), 145.8 ($PhCH_3$), 142.7 , 132.5 (PhS), 130.5 (Ph), 129.7 (Ph), 128.5 (Ph), 127.6 (Ph), 126.2 (Ph), 74.8 (CH), 69.8 ($OTsCH_2$), 48.0 (NCH_2), 24.6 (NCH_2CH_2), 22.1 ($PhCH_3$);

FT-IR: v 2924 (w), 1688 (s), 1597 (m), 1496 (m), 1427 (m), 1356 (s), 1241 (m), 1171 (s), 1095 (s),1021 (w) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{18}H_{19}NnaO_5S$ $[M+Na]^+$: 384.0876; found 384.0884;

m.p.: 143 – 146 °C;

3-(4-bromo-3-fluorophenyl)-5-(morpholinomethyl)-5λ^3-oxazolidin -2-one, 3.53



Following a procedure based on that reported by Wagner *et al*.[121] To a mixture of morpholine (0.2 mL, 0.23 mmol) and dibasic potassium phosphate hydrate (0.52 g, 0.23 mmol) in DMSO (1 mL) was added (3-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl-4-methylbenzenesulfonate (0.05 g, 0.11 mmol), and the resulting mixture was stirred at 60 °C for 18 hours. The resulting solution was cooled to

room temperature, diluted with ethyl acetate (5 mL) and water (5 mL), then extracted 3 times with 5 mL of EtOAc. The combined organics were washed with water (10mL) and concentrated under reduced pressure to give the product as a pale pink solid (0.040 g, 94%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.53 (dd, J_{HF} = 7.3, 2.8 Hz, $1H_{ar}$, Ph), 7.50 (d, J_{HH} = 8.0 Hz, $1H_{ar}$, Ph), 7.17 (dd, J_{HH} = 8.9, 2.6 Hz, $1H_{ar}$, Ph), 4.85-4.74 (m, 1H, $CH_2C\underline{H}CH_2$), 4.04 (app. t, J_{HH} = 8.8 Hz, 1H, $OCHC\underline{H_2}NCH_2$), 3.79 (dd, J_{HH} = 8.8, 7.0 Hz, 1H, $OCHC\underline{H_2}NCH_2$), 3.70 (t, J_{HH} = 4.5 Hz, 4H, $O(C\underline{H_2})_2$), 2.65-2.51 (m, 4H, $N(C\underline{H_2})_2$);

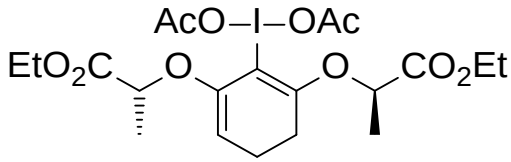
^{13}C NMR: (100 MHz, $CDCl_3$) δ 159.7 (d, J_{CF} = 246.0 Hz, CF), 154.5 (C=O), 139.3 (d, J = 9.9 Hz, $\underline{Ph}CH_3$), 133.8 (d, J = 1.6 Hz, PhS), 114.7 (d, J = 3.4 Hz,), 106.9 (d, J = 27.6 Hz), 103.5 (d, J = 21.3 Hz), 71.6 (CH), 61.8 ($O(\underline{C}H_2CH_2)_2$), 54.8 ($\underline{C}H_2N(CH_2CH_2)_2$, 49.0 ($N(\underline{C}H_2CH_2)_2$), 21.3 ($Ph\underline{C}H_3$);

FT-IR: v 2857 (w), 1742 (s), 1609 (w), 1497 (s), 1417 (s), 1335 (m), 1226 (s), 1112 (s), 1049 (s), 1012 (s) cm^{-1};

HRMS: (DESI-TOF) calculated for $C_{14}H_{16}FBrN_2O_3$ $[M+H]^+$: 359.0401; found 359.0409;

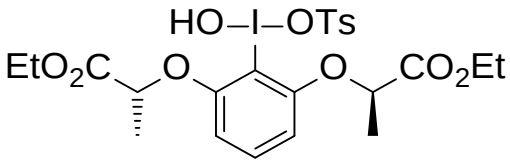
m.p.: 110 – 113 °C, (determined by DSC);

diethyl 2,2'-((2-(diacetoxy-l3-iodaneyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropanoate, 3.54



Using the method developed by Wirth and Farid.[123] A solution of iodoarene (0.19 g, 0.44 mmol) and Selectfluor® (0.78 g, 2.20 mmol) and (4.4 mL) AcOH in 14 mL MeCN was stirred overnight at rt. The solvent was evaporated in vacuo and 100 mL water was added to the residue, the resulting solution was extracted with (3 x 50 mL) DCM and washed with 100 mL water. The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure, used without characterisation.

(2*R*,2'*R*)-diethyl-2,2'-{[2-(hydroxy)(tosyloxy)-iodanyl)-1,3-phenylene]bis(oxy)}dipropanoate, 3.55



Using the method developed by Carman and Koser.[133] A hot solution (80 °C) of iodoarene diacetate (0.10 g, 0.18 mmol, 1 eq.) in dry MeCN (0.4 mL) was poured into a hot solution (80 °C) of *p*-PsOH.H_2O (0.05 g, 0.24 mmol, 1.3 eq.) in dry MeCN (0.4 mL). The solution was heated for 15 mins, then stirred overnight at room temperature. The solution was evaporated leaving an orange oil (~0.17 g, ~98%). The product was used without further purification or characterisation.

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