Development of Unconventional Amide Bond Forming Methodologies

Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

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Under the supervision of Prof. Stephen Connon

January 2020
Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others.

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Amy Maguire

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Abstract

A novel methodology for the protection of amines and diamines using 2,2-pyridil, under the influence of N-heterocyclic carbene (NHC) catalysis, has been developed. Extensive experimentation which included the design and synthesis of three generations of benzil substrates was necessary to identify 2,2-pyridil as an excellent amine acylating agent. This methodology is capable of distinguishing between two amines, characterised by small differences in steric bulk. One example which is particularly impressive is the ability of this NHC-catalysed system to distinguish between two secondary amines in a diamine differing by only one carbon unit; i.e. an N-Me substituted amine was exclusively acylated in the presence of an N-Et substituted unit.

Alkylation of the nitrogen atom of the subsequent pyridoyl amides derived from the chemoselective acylation of amines by 2,2-pyridil, allowed for amine deprotection. A novel set of conditions were developed which allowed for the deprotection without requiring the harsh acidic and basic hydrolytic conditions associated with cleaving benzoyl units from amines. Hereby, this methodology can be utilised as a highly chemoselective protecting group for amines and amino acids.

The development of a new strategy to carry out the aminolysis of tetrachloroisopropoxycarbonyl (TCIC) -substituted azlactones via a phenolic ester intermediate has been carried out. Due to the difficulties associated with controlling the addition of amines to azlactones under catalyst influence, the aminolysis of azlactones under DKR conditions to synthesise orthogonally protected peptides, has so far, to the best of our knowledge, not been achieved. Through use of a substituted phenolate anion, the alcoholysis of azlactones under the control of phase-transfer catalysis (PTC) furnished phenolate esters, which are readily displaced by an amine nucleophile to synthesise orthogonally protected amides and dipeptides. These reactions proceeded with high product yields however, the employment of chiral PTCs failed to invoke high product enantioenrichment. Further experimentation and computational studies are necessary to fully understand this mode of catalysis and may garner further insight into how enantioselectivity in the products may be achieved. However, this novel methodology is, to our knowledge, the first example of racemic azlactones being used to carry out peptide coupling without requiring a S,N-acyl transfer as with NCL or an O,N-acyl transfer as previously reported in the literature to achieve chemical ligation.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric-pressure chemical ionization</td>
</tr>
<tr>
<td>app. d</td>
<td>Apparent doublet</td>
</tr>
<tr>
<td>app. s</td>
<td>Apparent singlet</td>
</tr>
<tr>
<td>app. t</td>
<td>Apparent triplet</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-Bi-2-naphthol</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric(IV) ammonium nitrate</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>conc.</td>
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</tr>
<tr>
<td>conv.</td>
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</tr>
<tr>
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<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>CSP</td>
<td>Chiral stationary phase</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>Doublet of doublet of doublets</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DKR</td>
<td>Dynamic kinetic resolution</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
</tbody>
</table>
DMSO  Dimethyl sulfoxide
dr    Diastereomeric ratio
EDC   $N$-(3-Dimethylaminopropyl)-$N'$-ethylcarbodiimide
EDG   Electron donating group
$ee$  Enantiomeric excess
Ei    Electron ionisation
equiv. Equivalent
ESI   Electrospray ionization
Et    Ethyl
EtOAc Ethyl acetate
EtOH  Ethanol
EWG   Electron withdrawing group
EXSY Exchange spectroscopy
h     Hours
HFIP  1,1,1,3,3,3-Hexafluoroiso-propyl alcohol
HMBC  Heteronuclear Multiple Bond Correlation
HOAt  1-Hydroxy-7-azabenzotriazole
HOBt  1-hydroxybenzotriazole
HOMO  Highest occupied molecular orbital
HPLC  High Performance Liquid Chromatography
HRMS  High-resolution mass spectrometry
HSQC  Heteronuclear Single Quantum Coherence
$i$-  iso-
IPA   iso-propyl alcohol
$i$-Pr Isopropyl
IR    Infrared
IUPAC International Union of Pure and Applied Chemistry
KR    Kinetic resolution
lit.  Literature
LRMS  Low-resolution mass spectrometry
LUMO  Lowest unoccupied molecular orbital
m     Multiplet
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>m-</td>
<td>meta-</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine oxidases</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>ml/z</td>
<td>Mass/Charge</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>mol. sieves</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl-tert-butyl ether</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCL</td>
<td>Native chemical ligation</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NDMBA</td>
<td>N,N’-dimethylbarbituric acid</td>
</tr>
<tr>
<td>NEt3</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NMA</td>
<td>N-methylacetylamide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>o-</td>
<td>ortho-</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
</tr>
<tr>
<td>p-</td>
<td>para-</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase-transfer catalyst</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>p-TSA</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>s.t.p.</td>
<td>Standard temperature and pressure</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>t-</td>
<td>tert-</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-$n$-butyl ammonium fluoride</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetra-$n$-butyl ammonium bromide</td>
</tr>
<tr>
<td>TBACl</td>
<td>Tetra-$n$-butyl ammonium chloride</td>
</tr>
<tr>
<td>TBAOAc</td>
<td>Tetra-$n$-butyl ammonium acetate</td>
</tr>
<tr>
<td>TBAOBz</td>
<td>Tetra-$n$-butyl ammonium benzoate</td>
</tr>
<tr>
<td>$t$-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>$t$-BuOH</td>
<td>tert-Butyl alcohol</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TCIC</td>
<td>Tetrachloroisopropoxycarbonyl</td>
</tr>
<tr>
<td>TCP</td>
<td>$N$-tetrachlorophthaloyl</td>
</tr>
<tr>
<td>temp.</td>
<td>Temperature</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethyl-1-piperidinyloxy</td>
</tr>
<tr>
<td>$tert$-</td>
<td>tertiary-</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
</tbody>
</table>
Chapter 1  Carbenes

1.1.1  General overview
A carbene is a neutral species which contains a divalent carbon atom and is represented by the general formula R₂C:. Bearing a six-electron valence shell, carbenes do not satisfy the octet rule, making them a reactive species with properties similar to typical two-electron donors such as phosphines and amines. In 1835, Dumas attempted to free methylene (H₂C:) from its then believed hydrated complex, methanol (CH₂·H₂O) via treatment with sulfuric acid.¹ Although Dumas failed to generate the reactive intermediate methylene, Guether’s efforts proved more effective in 1862 when he generated dichlorocarbene (Cl₂C:) through the base-catalysed α-elimination of HCl from chloroform (or as Guether viewed it at the time, CCl₂·HCl).² Today, the most common methods to generate carbenes are from α-eliminations, deprotonation of a carbocation and formation from diazocarbonyl compounds and tosylhydrazones.³ Pioneering works by Büchner⁴ Curtius⁵ and Staudinger⁶ demonstrated the synthetic utility of these very interesting intermediates. Subsequently, carbenes have been introduced as valuable ligands in transition metal catalysis; as demonstrated initially by Fischer⁷ and Schrock⁸ and, over a century later, carbenes are still being studied due to their wide-ranging utility in many reactions of synthetic interest.

1.1.2  Singlet and triplet carbenes: structure and bonding
There are two classifications of carbenes based upon their respective electron configurations: singlet and triplet carbenes. The valence electrons of singlet carbenes are spin-paired while triplet carbenes contain two unpaired electrons. As carbenes contain only six valence electrons and must accommodate two substituents, there are two possible geometries that their carbon centre can adopt: linear or bent. Those with a linear geometry will have an sp-hybridised carbene centre, as is seen with alkynes. The bonding electrons are accommodated in the sp-orbitals while the two non-bonding electrons occupy two separate p-orbitals (Figure 1, A). If, on the other hand, the carbene centre adopts a bent geometry, the degeneracy of the molecule is broken and the resulting carbene is now sp²-hybridised.³ The electronic configuration of a carbene with bent geometry (which is more commonly found than those with a linear geometry) can occupy three degenerate sp²-orbitals and one p-orbital, which is higher in energy. The two possible electronic configurations for a carbene with a bent geometry are shown in Figure 1, B-C.
In the case of singlet carbenes, all electrons are spin-paired and housed in an \( sp^2 \)-orbital, leaving a vacant p orbital (Figure 1, B), whereas triplet carbenes contain two unpaired electrons, one in an available \( sp^2 \)-orbital and the other in a high energy p-orbital (Figure 1, C).\(^9\) The ground state multiplicity of a carbene carbon is influenced by the adjacent substituents. The influence of these substituents can be analysed based on their steric and electronic effects.

Steric effects associated with the carbene substituents play a pertinent role in dictating the carbene ground state electronic configuration. In triplet carbenes, as one electron is accommodated in a p-orbital and another in a non-bonding \( sp^2 \)-orbital, the electronic repulsions between these electrons and the neighbouring substituents is lessened resulting in larger bond angles (130-150°) being observed between the substituents (Figure 2).\(^3\) Meanwhile, analogous steric repulsion in singlet carbenes is much greater due to the presence of a pair of electrons in the \( sp^2 \)-orbital which repel the adjoining substituents-lessening the observed bond angle between them (100-110°).\(^3\)

It stands to reason that carbenes with bulky substituents will tend to adopt a triplet electronic ground state configuration in order to minimise the steric repulsions experienced by these bulky groups.\(^10,11\)
In general, carbenes are considered more stable when they possess a triplet ground state. This spin state is lower in energy due to the electronic repulsions required to pair the electrons in singlet carbenes. However, if a carbene has two electron-donating substituents (such as F, -Cl, -Br, -I, -NR₂, -PR₂, -OR, -SR, -SR₃) the carbene is predicted to be a bent singlet carbene. An example of this can be seen in dichlorocarbene (Cl₂C:). The lone pairs of the substituent chlorine atoms interact with the carbene carbon resulting in an increase in energy of the p-orbital, consequently favouring the non-bonding electrons to pair and move to a newly formed hybridised orbital (Figure 3). The stabilisation provided by the electronegative chlorine atoms in dichlorocarbene offsets the electronic repulsion associated with pairing the non-bonding electrons in a singlet carbene. Carbenes with electron-withdrawing substituents are also less electrophilic due to the increase in energy of the LUMO (Figure 3, this will be discussed further in Section 1.2).

Figure 3 Stabilisation of a singlet carbene by lone pairs on adjacent substituents

1.1.3 Typical reactivity of singlet and triplet carbenes

Carbenes are an electron-deficient species and can be considered analogous to carbocations in that they are highly electrophilic. However, unlike carbocations, carbenes are uncharged and so they can be attacked by nucleophiles that would not typically be considered as such, for example lone pairs, alkenes (electron-rich and electron-poor) and even alkanes.

Perhaps one of the most common uses of carbenes, and also one of the most common methods of synthesising cyclopropanes, is the reaction between a carbene and an alkene.
The spin-state of the carbene used in the cyclopropanation reaction determines the stereochemical outcome of the product.\textsuperscript{3} When a singlet carbene reacts, the mechanism is concerted and the stereochemistry of the alkene starting material is preserved in the cyclopropane product (Scheme 1). This is particularly impressive in the example below when (Z)-alkene 1 is used, as cis-cyclopropane 2 is the major product despite it being less stable than its trans counterpart 4.\textsuperscript{15}

\textbf{Scheme 1}  \hspace{1cm} Stereochemical outcome of cyclopropanations involving singlet carbenes

Cyclopropanation reactions with triplet carbenes on the other hand are non-stereospecific and so a mixture of products can be formed from a pure (Z)-alkene (Scheme 2).\textsuperscript{16}

\textbf{Scheme 2}  \hspace{1cm} Stereochemical outcome of cyclopropanations using triplet carbenes

The differences in stereochemical outcome of the reaction when triplet carbenes are used can be attributed to the stepwise reaction mechanism. Unlike the case with singlet carbenes; in which the reaction mechanism is concerted (Scheme 1), with triplet carbenes, a concerted reaction mechanism is impossible. Once the carbene carbon has added to the alkene, the resulting diradical intermediate 9 must now wait until one of the spins inverts for the second C-C bond to be formed (Scheme 3).\textsuperscript{3} In order for this spin-flipping to occur, intermediate 9 must collide with another molecule (usually a solvent molecule). However, this can be a slow process relative to the free rotation around the C-C bond in 9, thus the product can be a mixture of both cis- and trans-stereoisomers.
Mechanistic rationale for stereochemical outcome of triplet carbene cyclopropanations

As well as cyclopropanation reactions, carbenes are often used in insertion reactions with C-H bonds to form new C-C bonds. Similar to the cyclopropanation reaction, triplet carbenes are non-regioselective towards insertion. Transition metals (such as rhodium, ruthenium, iridium etc.) have been introduced in this process to stabilise the carbene and increase regioselectivity.\(^\text{17}\) This methodology has been used in the synthesis of natural products such as the work by Lee et al. to make the antibiotic platensimycin\(^\text{18}\) and by Cane and co-workers to produce pentalenolactone.\(^\text{19}\) Another frequent use of carbenes are in rearrangement reactions, perhaps the most notable of these being the Wolff rearrangement.\(^\text{20}\) In this carbene rearrangement, an \(\alpha\)-diazocarbonyl \(\text{12}\) undergoes decomposition by elimination of nitrogen gas to form an \(\alpha\)-keto-carbene intermediate \(\text{13}\) (Scheme 4). This intermediate undergoes a rapid [1,2]-alkyl/aryl shift to produce ketene \(\text{14}\), which can be hydrolysed to form carboxylic acids or intercepted with nucleophiles such as amines and alcohols to give amide or ester products \(\text{15}\), respectively.

**Scheme 4**  Mechanism of the Wolff rearrangement

### 1.1.4 Persistent carbenes

The electron deficient nature of free carbenes mean that they are traditionally considered unstable, transient intermediates, studied only indirectly, for example by trapping reactions. Despite this, much effort has gone into the isolation and study of carbenes; with initial reports dating as far back as 1835.\(^\text{21}\) Work by Wanzlick\(^\text{22-26}\) in the 1960s, Bertrand\(^\text{27,28}\) in the 1980s and Arduengo\(^\text{29}\) in the 1990s have resulted in the synthesis of an array of persistent carbenes (Figure 4).
While Bertrand et al. reported the first isolatable carbene stabilised by favourable interactions with adjacent phosphorus and silicon substituents in 1988, Arduengo and co-workers were the first to isolate a stable crystalline carbene: 1,3-di-1-adamantyl-imidazol-2-yldene (16, IAd). This discovery was spearheaded by earlier insightful studies by Öfele and Wanzlick into metal-carbene complexes.

With the isolation of 16, there has been an explosion of experimental and theoretical research into NHCs, with vast libraries of them having been synthesised. Carbene 16 is a diaminocarbene or as it will be referred to hereinafter, an N-heterocyclic carbene (NHC) and will be the carbene that is the subject of this thesis.

1.2 N-Heterocyclic carbenes
An N-heterocyclic carbene (NHC) is generally defined as a heterocyclic species, in which the carbenic carbon is adjacent to at least one nitrogen atom. In contrast to most ‘classical’ carbenes, NHCs have a singlet ground state electronic configuration. The inherent cyclic.

Figure 4  A selection of common B, N, O, Si, P and S-containing carbenes

Figure 5  IAd, the first stable crystalline carbene isolated by Arduengo et al.
conformation of NHCs contributes to the singlet state by forcing the carbene carbon into a bent, trigonal arrangement.\textsuperscript{32} The highest occupied molecular orbital (HOMO) of an NHC can be described as an sp\textsuperscript{2}-hybridised lone-pair, while the lowest occupied molecular orbital (LUMO) can be described as an empty p-orbital.\textsuperscript{32} The adjacent nitrogen atoms in NHCs stabilise the carbene carbon through a synergistic ‘push-pull’ effect (Figure 6).

![Figure 6](image)

**Figure 6** Schematic depiction of the ‘push-pull’ effect observed in NHCs

Electron density is inductively withdrawn from the carbene centre through the carbon-nitrogen σ-bond framework, concurrently, the nitrogen atom’s lone pair donates electron density into the empty p-orbital of the carbenic carbon. This stabilisation increases the energy gap between the HOMO and the LUMO making the LUMO sufficiently high in energy that it cannot readily be filled by electrons from a nucleophile. Therefore, NHCs are regarded as nucleophilic not electrophilic.

### 1.2.1 Historical perspective

As discussed in Section 1.1.4, Wanzlick found that the stability of carbenes can be enhanced by the addition of adjacent nitrogen atoms, which led to the synthesis of amino carbenes (depicted in Figure 4) and later NHCs.\textsuperscript{22–26} In 1960, Wanzlick and Schikora attempted to isolate a carbene from imidazolidine \textbf{17} via thermal elimination of chloroform to form 1,3-diphenylimidazolidin-2-ylidene (\textbf{18}, Scheme 5).\textsuperscript{23} Carbene \textbf{18} was not isolated as it was found to dimerise to form \textbf{19} due to its inherent reactive nature.

![Scheme 5](image)

**Scheme 5** Attempts by Wanzlick to isolate carbene \textbf{18}
Although Wanzlick postulated that the stability associated with NHCs was both sterically and (more importantly) electronically influenced, he failed to isolate a stable NHC in his lifetime. The first isolated carbene species, $\text{16}$, reported by Arduengo et al.$^{29}$ demonstrates the relative stability of the carbene carbon atom due to both electronic and steric effects of the NHC species (Scheme 6).

Scheme 6 Preparation of the first stabilised carbene by Arduengo et al.

Prepared via deprotonation of salt $\text{20}$ by sodium hydride to carbene $\text{16}$ is obtained as crystals, which are stable in the presence of both air and moisture.$^{29}$ Although the steric bulk of the adamantyl groups adjacent to the carbene carbon provide kinetic stabilisation of $\text{16}$, it is the electronic factors at play which contribute most to its unprecedented stability. Arduengo went on to synthesis an array of NHCs,$^{33–35}$ and today there are several types of NHCs (both achiral and chiral), available in the literature.

1.2.2 Classification and structure

With Wanzlick’s initial studies into NHCs focussing on those with an imidazoline core, research efforts since then have moved away from this structure. As mentioned in Section 1.2.1, Arduengo’s pioneering work in synthesising libraries of NHCs has inspired the development of a range of ion-based heterocyclic carbene salt precursors. Among those are thiazolium salts, deprotonated in situ to produce the active carbene, notably used by Ugai in 1943 to carry out the thiazolylidene-catalysed benzoin condensation using thiamine chloride ($\text{36}$, vitamin B1, Scheme 10).$^{36}$ The first commercially available carbene was reported by Teles and Enders in 1995.$^{37}$ The novel triazolium salt precursor, 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ium perchloroate ($\text{21}$, Scheme 7) underwent reaction with sodium methoxide to produce adduct $\text{22}$ which when heated to 80 °C undergoes thermal decomposition to produce triazolyllidene carbene $\text{23}$; which became the first carbene to be marketed commercially (ACROS).$^{38}$
Scheme 7    Teles and Enders synthesis of 23, the first commercially available carbene

Rovis et al. went on to develop novel achiral- and chiral-bicyclic triazolium salts which have seen triazolylidenes become perhaps the most commonly utilised NHCs in the field.\(^\text{39}\) This is due to their tunability in terms of structure and their enhanced stability which stems from the addition of another nitrogen atom in the heterocyclic ring that aids in stabilising the carbene through the synergistic ‘push-pull’ effect (discussed in Section 1.2). There are numerous examples of triazolium-based NHC precatalysts in the literature, a sample of which\(^\text{39–43}\) is shown below in Figure 7. Each of these precatalyst salts can be deprotonated by a base to give the active carbene species.

![Scheme 7](image)

**Figure 7**    A selection of triazolium precatalysts currently used in the field

1.3    \textit{N}-Heterocyclic carbenes and the Benzoin condensation

The use of NHCs as ligands for metal-based catalysis is well studied,\(^\text{32}\) however due to their low cost and toxicity, the use of NHCs as alternatives to transition-metal catalysis has garnered much interest. While the use of NHCs as organocatalysts dates back to their application by Ugai in 1943,\(^\text{36}\) following reports by Arduengo and Enders in the 1990s, there has been much research conducted in this area.\(^\text{44,45}\) Aside from the reduced cost and low-toxicity associated with using NHCs as organocatalysts, the primary advantage with their use is the ability of NHCs to reverse the polarity of a reactant in a reaction, coined by Seebach as an ‘\textit{umpolung}’ reaction’.\(^\text{46}\) Although there are many organocatalytic reactions that NHCs
have been employed in, the most famous and well-studied amongst these is possibly the Benzoin condensation.

1.3.1 Discovery of the Benzoin condensation

The earliest documented benzoin condensation was carried out by Liebig and Wöhler in 1832. While carrying out research on bitter almond oil, they found the self-condensation of benzaldehyde (30) to the α-hydroxyketone benzoin (31) occurred in the presence of a cyanide ion (generated from hydrogen cyanide under basic conditions, Scheme 8).

Scheme 8 The first benzoin condensation carried out by Liebig and Wöhler

Since the discovery of the self-condensation of 30, it took more than 70 years for the mechanism of this reaction to be published and the role of cyanide in this reaction to be explained.48

1.3.2 Mechanism of the reaction: cyanide and thiamine-mediated benzoin condensation

In 1839, Zinin introduced the first cyanide-mediated catalytic benzoin condensation, however it was in 1904 that Lapworth proposed a possible reaction mechanism (Scheme 9).48 In Lapworth’s proposed mechanism, the first step in the reaction is a nucleophilic attack of a cyanide ion on 30 to form oxyanion 32. Upon protonation of oxyanion 32, a neutral species; cyanohydrin 33, is formed. The acidic α-proton of 33 is deprotonated to form an acyl anion equivalent 34a which can be depicted as the vinylidene amide 34b. Nucleophilic attack of 34a upon another equivalent of 30 results in the formation of oxyanion 35, which upon proton transfer leads to tetrahedral intermediate 36, that collapses to render benzoin (31) and regenerates a cyanide ion.
In 1943, Ugai discovered that thiazolium salts can replace the cyanide ion in the self-condensation of \(30\) to \(31\). However, Breslow was the first to investigate this process and establish a mechanism in 1958 (Scheme 10). Similar to the role of the cyanide anion in Lapworth’s proposed mechanism (Scheme 9), Breslow postulated that triethylamine deprotonates the C-2 position of the thiazolium salt \(36\) to yield the active carbene species \(37\). A reversible nucleophilic attack of \(37\) on \(30\), forms tetrahedral intermediate \(38\), which upon proton transfer furnishes the resonance-stabilised hydroxylenamine intermediate \(39\), now commonly known as the Breslow intermediate. This umpolung species \(39\) attacks another molecule of \(30\) to form intermediate \(40\). Following a proton transfer \(41\) is formed, after which the active carbene species \(37\) is eliminated and formation of \(31\) takes place.

During his research into the mechanism of the benzoin condensation, Breslow also clarified that it is in fact the thiazolium salt that is deprotonated to form the active carbene species in situ, thus the thiazolium salt is acting itself as a precatalyst.
1.4 **N-Heterocyclic carbene-mediated oxidative esterifications and thioesterifications**

The prevalence of the ester and thioester functional group in both nature and synthetic chemistry cannot be overstated.\(^{52,53}\) Esters are most commonly accessed by activation of the parent carboxylic acid via an acyl chloride or an anhydride followed by acyl transfer to a nucleophilic alcohol. Similarly, thioesters are most commonly synthesised by the reaction between an acid chloride and an alkali metal salt of a thiol.\(^ {54}\) Due to the synthetic importance of esters and thioesters, a methodology that avoids the use of stoichiometric reagents required in their syntheses is desirable, therefore, research into the NHC-catalysed esterification and thioesterification of aldehydes has been undertaken.

### 1.4.1 Studies with external oxidants

In 2007, Scheidt reported an NHC-catalysed oxidative esterification of aldehydes in the presence of an external oxidant.\(^ {55}\) This work comprised a one-pot conversion of allylic, benzylic and propargylic alcohols to esters using triazolium precatalyst 24, DBU and a large excess of MnO\(\text{2}\) as the oxidant (Scheme 11).
Scheme 11  First reported oxidative esterification by Scheidt

In Scheidt’s proposed mechanism (Scheme 12), alcohol 42 is first oxidised to aldehyde 45 by MnO₂. Simultaneously, triazolium precatalyst 24 is deprotonated to the active NHC species 44 by DBU, which then nucleophilically attacks aldehyde 45 to form tetrahedral intermediate 46. Intermediate 46 then has two fates; proton transfer to form the Breslow intermediate 47 or, fast oxidation by excess MnO₂ to form the electrophilic acyl azolium ion 48. Unsurprisingly, 46 undergoes the faster reaction to acyl azolium ion 48, thus suppressing formation of the Breslow intermediate 47. Acyl azolium ion 48 is then attacked by an alcohol to form ester 43 and regenerate the active carbene species 44.

Scheme 12  Scheidt’s proposed pathway for the tandem oxidation process

Although a synthetically useful development, Scheidt’s work is limited to allylic, benzylic and propargylic alcohols, but does allow for the use of a range of nucleophilic alcohols. This report detailed the desymmetrisation of a meso-1,2-diol when it was used as the nucleophilic component in the presence of a chiral triazolium precatalyst. The following year, Schiedt went on to further expand upon this work by exploring the scope of the unactivated aldehydes being used. Modification of the solvent used and the catalyst structure allowed for a broad scope of coupling partners to be tolerated in this reaction, with epimerisable
aldehydes being transformed to the corresponding esters without loss of enantiomeric excess.\textsuperscript{56}

However, in the interim, Connon and co-workers published a report on the NHC-mediated oxidative esterification of aldehydes with the use of an external oxidant.\textsuperscript{57} They reported the esterification of a range of aldehydes with nucleophilic alcohols in moderate to excellent yields, in the presence of thiazolium precatalyst 49, triethylamine and azobenzene (50) as the oxidant (Scheme 13). This methodology exhibited a wide substrate scope with respect to the aldehyde component; both aromatic (electron-rich and electron-deficient) and aliphatic aldehydes were compatible, as were both primary and secondary alcohol coupling partners.

\begin{equation}
\text{O} \quad \text{H} \quad + \quad \text{R}^2\text{OH} \quad \xrightarrow{49 \text{ (5 mol\%), } \text{NEt}_3 \text{ (7.5 mol\%)}} \quad \text{R}^1\text{OR}^2 \quad \text{up to 97%}
\end{equation}

\textbf{Scheme 13} Connon co-worker’s NHC-catalysed aldehyde esterification

Interest in other oxidants have since been explored, such oxidants include; nitrobenzene,\textsuperscript{58} TEMPO,\textsuperscript{59} diphenoquinone\textsuperscript{60} and phenazine.\textsuperscript{61}

Although there are several publications detailing the NHC-catalysed oxidative esterification of aldehydes, fewer reports have investigated the analogous NHC-catalysed thioesterification of aldehydes.

Murata was the first to produce thioesters \textit{via} an NHC-catalysed oxidative thioesterification of an aldehyde using thiazolium precatalyst 51 (Scheme 14).\textsuperscript{62} Although this was the first example of such, the reaction was limited in scope, only a modest selection of \( p \)-substituted aromatic aldehydes were tolerated, while octanethiol was the only thiol employed in this particular report. The reaction could only be carried out using azobenzene (50) as the oxidant, which resulted in the formation of an unwanted side-product (acylated hydrazobenzene 52 formed from the \textit{in situ} reduction of azobenzene followed by acylation by the acyl azolium ion).
Scheme 14  Thioesterifications carried out by Murata et al. in 2005

The following year, Sohn and Bode also carried out the NHC-catalysed oxidative esterification and thioesterification of aldehydes. A range of enantiopure formylcyclopropanes were employed in this reaction, however the scope of the thiols used was limited with only the long-chain saturated thiol, dodecylmercaptan being utilised.

Takemoto published an extensive study into the NHC-catalysed thioesterification of aldehydes in 2011 using phenazine as the external oxidant (Scheme 15). Varying the NHC precatalyst and base used, a wide range of both aromatic and aliphatic aldehydes were tolerated in this reaction, furnishing the corresponding thioesters in moderate to excellent yields (60-99%). Furthermore, both alkyl and aryl thiols could be employed in this reaction.

Scheme 15  Takemoto’s NHC-catalysed thioesterification of aldehydes

Following Takemoto’s report, further investigation into these types of thioesterifications have been carried out. Yadav detailed the NHC-catalysed thioesterification of aromatic aldehydes and enals using disulfides as the thiol source and DEAD as the oxidant, to furnish the corresponding thioesters and \((\alpha,\beta\)-unsaturated thioesters in good to excellent yields. While Jang et al. demonstrated the NHC-catalysed oxidative coupling of a range of aromatic aldehydes with alcohols and thiols using TEMPO as the oxidant. Boydston and co-workers have also reported the thioesterification of aromatic and aliphatic aldehydes using thiols and
an anodic electrochemical oxidation to replace the need for a stoichiometric external oxidant.\textsuperscript{66}

### 1.4.2 Studies involving internal redox

Fewer studies have been carried out in the area of oxidative esterifications using air or oxygen as the oxidant. Most systems which negate the need for added stoichiometric oxidants depend upon a cooperative metal/NHC catalysis that employs molecular oxygen as the terminal oxidant, to re-oxidise the metal centre.\textsuperscript{67,68} While Yashima demonstrated NHC-catalysed aerobic esterifications using a flavin-derived co-catalyst\textsuperscript{69} there are limited studies on such esterifications using strictly aerobic, oxidative conditions.

Yoshida \textit{et al.} were the first to report the NHC-catalysed aerobic oxidation of aromatic aldehydes to the corresponding esters.\textsuperscript{70} Their work focused on transformations of aromatic aldehydes to carboxylic acids in the presence of a sulfoxyalkyl substituted precatalyst \textsuperscript{55}, DBU and using DMF/water as the solvent system (Scheme 16). To further demonstrate the potential of this type of catalysis, they carried out both esterifications and amidations.

![Scheme 16](image)

**Scheme 16** Aerobic aldehyde carboxylation using an imidazolium precatalyst

Yoshida’s suggested mechanism is reliant on the electron-withdrawing effect of the \textit{p}-nitro group, however his mechanistic rationale fails when the nitro group is moved to any other position on the aromatic ring.\textsuperscript{70}

Liu \textit{et al.} detailed the NHC-catalysed oxidative esterification of \textit{\alpha,\beta}\textendash unsaturated aldehydes with cinnamyl bromides using either air or MnO\textsubscript{2} as the oxidant in 2011.\textsuperscript{71} As well as providing a new protocol for esterifications of enals and cinnamyl bromide derivatives, Liu carried out mechanistic studies to ascertain information about the reaction pathway. Through isotope labelling experiments, the author concluded that the reaction path passes through an oxygen insertion type mechanism, which has subsequently been termed the ‘oxygenative’ esterification pathway (see Section 1.4.3). Two years later, Ukaji published his work on the NHC-catalysed oxidative coupling of aldehydes with \textit{N}-acylureas under aerobic conditions.\textsuperscript{72} Using sets of experiments to examine the mechanism further (although they
did not carry out isotope labelling experiments) they found the reaction to also proceed \textit{via} an ‘oxygenative’ pathway, as suggested earlier by Liu.

NHC-catalysed aerobic esterifications of aldehydes with alcohols, without the need for added oxidants or co-catalysts, was reported in 2013 by Connon co-workers\textsuperscript{42} They reported the esterification of a range of aromatic aldehydes to the corresponding esters using precatalyst 25, DBU and a THF/alcohol solvent system at room temperature, under aerobic conditions (Scheme 17).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {$\text{R}^1\text{CHO}$};
\node (b) at (1,0) {$\text{R}^1\text{C}=\text{O}$};
\node (c) at (2,0) {$\text{R}^1\text{COO}\text{R}^2$};
\node (d) at (2,-1) {$\text{N}\equiv\text{N}$};
\node (e) at (2,-2) {$\text{I}^{-}$};
\node (f) at (3,0) {$\text{R}^1\text{C}=$};
\node (g) at (3,-1) {$\text{N}\equiv\text{N}$};
\node (h) at (3,-2) {$\text{I}^{-}$};
\node (i) at (4,0) {$\text{DBU (1.1 equiv.)}$};
\node (j) at (4,-1) {$\text{THF/R}^2\text{OH (1:1)}$};
\node (k) at (4,-2) {$\text{R}^1\text{C}=$};
\node (l) at (4,-3) {$\text{N}\equiv\text{N}$};
\node (m) at (4,-4) {$\text{I}^{-}$};
\node (n) at (5,0) {$\text{up to 96\%}$};
\node (o) at (5,-1) {$\text{rt, air}$};
\node (p) at (5,-2) {$\text{25}$};
\draw[->] (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g) -- (h) -- (i) -- (j) -- (k) -- (l) -- (m) -- (n) -- (o);
\end{tikzpicture}
\end{center}

Scheme 17 Connon co-worker’s NHC-catalysed esterification without the use of a co-catalyst or stoichiometric oxidant

Under the optimised reaction conditions, the esterifications proceeded successfully with aromatic aldehydes (electron-neutral, activated and deactivated were all tolerated) furnishing esters in moderate to excellent yields (up to 96%). \textit{Ortho}-substituted aldehydes did not perform well in this reaction with lower yields being observed (e.g. \textit{o}-tolualdehyde: 28% yield), while aliphatic aldehydes also were also not compatible with this reaction (hydrocinnamaldehyde, 15%). It should also be noted that this system requires the use of solvolytic alcohol which is not practical for an atom economic process.\textsuperscript{73} Although limited to aromatic aldehydes, this report was the first NHC-catalysed aerobic esterification of aldehydes without the employment of external additives.

1.4.3 \textbf{Proposed mechanism: oxygenative and oxidative pathways}

Prior to 2013, there were two proposed mechanisms for the NHC-catalysed esterification of aldehydes; these were classified as ‘oxidative’ and ‘oxygenative’ (Scheme 18).\textsuperscript{74} The manner in which the Breslow intermediate is oxidised distinguishes which pathway (‘oxidative’ or ‘oxygenative’) takes place. The initial steps in both pathways are the same; precatalyst 56 is deprotonated to produce the activated NHC 57, which, upon addition to the carbonyl moiety of aldehyde 58, forms the Breslow intermediate 59. It is at this stage of that the ‘oxidative’ and ‘oxygenative’ pathways diverge. In pathway A, the ‘oxidative’ pathway, the Breslow intermediate 59 is oxidised to the acyl azolium ion 60 by an external oxidant. The acyl azolium ion subsequently undergoes nucleophilic attack by an alkyl alcohol 61 to afford tetrahedral intermediate 62. Subsequent collapse of intermediate 62 results in formation of ester 63 and regeneration of carbene 56.
In pathway B, the ‘oxygenative’ pathway, the fate of the Breslow intermediate 59 differs in that it is oxidised by molecular oxygen rather than a stoichiometric oxidant. Transfer of an oxygen molecule to 59 establishes the internal peroxy Zwitterion 64, which subsequently reacts with another molecule of aldehyde 58 (via peroxyacid intermediates) or enaminol 59 to form carboxylate ion 65. The carboxylate ion can form the corresponding carboxylic acid, 66, under acidic conditions or form an ester, 67, if trapped by an alkyl halide.71,75

![Scheme 18](image)

**Scheme 18** Current mechanistic rationales for NHC-catalysed oxidative esterifications using either molecular oxygen or an external oxidant

Until 2013, the aforementioned ‘oxygenative’ and ‘oxidative’ pathways were the two widely accepted rationales for the oxidative esterification of aldehydes via NHC catalysis. Having previously developed a new protocol for NHC-catalysed aerobic esterifications of aldehydes,42 Connon and co-workers carried out an array of experiments to probe the reaction mechanism further.76 Interest in further exploring this mechanism arose from the reaction between benzaldehyde (30) and isopropanol under the reaction conditions outlined in Scheme 17. They observed that isopropanol, a more hindered, less acidic alcohol, was inert in this reaction. They postulated that if the reaction proceeds through the highly electrophilic acyl azolium ion 60, steric hindrance should not affect the esterification
reaction, regardless of the alcohol. A mechanistic rationale of Connon’s proposed NHC-catalysed oxidative esterification is detailed in Scheme 19.

Scheme 19  Mechanistic rationale for the NHC-mediated oxidative esterification proposed by Connon and co-workers.\textsuperscript{76}

Precatalyst 25 is deprotonated to give the active carbene species 68, which attacks 30 to form the Breslow intermediate\textsuperscript{51} 69. The Breslow intermediate 69 subsequently attacks another molecule of 30, which results in elimination of carbene 68 and formation of benzoin (31). In the presence of DBU and oxygen, 31 is oxidised to a highly electrophilic species, benzil (70). As it was previously suggested that the reaction did not proceed through the acyl triazolium ion, they proposed that 70 is attacked by another molecule of carbene 68 to furnish tetrahedral intermediate 71. It is thought that intermediate 71 is attacked by methanol, likely under the influence of intramolecular general base catalysis, to generate intermediate, 72. Hemiacetal 72 can collapse to regenerate 69 and eliminate methyl benzoate (73) as the major product.

Additional observations were made while carrying out experiments to rationalise the reaction mechanism. Benzoin (31) will act as a nucleophile in the presence of oxygen, 70 and carbene
68. Under these conditions, 31 attacks the tetrahedral intermediate formed between 70 and 68 to form 74, the hydroacylation product. If 74 is further exposed to carbene 68, DBU and methanol, 73 can be formed via intermediate 75.

In another experiment, it was observed that if 70, in the presence of methanol but the absence of oxygen, is attacked by the nucleophilic Breslow intermediate 69, intermediate 76 is formed and carbene 68 is regenerated. In the presence of another molecule of 68, DBU and methanol, intermediate 76 is cleaved to form 31 and 73 via hemiacetal 77.

This mechanistic rationale is plausible as all the compounds highlighted in Scheme 19 along with benzil and benzoin, have either been isolated or detected in situ using ^1^H NMR spectroscopic methods.

1.5 N-Heterocyclic carbene mediated oxidative amidations

The amide functional group is ubiquitous throughout natural products, the pharmaceutical industry and synthetic chemistry, therefore it is surprising that there are a limited number of one-pot catalytic strategies for their syntheses. The most utilised methodologies for the synthesis of amides requires the stoichiometric activation of a carboxylic acid with a coupling reagent to form an activated acyl species, which is reacted with an amine to render the desired amide. The importance of amides mandates exploration into their synthesis by catalytic means, from alternative starting materials. In recent years, NHCs have become a popular mode of catalysis for amide bond formation.

1.5.1 Amidation of aldehydes via internal redox

Rovis demonstrated an example of an NHC-catalysed oxidative amidation in 2004. In the presence of NHC triazolium precatalyst 26, α-haloaldehydes were transformed into the corresponding esters or amides in good to excellent yields (Scheme 20).

![Scheme 20](image)

**Scheme 20**  Rovis et al.’s NHC-catalysed oxidative amidation of α-haloaldehydes

This methodology tolerated a range of nucleophiles; primary, secondary and aromatic alcohols as well as aniline, (the only example of an amidation in this paper). Rovis proposed that this mechanism proceeds via an internal redox pathway (Scheme 21).
In Rovis’ proposed mechanism, addition of active carbene species 80, to α-haloaldehyde 78 initiates formation of the Breslow intermediate 82 via oxyanion intermediate 81. The presence of a leaving group (i.e. the α-halogen atom) in 82 allows for production of enol 83 which, upon tautomerisation, forms the acyl azolium ion 84. This species can be trapped by a nucleophile to furnish ester/amide 79 and regenerate catalyst 80. Rovis provided a more in-depth account of the amidation reaction three years later. In this study he highlighted the use of 1-hydroxy-7-azabenzotriazole (HOAt) as a co-catalyst to assist in the internal redox reaction, which allowed for utilisation of a wider range of α-haloaldehydes and amines (Scheme 22).

Rovis suggested that HOAt was acting in a second catalytic cycle (Scheme 23) accompanying the NHC cycle detailed in Scheme 21. Upon formation of acyl azolium ion 84 (Scheme 21), it is intercepted by HOAt to form active ester 87 and regenerate 80. Attack
of 87 by an amine affords amide 88, and regenerates HOAt, which can now enter another catalytic cycle.

Scheme 23  Rovis’ mechanism for HOAt assisted NHC-catalysed oxidative amidation

The use of HOAt as a co-catalyst allowed for a variety of amines including; primary amines, secondary amines, electron-rich and electron-deficient aryl amines, Weinreb amine and amino esters to be employed in this reaction. Tolerance of a variety of α-haloaldehydes were also accounted for; both α- and β-branched aldehydes were possible coupling partners in this α-redox amidation reaction.

Concurrently, Bode published his findings into NHC-catalysed internal redox amidations of α-functionalised aldehydes. Similar to Rovis’ work, Bode found that in the presence of an appropriate NHC precatalyst, 89, base and co-catalyst, imidazole (90) - α-functionalised aldehydes can be transformed to the corresponding amides in moderate to excellent yields (Scheme 24).

Scheme 24  Bode’s NHC-catalysed oxidative amidation of α-functionalised aldehydes assisted by imidazole

A suite of amines were viable reaction partners, with primary and secondary amines, anilines and hydroxylamines all being tolerated. In terms of suitable α-functionalised aldehydes, a variety of formyl cyclopropanes were found to be efficient in this reaction. Alongside formyl cyclopropanes, α,β-unsaturated aldehydes were found to be a feasible choice of acyl donor, however, DIPEA was required as the base in reactions where enals are being used. The mechanism proposed by Bode was similar to that postulated by Rovis (Schemes 21 and 23).
Bode rationalised that the acyl azolium ion, analogous to 84, generated as demonstrated in Scheme 21, is intercepted by the co-catalyst imidazole (90) to form an activated carboxylate. Nucleophilic attack of this activated carboxylate by an amine generates amide 92 and releases imidazole.

1.5.2 Oxidative amidation of aldehydes via an active ester intermediate

Another example of NHC-mediated amide bond formation is the oxidative amidation of aldehydes via an active ester intermediate. In 2010, Studer reported NHC-catalysed amidations of aldehydes in the presence of an organic oxidant and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP, Scheme 25).\(^8\) In Studer’s proposed mechanism, nucleophilic attack of an active carbene species derived from NHC 24 on aryl and alkenyl aldehydes 93, followed by proton transfer, yields the Breslow intermediate 96. Oxidation of the 96 by an organic oxidant, 3,3’,5,5’-tetra-tert-butyldiphenoquinone (94) renders acyl azolium ion 97. Interception of 97 by HFIP forms the active ester intermediate 98 which upon interception by an amine nucleophile, generates amide 95 and HFIP as the by-product.

**Scheme 25**  Studer’s protocol for the oxidative amidation of aldehydes via an active ester intermediate

The scope of Studer’s report was limited to aryl and alkenyl aldehydes. Jiao et al. went on to further exploit the intermediacy of hexafluoroisopropyl esters, to form amides from NHC-catalysed oxidative esterifications of bromoenals and α,β-dibromoenoals.\(^8\) Again this process was very limited in scope with regards the aldehyde component of the reaction and required HFIP and the amine nucleophile to be employed in excess (1.5 and 2.5 equivalents, respectively).
In 2012, Yamada designed a methodology for the formation of amides from \(\alpha\)-unbranched aldehydes via an active ester intermediate (Scheme 26).

**Scheme 26** Amidations of \(\alpha\)-unbranched aldehydes carried out by Yamada et al.

In Yamada’s report, aldehyde 99 is first functionalised at the \(\alpha\)-position via formation of enamine 101 followed by electrophilic chlorination by \(N\)-chlorosuccinimide (NCS, Scheme 27). Imine 102 obtained by \(\alpha\)-chlorination of 101 can be hydrolysed to form aldehyde 103, which is subsequently attacked by the active NHC species generated from precatalyst 29. Elimination of the \(\alpha\)-chloro group followed by tautomerisation of the Breslow intermediate 104 leads to the formation of acyl azolium ion 106. Transfer of the acyl functional group of 106 to 1-hydroxybenzotriazole (HOBr) forms the active ester intermediate 107 which can be intercepted by an amine to form the desired amide 100.

**Scheme 27** Mechanism of Yamada’s amidations of \(\alpha\)-unbranched aldehydes
1.5.3 One-step oxidative amidations of aldehydes and benzils

While there is a plethora of methodologies available pertaining to the NHC-catalysed oxidative esterification of aldehydes (see Section 1.4). The analogous reaction for the synthesis of amides in one-step (without the need to have specific functionalities in the aldehyde partner or employ the use of an active ester intermediate) has been relatively underexplored by comparison.

Maheswari and co-workers showed in 2015 that aromatic aldehydes could be converted to the corresponding amide when catalysed by NHC 108, using NBS as a stoichiometric oxidant (Scheme 28, A).\textsuperscript{85} Good yields of the amides were reported (62-83% yields), but substrate scope was limited due to the restrictions imposed with using NBS as the oxidant. The following year, Brown et al. reported an innovative method involving NHC-catalysed oxidative amidations using anodic oxidation in flow.\textsuperscript{86} This methodology eliminates the need to use a stoichiometric oxidant additive or a pre-existing functionality within either substrate (Scheme 28, B). Although Brown reported high yields of amide products, this process does require the use of stoichiometric loadings of the thiazolium ion precatalyst 109 and the examples in this publication were limited to primary amines. Recently, Biju carried out oxidative amidations of aryl and vinyl aldehydes (used in excess, 2 equivalents) with the specialised amine, 2-aminobenzothiazole (110) using precatalyst 26 and oxidant 94 (Scheme 28, C).\textsuperscript{87} Several examples were reported in good to excellent yields (up to 93%) but the reaction was only shown to occur using amine 110 and its derivatives.
While carrying out mechanistic studies into the NHC-catalysed oxidative esterification of aldehydes, Connon and co-workers showed that benzaldehyde (30) could be converted to the corresponding pyrrolidine amide, albeit in low yield, under aerobic conditions (Scheme 29). The catalytic cycle for this reaction is the same as described in detail in Section 1.4.3 (Scheme 19) however, the alcohol nucleophile is replaced with an amine (pyrrolidine in the case of Scheme 29). Lower yields when pyrrolidine, a more nucleophilic but less acidic nucleophile, was used in this reaction were attributed to the additional steric bulk associated with the use of pyrrolidine, relative to the analogous alcohol nucleophile, methanol. Pyrrolidine encounters steric clashes with the phenyl group of 112 (Scheme 29) and its attack on the carbonyl of 112 is further hampered as doing so forms a congested quaternary centre adjacent to another quaternary centre (the preceding steps to 112 in the catalytic cycle are intermediates 68 to 71, detailed in Scheme 19). It is also worth noting that the esterification outlined in Scheme 17, required the use of the alcohol nucleophile as the solvent in the reaction, whereas pyrrolidine was employed in the analogous amidation reaction in a comparatively low excess of 2.5 equivalents (Scheme 29).
Scheme 29  Connon and co-workers oxidative amidation of benzaldehyde reported in 2013

Following this initial finding, Connon went on to develop an efficient NHC-catalysed oxidative amidation methodology which uses phenazine (53) as the stoichiometric oxidant. Initially Connon and co-workers used the reaction conditions as outlined in their earlier work into NHC-catalysed oxidative esterifications under aerobic conditions. However, replacement of methanol with pyrrolidine led to poor yields regardless of varying the solvent, reaction concentration, temperature, base, catalyst structure (both triazolium and thiazolium salt precatalysts were evaluated) and loadings of the amine nucleophile. Due to the low product yields observed, despite considerable endeavours in trying to optimise this reaction, Connon and co-workers investigated the step in the catalytic cycle attributing to such low yielding amide formation, when analogous esterifications proceeded so well.

As discussed in Section 1.4.3, benzoin (31) is oxidized to benzil (70) an electrophilic α-diketone, which undergoes nucleophilic attack by the active carbene species 68. The rest of the catalytic cycle proceeds as previously outlined (Scheme 19). Armed with this knowledge, 31 and 70 were both treated with pyrrolidine under the aerobic oxidative reaction conditions described in Scheme 29. The use of 31 as the electrophilic partner (Scheme 30, A) led to a low yield of amide 111 (26% yield), while use of 70 (Scheme 30, B) resulted in an improved yield of 66%.

Scheme 30  Oxidative amidation of benzoin and benzil using air as the oxidant
A competition reaction was carried out in this report by Connon and co-workers, to highlight the inferiority of the amine nucleophile in comparison to its alcohol counterpart. Benzaldehyde (30) was reacted with equimolar quantities of benzyl alcohol and pyrrolidine under the standard aerobic oxidative reaction conditions (Scheme 31). This experiment demonstrated that the alcohol nucleophile is far superior to the amine as ester 113 was formed in 76% yield while amide 111 was produced in only 24%. Interestingly, when 30 was reacted with benzyl alcohol, in the absence of pyrrolidine, no side-product (the carboxylic acid salt of DBU, 114) was detected, while the analogous reaction using pyrrolidine, without benzyl alcohol, produces the salt side product as the major product of the reaction. This insight led the authors to determine that in the case of amidations, which are slower relative to esterifications, an alternative, deleterious, aerobic oxidation pathway is at play, which causes formation of salt 114 as the major product of the reaction and, which cannot be suppressed upon rigorous drying of all reaction components.

![Scheme 31](image)

**Scheme 31**  Mechanistic experiment using benzyl alcohol and pyrrolidine

As a result, the removal of air and the screening of a wide array of oxidant additives was undertaken. Phenazine (53) was found to be the optimal oxidant in this amidation reaction and could be used in stoichiometric loadings (1 equivalent), and it could be recovered and recycled at the end of the reaction. The use of phenazine also allowed for the loading of amine used to be lowered from a relatively large excess (2.5 equivalents) to 1.2 equivalents. The yield of this reaction was enhanced further by use of a cooperative nucleophilic co-catalyst. It was reasoned that a nucleophilic co-catalyst could aid in another sluggish step in the catalytic cycle, attack of the amine on the catalyst-benzil adduct 112 (Figure 8). As this step is generally base-catalysed and results in the formation of an adduct with adjacent quaternary carbon centres, thought to be extremely sensitive to steric bulk of the nucleophile, Connon and co-workers hypothesised that the intervention of a nucleophilic co-catalyst
could aid in promoting higher yields of amide products. A screen of co-catalysts found 1,2,4-triazole (115) to be the most efficient in this transformation.

![Figure 8](image-url)

**Figure 8** Role of a nucleophilic co-catalyst in the NHC-catalysed oxidative amidation

With an optimised set of reaction conditions in hand, Connon demonstrated that the scope of this reaction could be extended to a range of aromatic aldehydes (including those with ortho-substituents) and both primary and secondary amines, producing a range of amides in good to excellent yields (Scheme 32). This methodology culminated in the one-step synthesis of the MAO-inhibitor drug, moclobemide (Hoffman-La Roche) in 92% yield from p-chlorobenzaldehyde and the commercially available amine, 4-(2-aminoethyl)morpholine.

![Scheme 32](image-url)

**Scheme 32** Connon’s optimised reaction conditions and the structure of MAO-inhibitor moclobemide

### 1.6 Amine protecting groups and N-protecting groups for amino acids

The propensity of basic nitrogen atoms to partake in unwanted side reactions often renders N-protectings necessary in organic synthesis. There are criteria that must be adhered to when developing new protecting groups; such as the stability of the protecting group to a range of reaction conditions, readily available starting materials and relative ease of deprotection.\(^89\) However, it is worth noting that due to the poor atom-economy associated with using protecting groups, their use should be minimised in an optimal synthetic route.\(^90\) The development of novel amine protecting groups (particularly those capable of being installed
chemoselectively) is an area of research that begs attention, particularly in the areas of peptide, nucleoside and polymer synthesis.\textsuperscript{89}

1.6.1 Commonly used amine protecting groups: an overview

A wide array of amine protecting groups are currently available and broadly speaking, amine protecting groups can be categorised into three main types: those that are acid labile, base labile and ‘others’ (cleaved by hydrogenolysis, fluoride ion \textit{etc.}). The most common amine protecting groups arise from the formation of amides, imides and carbamates respectively, with benzyl and sulfonamide derived protecting groups also commonly employed in organic synthesis.\textsuperscript{91} The installation of these protecting groups is generally carried out by the reaction between the amine of interest with a dicarbonate or an activated acid derivative. As there are a vast number of amine protecting groups available, only a selection of commonly employed strategies will be discussed in this thesis.

1.6.1.1 Acid-labile amine protecting groups

tert-Butoxycarbonyl (Boc, Figure 9) is one of the most frequently used acid-labile N-protecting groups in organic synthesis.\textsuperscript{92,93} The use of Boc as a protecting group for amino acids and in peptide synthesis has been widely studied.\textsuperscript{94,95} It is installed by reaction of the amine with di-\textit{tert}-butyl dicarbonate and is most often removed by treatment with 25-50\% TFA in CH\textsubscript{2}Cl\textsubscript{2}. Trityl (Trt) is a bulky amine protecting group (Figure 9), which is generally installed by reaction between the amine of interest and trityl chloride under basic conditions. The bulkiness of a trityl group can protect the \(\alpha\)-proton of a trityl-protected amino acid from base abstraction and subsequent racemisation.\textsuperscript{96} One of the most common methods to deprotect a trityl group is with 1\% TFA in CH\textsubscript{2}Cl\textsubscript{2}. Orthogonal deprotection strategies, \textit{i.e.} the ability to remove one protecting group selectively in the presence of other protecting groups, are necessary in multi-step syntheses. In order to achieve this, acid-labile protecting groups that can be deprotected at varying pHs have been developed. \(a,a\)-Dimethyl-3,5-dimethoxybenzyloxy carbonyl (Ddz,\textsuperscript{97} Figure 9) can be deprotected using 1-5\% TFA in CH\textsubscript{2}Cl\textsubscript{2} while 2-(4-biphenyl)isopropoxy carbonyl (Bpoc)\textsuperscript{98} can be removed with as little as 0.2-0.5\% TFA in CH\textsubscript{2}Cl\textsubscript{2}. Clearly, selective deprotection can be carried out using just the small sample of protecting groups outlined above due to their variant ability to withstand acidic conditions.
Figure 9   A selection of commonly used acid-labile N-protecting groups

1.6.1.2 Base-labile amine protecting groups

Some commonly used base-labile N-protecting groups include 9-fluorenylmethoxycarbonyl (Fmoc),<sup>99,100</sup> 2-(4-nitrophenylsulfonyl)ethoxycarbonyl (Nsc)<sup>101</sup> and N-tetrachlorophthaloyl (TCP, Figure 10).<sup>102</sup> Fmoc is widely used in peptide synthesis as a base-labile amino protecting group.<sup>91</sup> Its deprotection is generally carried out by secondary amine bases (piperidine is most often used as the base of choice)<sup>99,100,103</sup> and while Fmoc is stable to acid, under certain circumstances (in cases where Pd/C or PtO<sub>2</sub> are used as catalysts), it can be removed by catalytic hydrogenolysis. Nsc has become an attractive base-labile protecting group alternative to Fmoc in peptide synthesis.<sup>104–106</sup> Crystalline in structure, Nsc-amino acids are more soluble in organic solvents than their Fmoc-protected counterparts. Like Fmoc, Nsc can be deprotected under mild conditions, using organic amine bases such as piperidine or DBU.<sup>101</sup> TCP differs from other base-labile protecting groups as it masks the amine as an imide rather than an amide. The imide functionality makes the TCP group stable to most deprotection strategies (acid, base, hydrogenolysis) however, addition of the four chlorine atoms on the aromatic ring means that it can be removed under mild conditions using either hydrazine or 1,2-diamines in organic solvents.<sup>102</sup> It has been employed in recent times as a protecting group for amino acids,<sup>102,107,108</sup> and, previous to this, it was used as a protecting group in carbohydrate synthesis.<sup>109</sup> Installing the TCP group previously required heating the amine being protected at elevated temperatures, using Dean-Stark apparatus with tetrachlorophthalic anhydride however, milder conditions have since been developed which use microwave irradiation to achieve protection.<sup>110</sup> p-Methoxyphenyl (PMP) is another protecting group that can readily protect both amines and alcohols<sup>111,112</sup> and is cleavable at low pHs in aqueous media using ceric(IV) ammonium nitrate (CAN).<sup>112</sup>
1.6.1.3 Protecting groups removed under specialised conditions

There are several other sets of conditions that can be used to deprotect amino-protecting groups aside from acids and bases. Benzoylcarbonyl (Z, Figure 11) is perhaps the most extensively used α-amino-protecting group for peptide synthesis, and its deprotection is achieved by either catalytic hydrogenolysis or by use of harsh acidic conditions.\textsuperscript{113} Allyloxycarbonyl (Alloc, Figure 11) can be deprotected from amino acids using a palladium-catalysed system in which the allyl group is transferred to a nucleophile or a scavenger in the presence of a proton source.\textsuperscript{114} 2,2,2-Trichloroethyloxycarbonyl (Troc,\textsuperscript{115} Figure 11) is an N-protecting group that can be deprotected selectively in the presence of Z, Boc, Fmoc, and Alloc groups which make it very useful when an orthogonal deprotection approach is necessary. Troc can be removed \textit{via} a reduction reaction using zinc in acetic acid or other reducing agents.\textsuperscript{115,116} \textit{p-Nitrobenzoyloxycarbonyl} (\textit{pNZ})\textsuperscript{117} is a commonly utilised N-protecting group which is useful in the synthesis of complex peptides and can is used to lessen the instances of unwanted side reactions.\textsuperscript{118} \textit{pNZ} is more stable to strong acids than the frequently used protecting group Z and is typically cleaved by reduction with tin(II) chloride in nearly neutral conditions (1.6 mM HCl\textsubscript{(dioxane)}) in solid-phase synthesis\textsuperscript{118} and in solution synthesis it can be removed by catalytic hydrogenolysis or Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4}.\textsuperscript{119} Photolabile protecting groups are also available for use in organic synthesis. \textit{o-Nitrobenzoyloxycarbonyl} (\textit{oNZ}) is cleavable using additives such as N\textsubscript{2}H\textsubscript{4}, NH\textsubscript{2}OH-HCl at wavelengths greater than 320 nm.\textsuperscript{120} while 2-(2-Nitrophenyl)propyloxycarbonyl (NPPOC) cleaved at $\lambda = 365$ nm and is cleaved faster than other photolabile groups.\textsuperscript{121}
1.6.2 Methods to selectively protect amines

The chemoselective acylation of primary amines over secondary amines in polyamines have been reported a number of times in the past few years\textsuperscript{122–126} as have the use of biomolecules to selectively acylate amines.\textsuperscript{127,128} However, the development of a selective acylation method that could serve as a robust protecting group has been far less successful. There are examples of tert-butoxycarbonyl (Boc) being used to selectively mono-Boc protect diamines, however these examples either use the amine in a large excess with respect to di-tert-butyl dicarbonate\textsuperscript{129} or require the use of highly corrosive HCl gas in the reaction.\textsuperscript{130}

An interesting study into the selective acylation of diamines was recently carried out by Doyle\textit{et al.}\textsuperscript{131} Using 5-benzoyl-3-(cyclopent-1-en-1-yl)-5-phenyl-1,5-dihydro-4\textsubscript{H}-pyrazol-4-one (117, BCCP, Scheme 33) as an acyl transfer reagent, a single benzoyl group could be installed to a range of di- and polyamines in excellent yields (86-99\%) and with exquisite selectively (only one example out of fourteen failed to achieve 100\% selectivity with regards to the acylation of the least sterically hindered amine). For example, 1,2-diaminopropane (116) is selectively benzoylated by 117 to furnish the monobenzoyl-protected amide 118 in an excellent yield of 98\%. While the selectivity observed by 117 is comparable to that seen in biocatalysis, the non-trivial synthesis of 117 from expensive starting materials, and more pertinently, the harsh acidic/basic conditions required to cleave $N$-benzoyl amides,\textsuperscript{132} means that other alternatives to selectively protect di- and polyamines require further investigation.
Thus far, amine protecting groups are limited by their inability to distinguish between amines in distinct yet sterically similar environments. Taking amine 120 for example (Figure 12), there are currently no known amine protecting groups that could selectively protect the N-methyl terminus while leaving the N-ethyl terminus ‘free’ or *vice versa*. In order to carry out such a protection, many protecting group manipulations must be carried out which will result in reduced yields and poor atom economy. The present deficit in this methodology prompted the development of a selectively installable amine protecting group which could be deprotected under mild conditions.

**Figure 12**  Diamine 120

### 1.7 Native chemical ligation (NCL)

Native chemical ligation (NCL) is a method of peptide synthesis which allows two or more unprotected peptides or protein segments to be coupled together to synthesise moderately sized proteins (less than 200 amino acids).

#### 1.7.1 General overview

NCL was first reported by Kent *et al.* in 1994 as a novel method to produce proteins using a C-terminal thioester with an N-terminal cysteine residue. The general principle of native chemical ligation is shown below in Scheme 34.
In the general mechanism of NCL, the first step is a transthioesterification between a C-terminal thioester peptide (121) and an N-terminal cysteine residue (122) which furnishes a peptide (123, Scheme 34). This transthioesterification event introduces a thioester adjacent to a reactive amine in peptide 123, which allows a spontaneous $S,N$-acyl transfer via a 5-membered cyclic transition state to form peptide 124. This $S,N$-acyl transfer shifts the original C-terminal carbonyl onto the N-terminal amine and in doing so, forms a native peptide bond. While NCL is an efficient and commonly used method to produce peptides, it is limited in that it requires a cysteine residue at the ligation site. Cysteine is a relatively rare amino acid which has caused the requirement for the development of numerous methods to enhance the scope of NCL. A novel chemical ligation methodology, which could directly link the N-terminus of one amino acid or peptide residue, with the C-terminal carbonyl of another, would be the gold standard for chemical ligation technologies to produce peptides and proteins.

### 1.8 Dynamic kinetic resolution (DKR) of racemic azlactones

The dynamic kinetic resolution (DKR) of racemic, $\alpha$-substituted azlactones by alcohols, thiols and amines is a powerful tool in synthetic organic chemistry to produce both, natural and unnatural, enantioenriched amino acids. Azlactones can be easily accessed through $N$-acylation of amino acids, followed by dehydrative cyclisation to furnish the desired product. Azlactones are $\alpha$-acidic, making them readily enolisable and so, they are an excellent substrate for DKR (this will be elaborated on further in Section 1.8.2).
1.8.1 DKR: core concepts

A racemic mixture of compounds can be resolved into their enantiopure forms by means of kinetic resolution (KR). In an achiral environment, enantiomers possess identical physical and chemical properties. However, in the presence of a chiral catalyst, these enantiomers can be discriminated through the formation of two diastereomeric transition states. As depicted in Figure 13, KR can be achieved if there is sufficient difference in the rate of reaction between $k_R$ and $k_S$. In other words, if the more reactive enantiomer, $S_R$ in this case, reacts much faster than the less reactive partner, $S_S$, kinetic resolution can be achieved. With KR, the maximum yield of enantiopure product that can be achieved is 50%, while the remainder of the mass balance is made up of unreacted starting material $S_S$. Sharpless et al. showed that the remaining starting material left over from a KR process, could be obtained in nearly optical purity, if conversion of the reaction can exceed 50%. As a kinetic resolution process can never obtain a 100% yield of product, it is not considered atom economical.

DKR was introduced as a means to overcome this problem of wasted starting material.

![Kinetic Resolution and Dynamic Kinetic Resolution](diagram)

**Figure 13** Basic principles of kinetic resolution and dynamic kinetic resolution

DKR relies on the ability of the racemic substrate to be epimerised in situ and in doing so, the racemic mixture can be converted into a single enantiomer product. In a DKR process (Figure 13), the fast reacting enantiomer, $S_R$, undergoes kinetic resolution to give the product, $P_R$. Concurrently, as $S_R$ is being consumed and converted to $P_R$, the slow reacting enantiomer, $S_S$, is racemised in situ to produce more of the fast acting enantiomer, which accounts for the 100% theoretical yield of $P_R$ in an optimised set of reaction conditions.

For this to be a highly selective process, the rate at which $S_S$ is racemised to $S_R$ must be faster than the rate at which $S_S$ is converted to product (i.e. $k_{rac} > k_R > k_S$). The in situ racemisation of the substrate can be carried out chemically, biocatalytically or can even occur spontaneously, however, the conditions required to do so must be sometimes carefully chosen to avoid racemising the product.
1.8.2 DKR of azlactones via alcoholysis and thiolysis

Alcoholysis is one method by which racemic azlactones can be resolved to produce enantioenriched $\alpha$-amino acids by DKR. As outlined in Section 1.8, the $\alpha$-acidity of azlactones make them ideal substrates for DKR. An overview of the DKR of azlactones via alcoholysis is shown below in Scheme 35. High levels of enantioselectivity in the products are achievable if the rate of racemisation of the azlactone exceeds that of alcoholysis of the slow reacting enantiomer.

Scheme 35  DKR of azlactones by alcoholysis: a general overview of the process

In 1993, Sih et al. reported a successful, enzymatic variant for azlactone DKR to produce enantioenriched $\alpha$-amino acids.\textsuperscript{144} However, due to the limited substrate scope associated with using enzymes to promote this transformation, the development of non-enzymatic variants have been developed.

1.8.2.1 Ti-TADDOLate-catalysed DKR of azlactones

Seebach reported the first non-enzymatic example of azlactone DKR via alcoholysis using the Lewis acid promoter Ti-TADDOLate (125, Scheme 36).\textsuperscript{145} This protocol furnished product 127 from phenylalanine-derived azlactone 126 in 75% yield and 70% ee, albeit with a long reaction time (6 days).

Scheme 36  Ti-TADDOLate-promoted DKR of azlactones carried out by Seebach et al.
As this methodology relied on long reaction times and stoichiometric loadings of 125, Seebach and co-workers attempted to address these problems and create a more efficient process. While the promoter loading could be reduced from 1.2 equivalents to 0.7 equivalents, with the addition of an achiral alkoxide source to regenerate the active catalyst in situ, this methodology proved to be limited in scope; only azlactones derived from phenylalanine and its analogues could be used. This protocol was inferior to the enzymatic alternatives already available in the literature at the time.

### 1.8.2.2 Acyl transfer catalysts for the DKR of azlactones

In 1998, Fu et al. published their findings into a non-enzymatic DKR of azlactones via alcoholysis. This methodology employed the use of 128, a chiral, DMAP-derived catalyst to promote the reaction, and furnish the ring-opened products in high yields and ees of up to 78% (Scheme 37). While this publication was seminal in the field, the process tolerated only methanol, ethanol and isopropanol as the nucleophilic alcohol partner. As the steric bulk of the alcohol nucleophile was increased (methanol vs. isopropanol), an increase in ee was observed, however this did result in a substantial loss in rate (50% conversion was observed after one week, when using isopropanol as the nucleophile).

![Scheme 37](image)

**Scheme 37**  DKR of azlactones via alcoholysis, catalysed by Fu’s DMAP-derived catalyst 128

In recent years, Birman and co-workers have reported the use of a benzotetramisole catalyst 129 for the DKR of azlactones (Scheme 38). Catalyst 129 was able to promote this transformation to furnish di(1-naphthyl)methyl esters of α-amino acids (such as 132) in good-to-excellent yields, especially when C-4 arylazlactones such as 130 were employed. While other alcohols were screened in this investigation, the use of di(1-naphthyl)methanol (131) was required to produce synthetically-useful levels of enantioenrichment. The scope of this methodology was broad with respect to the amino acid subunit. Structural variation of the azlactone substrates resulted in only small changes in enantioselectivity. Later, Birman
went on to publish the stereochemical rationale for the observed enantioselectivity, which was explained by \( \pi-\pi \) interactions between the substrate and catalyst.\(^\text{149}\)

**Scheme 38** Birman benzotetramisole-catalysed synthesis of di(1-naphthyl)methyl esters of \( \alpha \)-amino acids

### 1.8.2.3 DKR of azlactones via Brønsted acid catalysis

Further to his studies into the DKR of azlactones by alcoholysis catalysed by acyl transfer catalysts (Section 1.8.2.2, Scheme 38), Birman also utilised a chiral Brønsted acid catalyst to promote this transformation (Scheme 39).\(^\text{150}\) Using a disubstituted BINOL phosphoric acid derivative 133, this DKR process was tolerant of a range of different alcohols, however, sterically encumbered alcohol 1-naphthyl-CH\(_2\)OH (135) was required to bring about the highest enantiomeric excesses (up to 92%). Maintaining an aryl group at the C-2 and C-4 position of the azlactone resulted in optimum ee; the enantiomeric excess of this reaction dropped in the presence of 4-alkyl derivatives (29–59\% ee was obtained when an alkyl substituent was present at C-4).

**Scheme 39** Brønsted acid catalysed DKR of azlactones reported by Birman et al.
1.8.2.4 Bifunctional organocatalysts for the DKR of azlactones by via alcoholysis and thiolysis

The first to report the DKR of azlactones using a chiral bifunctional, organocatalyst to promote this transformation was Berkessel et al. in 2005. Berkessel utilised azlactones derived from natural and unnatural amino acids, in conjunction with allyl alcohol and urea-based, bifunctional, chiral organocatalysts to form the corresponding ring-opened products in good to excellent ees (Scheme 40). The initial study used urea catalyst 137, which furnished the ring-opened allylic ester 140 with respectable yield and enantiomeric excess. A second generation thiourea-based catalyst 138 (Scheme 40) was developed in a follow-up report by Berkessel and co-workers. Thiourea catalyst 138 promoted the reaction in excellent enantioselectivities, at the expense of product yields (Scheme 40, for example the yield of 140 reduces from 76% to 59% when 138 in used in place of 137).

Scheme 40  Bifunctional thiourea catalysts used by Berkessel et al. for the DKR of azlactones

The following year, Berkessel published an in-depth study into the catalyst optimisation of this reaction (in which a suite of catalysts were tested). It is postulated that the bifunctional catalyst binds to the carbonyl of the azlactone via hydrogen bonding, in doing so the azlactone is activated towards both enolisation and alcoholysis (Figure 14). Simultaneously, the amine functionality contained in the catalyst both catalyses racemisation of the azlactone and enhances nucleophilicity of the pronucleophile via hydrogen bonding.
Proposed activation of an azlactone and an alcohol by a bifunctional (thio)urea catalyst

In 2008, Connon and co-workers published their findings into the DKR of azlactones by alcoholysis and thiolysis using *cinchona* alkaloid-derived catalysts. Yields and enantiomeric excesses in this study were comparable to those reported by Berkessel in the alcoholysis of azlactones (Scheme 4 A, up to 88% ee) however, it was the thiolysis reported by Connon and co-workers that was of particular importance in this report. As discussed in Section 1.7, thioesters are important substrates for NCL, a ligation technology used to synthesise peptides and proteins. While the thioester products in this publication are not directly suitable for NCL, the development of this methodology was still of potential synthetic utility. The DKR of azlactone was carried out via thiolysis using cyclohexyl thiol in the presence of *cinchona* alkaloid-derived catalyst, to form the corresponding thioester in an excellent yield (90%) and with moderate enantioselectivity (64% ee, Scheme 4B).

Scheme 41  Alcoholysis and thiolysis of azlactones using bifunctional catalyst

Following on from their 2008 report, in 2013 Connon and co-workers went on to resolve the previous problems observed with the enantiomeric discrimination in the thiolysis of azlactones.
Cinchona alkaloid-derived catalyst 145 catalysed the thiolysis of a suite of azlactones with up to 92% ee, albeit with low to moderate yields of the thioester products, 147 (Scheme 42, 24-60% yield). The low yields observed in this reaction were explained by deactivation of the catalyst in the reaction through formation of a nonreacting ion pair with the azlactone, caused by hydrolysis of the azlactone (the use of molecular sieves and anhydrous solvent failed to prevent hydrolysis).

![Scheme 42](image)

**Scheme 42** Optimised DKR of azlactones via thiolysis reported by Connon and co-workers

In 2012, Song reported that the use of traditional (thio)urea modified cinchona alkaloid-based catalysts can be problematic due to their propensity to self-associate. Song found that these (thio)urea biofunctional organocatalysts can form aggregates via hydrogen-bonding in a concentration-dependant manner. This phenomenon means that the availability of reactive catalyst in the reaction mixture is greatly diminished, resulting in dramatic losses in enantioselectivity as the concentration increases. In order to overcome this problem, Song designed an array of C2-symmetric alkaloid-based organocatalysts such as 148 depicted in Scheme 43. Song observed by both NMR spectroscopy and x-ray crystallography, that this type of catalyst did not self-associate. Furthermore, Song carried out the DKR of azlactone 139 using 148 via alcoholysis (using allyl alcohol) to furnish 149 in an excellent yield and with high levels of enantioselectivity (95% yield, 94% ee, Scheme 43). A range of both natural and unnatural amino acid-derived azlactones performed well in this reaction; using catalysts of type 148 and its derivatives. The products were synthesised in high yields, and in excellent enantioselectivities (86-95% yields, 73-91% ee). The reaction benefited from further enhancement in ee upon cooling: 149 was obtained in 98% yield and 97% ee when the reaction was cooled to -20 °C.
Scheme 43  Song’s DKR of azlactones promoted by catalyst 148

Carrying on from their work on the DKR of azlactones by thiolysis and alcoholysis,154 Connon and co-workers published a novel methodology for the asymmetric DKR of modified aryl azlactones.156 In this study the DKR of tetrachloroisopropoxycarbonyl (TCIC) substituted-azlactones such as 150 was carried out via alcoholysis using Song’s C2-symmetric bifunctional organocatalyst 151 (Scheme 44).155 Promoted by 151, azlactones of type 150 underwent alcoholysis with benzyl alcohol. Following treatment with an amine base (DABCO), the corresponding N-phthalamido-protected amino ester 152 was furnished in one-pot, with excellent yields and enantioselectivities (Scheme 44). Orthogonally protected amino acids, such as 152, can be treated with 1,2-diamines to deprotect the TCIC moiety, producing free amine 153 in an excellent yield. Alternatively, 152 can undergo hydrogenolysis to yield N-protected acid 154 in near quantitative yield (Scheme 44). This methodology solved one of the long-standing problems associated with the DKR of azlactones: generating products with useful protecting groups incorporated in their structure.
Scheme 44  DKR of TCIC-substituted azlactones and a subsequent orthogonal deprotection route

This report also detailed the use of serine-protected derivatives 155 as nucleophiles to carry out the azlactone ring-opening step (Scheme 45). Following alcoholysis of 151 by amino acid 155, promoted by 151, orthogonally-protected tripeptide 156 is produced in 81% yield and 95:5 d.r. Deprotection of the Boc group of 156, followed by a base-catalysed O,N-acyl transfer, produced the corresponding protected tripeptide 157 in an excellent yield (90%) and maintaining high levels of diastereoselectivity (95:5 d.r.).
1.8.3 DKR of azlactones via aminolysis: scope and limitations with current methodologies

While the alcoholysis and thiolysis of azlactones have been well studied (Section 1.8.2), analogous investigations into the aminolysis of azlactones are much less prevalent in the literature. Amarante used (±)-CSA as a Brønsted acid catalyst to perform the aminolysis of azlactones racemically using a small pool of amines while Dujardin ring-opened 2-methylalanine-derived azlactones with amines, uncatalysed, to prepare vinyl ether linkers used in the preparation of (±)-2-deoxy-glycoside. Other examples of azlactone aminolysis have been carried out using chiral starting materials (chiral azlactones and amines). Although there are examples where chiral starting materials have been used in the aminolysis of azlactones, the diastereoselectivities of the corresponding products were not always satisfactory. Other methodologies require harsh reaction conditions such as: high temperatures, the use of a strong Lewis acid and long reaction times, to achieve aminolysis.

Scheme 45  The DKR-peptide coupling methodology designed by Connon and co-workers

![Scheme Diagram](image-url)
Limited examples of the DKR of azlactones by aminolysis exist due to the challenges associated with using amines as the nucleophilic partner in this transformation. Amines are inherently highly nucleophilic in nature and so can ring-open azlactones without catalyst assistance.

In 2016, the Shi group carried out the DKR of azlactones via aminolysis using carefully designed amine nucleophiles, which they envisaged would circumvent the unwanted reactivity of the amine, as previously discussed. They designed anilines of type 160 (Scheme 46) as the amine, which contained both a sterically bulky group and an activating group. The DKR was catalysed by Brønsted acid catalyst 158, which is thought to form hydrogen bonding interactions with 160 and azlactone 159, allowing access to enantioenriched bisamides of type 161 (Scheme 46). Excellent yields (up to 99% yield) and enantioselectivities (up to 99% ee) were obtained with this methodology and it allowed for a range of azlactones to be used. However, the scope of the nucleophile was more restricted, for example, the use of simpler amines (such as unsubstituted aniline) to a significant loss in enantiomeric excess (only 37 % ee).

![Scheme 46](image)

**Scheme 46**  DKR of azlactones via aminolysis using Brønsted acid catalyst 158

Although the aminolysis of azlactones by a DKR process has been carried out using Brønsted acid catalysis, the limited scope of the amine nucleophile means that more investigation into this protocol is necessary. Presented with this challenge, one of the aims of this thesis was
to use *cinchona* alkaloid-derived organocatalysts to carry out the DKR of TCIC-substituted azlactones *via* aminolysis, and in doing so, develop a novel ligation protocol for the synthesis of orthogonally protected peptides. The inability to carry out the aminolysis of azlactones directly has held the field back and has deprived the community of a methodology capable of dynamically kinetically resolving a racemic amino acid-derived azlactone (of the practitioners choosing which would could have any useful residue attached) which simultaneously coupling it to a peptide chain.
Chapter 2 Synthesis of an NHC-catalysed novel amine protecting group

2.1. Selective acylation of diamines via NHC catalysis using benzil

While carrying out the NHC-catalysed oxidative amidation of aldehydes, Connon and co-workers noted that a crucial step in the catalytic cycle is attack of an amine on the catalyst-benzil adduct 112 (Scheme 29, Section 1.5.3).\(^8\) This step is thought to be extremely sterically sensitive as it results in the formation of an adduct with adjacent all-quaternary carbon centres. Connon and co-workers overcame the low yields observed in the amidation of aldehydes in their 2017 report with the use of a nucleophilic co-catalyst, 1,2,4-triazole (115, Scheme 32, Section 1.5.3). Although a solution to the low amide yields was developed in this publication,\(^8\) the mechanistic information gathered while solving this problem prompted another investigation. It was hypothesised that if 112 is sufficiently sensitive to steric hinderance in the amine nucleophile, it was possible that intermediate 112 could distinguish between sterically similar, yet distinct, nitrogen atoms in a di- or polyamine, preferentially acylating the least sterically encumbered nitrogen atom in the system. In order to test this hypothesis, Dr Vikas Kumar was charged with the task of reacting various diamines with benzil (70), under the standard reaction conditions set out in the NHC-catalysed oxidative amidation of aldehydes (Scheme 32, Section 1.5.3).\(^8\) When diamines 162-164 were utilised in this reaction, amides were formed selectively, at the least hindered nitrogen atom in the system (Scheme 47).

![Scheme 47](image)

Scheme 47 Selective acylation of diamines via NHC-catalysed direct amidation
When diamine 162 was employed in this amidation reaction (Scheme 47), amide 165 was formed exclusively (83% yield). This result was in keeping with the hypothesis that intermediate 112 would only allow the least sterically hindered primary amine to be acylated. In this reaction, amide 168, in which the benzylation occurs at the more hindered secondary amine was not observed. Similarly, amide 166 was formed with 100% selectivity, in 79% yield, when diamine 163 was used in this reaction. Again, the less hindered primary amine was acylated exclusively; no trace of acylation at the secondary amine (amide 169) was observed. When diamine 164 was evaluated in this amidation protocol, 170 was formed (62% yield) with acylation occurring at the least sterically hindered secondary amine of 164, again, with 100% selectivity. In order to showcase the remarkable selectivity offered by this reaction when using sterically distinct diamines, 120 screened in this reaction (Scheme 48). Under the standard NHC-catalysed oxidative amidation conditions, acylation occurred selectively at the N-methyl terminus of 120, forming amide 171 (56% yield), while amidation at the N-ethyl terminus, 172, was not observed (Scheme 48). This exquisite selectivity is rarely observed in standard amide bond forming procedures unless effective protecting group strategies are in place.

![Scheme 48](image)

**Scheme 48** Selective amidation of diamine 120 via NHC catalysis

As a result of the unprecedented selectivity observed in amine acylation using 70, it was decided that a benzil derivative would be the structural basis for protecting group design. As an addition to being a highly electrophilic species, benzil is also the oxidised form of an aromatic aldehyde and thus is a step further along in the catalytic cycle described in Scheme 19 (Section 1.4.3).

### 2.2 Investigation into the selectivity of traditional amine acylations

In seeking the development of a novel amine protecting group, it was decided to first investigate the potential selectivity observed in traditional amine acylations. The reaction chosen for this investigation was the N-benzylation of various diamines with benzoyl chloride (173), a commonly used acylating agent in organic synthesis. The benzoyl moiety
is installed by reaction of 173 with an amine in the presence of a base, in various organic solvents (Table 1).

Table 1  Screening for selective acylation of diamines using benzoyl chloride

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>concentration (M)</th>
<th>temperature (˚C)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>selectivity&lt;sup&gt;b&lt;/sup&gt; 174:166:169</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0.4</td>
<td>rt</td>
<td>49</td>
<td>100:0:0</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>0.1</td>
<td>rt</td>
<td>50</td>
<td>100:0:0</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0.1</td>
<td>-30</td>
<td>46</td>
<td>100:0:0</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0.1</td>
<td>-78</td>
<td>50</td>
<td>100:0:0</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>rt</td>
<td>48</td>
<td>100:0:0</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>-30</td>
<td>50</td>
<td>100:0:0</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>-78</td>
<td>45</td>
<td>100:0:0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield. <sup>b</sup>Refers to the acylation at both nitrogen atoms compared to mono-acylation at one N-terminus; determined by analysis of the 1H NMR spectrum of the crude reaction mixture.

Initial experiments were carried out using similar conditions to those employed in the NHC-catalysed oxidative amidation protocol (see Section 1.5.3). Diamine 163 was reacted with 173 in THF at room temperature (Table 1, entry 1). This resulted in 163 being acylated at both nitrogen atoms, indiscriminately, to yield bis-acylated 174 in 49% yield, with 51% of 163 being returned unreacted. Attempts were made to promote selectivity by decreasing the concentration of the reaction from 0.4 M to 0.1 M (Table 1, entry 2) and again, 174 was the sole product observed (50% conversion to 174, 50% of 163 remained as observed by 1H NMR spectroscopy after 24 hours). The reaction was cooled from ambient temperature to -30 ºC (Table 1, entry 3) and -78 ºC (Table 1, entry 4) respectively, in an attempt to promote selectivity and again, 174 was the only observed product of the reaction. As THF is not
traditionally the solvent of choice for the acylation of amines in this manner, CH$_2$Cl$_2$, the solvent more typically associated with such reactions was used. At room temperature at a concentration of 0.1 M, the use of CH$_2$Cl$_2$ failed to result in any selectivity in the reaction (Table 1, entry 5). Cooling the reaction to -30 °C (Table 1, entry 6) and -78 °C (Table 1, entry 7) respectively, was again inefficient in promoting chemoselective nitrogen acylation.

In each case discussed above, the mono-acylated amides 166 and 169 were not observed. It was postulated that, as the more nucleophilic secondary amine of 163 is likely acylated first to form 169, the newly acylated nitrogen atom may then accelerate acylation of the free primary amine (possibly assisted via hydrogen-bonding interactions) to form 174. This rationale explains why the mono-acylated amides 166 or 169 respectively, were not formed under any of the conditions employed in this investigation.

2.3 Design of the first-generation protecting group

It was ascertained that a traditional method of amine acylation failed to provide any regioselectivity when a diamine was employed in the reaction (Section 2.2). This, coupled with the exquisite selectivity observed in the one-step oxidative amidations of sterically similar amines detailed in Section 2.1, prompted the design of a selectively installable amine protecting group. It was demonstrated that NHC-mediated acylations of diamines occurred at the least hindered nitrogen atom with 100% selectivity (Schemes 47 and 48). However, these reactions generate amides protected as benzoyl derivatives. Benzoyl amides usually require harsh conditions to achieve hydrolysis (e.g. hydrobromic acid and acetic acid under reflux for 6 hours or using sodium hydroxide under reflux)\textsuperscript{132,166} and, as such, are an impractical choice as a protecting group for all but the simplest molecules. An alternative design was, therefore, required.

The core structure for the protecting group design was that of a substituted benzil. It was recognised that the benzil moiety could be modified with a group which would allow for the release of the protected amine under mild conditions. It was hypothesised that the release of the amine would be easiest if the moiety carrying out the deprotection (\textit{i.e.} a nucleophile which would attack the amide carbonyl) was installed ortho- to the amine being deprotected. As previously discussed, this catalytic cycle (Scheme 19) passes through sterically encumbered intermediates, thus, the introduction of an ortho-substituent in the benzil moiety would further hinder these intermediates, likely resulting in low yields of the amide product. A test reaction was carried out with benzil 175 (derived from $o$-tolualdehyde (176)) under the standard reaction conditions outlined in Scheme 32, to ascertain if ortho-substitution would cause the oxidative amidation reaction to be retarded. Unsurprisingly, the desired
amide 177 was not formed, instead aldehyde 176 was recovered (Scheme 49). The inability of 175 to perform in the amidation reaction is likely attributable to the tetrahedral intermediate formed (analogous to 112, Scheme 29) being too sterically hindered to undergo nucleophilic attack by pyrrolidine. The reversibility of the preceding steps in the catalytic cycle means that the reaction can proceed backwards, eventually reforming 176.

**Scheme 49  Attempted oxidative amidation of 175**

In order to overcome the problems associated with ortho-substitution of the acylating agent, it was reasoned that altering the electronic characteristics of the benzil core would allow for the problems with steric bulk in the acylating agent to be overcome. Consequently, the first-generation protecting group design is based on the model system depicted in Figure 15.

**Figure 15  Model compound for first-generation protecting group design**

Considering this model system, it was proposed that an alcohol masked as a silyl ether could serve as the internal nucleophile intended for amine deprotection. It was reasoned that the silyl ether could be cleaved with fluoride, to reveal the alkoxide/alcohol in situ, which would then close to ‘release’ the amine. In order to alter the electronic characteristics of the benzil core, it was decided to instead use a 2,2’-pyridil. It was postulated that the nitrogen atom of pyridil would greatly activate the C-2 position, making it more electrophilic and primed towards attack by an amine nucleophile, while nitrogen itself is relatively small and would not cause further steric hindrances to this already sterically sensitive system. As shown by Connon and co-workers, pyridine-derived aldehydes are competent coupling partners in
NHC-catalysed oxidative amidation reactions (*e.g.* 2-pyridinecarboxaldehyde: 81% yield). The first-generation substrate 178 is shown in Figure 16.

![Image of molecule 178]

Figure 16 First generation acylating agent

### 2.3.1 First-generation substrate: deprotection studies

In order to determine suitable deprotection conditions, the final amide product (after desilylation) 179 was synthesised via a standard amide bond-forming methodology. Amide 179 was then subjected to both acidic and basic conditions, to determine if either could promote ring closure and release of the protected amine (Scheme 50).

![Scheme 50 Deprotection of protected amine 179]

Ring closure and ‘release’ of amine 181 was achieved under acidic conditions using hydrochloric acid (1.5 M, 1.0 equivalent, room temperature, condition set A) resulting in the formation of lactone 180 in a moderate yield of 64% and the now deprotected amine being obtained as its hydrochloride salt, 181. Basic conditions were also evaluated in this reaction. The base-mediated cyclisation was attempted using DBU and sodium hydride at both room temperature and under reflux respectively, condition sets B and C. In all base-mediated
reactions, 180 was not formed. Further optimisations of this reaction have not been carried out at present. Although not a perfect deprotection strategy to obtain protected amine 179, the acid-mediated protocol, condition set A, was deemed adequate and attention was then turned to the synthesis of substrate 178 and its evaluation in the NHC-catalysed oxidative amidation protocol.

2.3.2 Synthetic route towards first-generation substrate 178

The key step in developing a synthetic route towards benzil 178 was forming the characteristic diketone. It was decided to attempt to couple aldehyde 188 in a benzoin condensation to form 178. It was envisaged that if aldehyde 188 (Scheme 51) was to partake successfully in the benzoin condensation, it would likely also participate well in the NHC-mediated oxidative amidation.

The first step in the synthesis of 178 was esterification of commercially available 2,3-pyridinedicarboxylic acid (183) to dimethyl ester 184 via a Fischer esterification, which proceeded in a moderate 74% yield (Scheme 51). The reduction of 184 to diol 186 was more challenging than initially anticipated. Following a protocol devised by Yoshiizumi et al., attempts were made to reduce 184 with sodium borohydride (NaBH₄). Although Yoshiizumi did not report any problems with the work-up procedure in this reaction (they report an 85% yield of 186; addition of hot ethanol to the reaction mixture and a subsequent hot filtration furnished the pure product in their report), numerous attempts to reproduce this work-up procedure and yield all failed. Typically, sodium borohydride reductions are quenched with an aqueous acid solution (such as HCl), however, diol 186, generated from this reduction reaction is particularly water soluble and so, aqueous acid was not a viable option to quench the reaction. Attempts were made to carry out an aqueous work-up on this reaction and simply retrieve 186 from the resulting aqueous layer. Unfortunately, it proved to be too difficult to separate 186 from the many boron salts (derived from NaBH₄), formed after the reaction was quenched. Alternative work-up procedures which did not require aqueous conditions, included the use of both methanolic and gaseous HCl were evaluated. Methanolic HCl was required in large volumes to quench reactions carried out on larger scales and due to its expense, it was not feasible for such work-up strategies. Gaseous HCl was impractical to generate in the laboratory on a regular basis and so this methodology was not investigated further. Other reducing agents; lithium aluminium hydride (LiAlH₄) and lithium borohydride (LiBH₄) were also employed in this reaction with little success; again, the work-up procedures proved difficult and low yielding due to the water solubility of the product. Following numerous unsuccessful endeavours to optimise the reducing agents and
work-up conditions, attempts to functionalise 186 *in situ* were carried out, consequently negating the need to work-up the reduction reaction entirely. Following the reduction of 184, the regents required to carry out acetylation of 186 (excess acetic anhydride, base and catalytic DMAP) was added directly to the reduction reaction mixture to yield 185. The *bis*-acetylated product 185 was subsequently deprotected under basic conditions, (solid K$_2$CO$_3$ was used to avoid aqueous conditions), to furnish 186. Silyl protection of 186 with tert-butyldimethylsilyl (TBS) was obtained in a moderate yield of 51%, this is due to a mixture of TBS-protected products being formed (*mono*, *bis*-protected and un-protected diol). *Bis*-protected and unreacted diol could be recycled as the *bis*-protected product is easily cleaved to reform 186 with tetrabutylammonium fluoride solution (TBAF). Following protection, 187 was oxidised to aldehyde 188 which was coupled *via* benzoin condensation,$^{169}$ using catalyst 27, to render the benzoin product 189, which was subsequently oxidised to the desired diketone, 178.

![Scheme 51](image)

**Scheme 51** Synthetic route to 178

### 2.3.3 Evaluation of 178 in NHC-catalysed oxidative amidations

Preliminary experiments were carried out to ascertain the efficiency and selectivity of substrate 178 in NHC-catalysed oxidative amidations. Substrate 178 was evaluated in this reaction, using the standard reaction conditions outlined in Connon and co-worker’s 2017 publication (Scheme 32, Section 1.5.3).$^{88}$ Both amines and diamines were investigated as
substrates in this reaction and the results of this substrate evaluation are displayed in Table 2.

**Table 2** NHC-mediated oxidative amidations between 178 and various amines

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>selectivity&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyrrolidine</td>
<td>97</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>piperidine</td>
<td>64</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;NNHH</td>
<td>51</td>
<td>100:0</td>
</tr>
<tr>
<td>4</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;&lt;br&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>63</td>
<td>100:0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield. <sup>b</sup>Refers to the acylation at the least hindered amine compared to the more hindered; N-atom determined by analysis of the 1H NMR spectrum of the crude reaction mixture.

A high yield (97%) was obtained when pyrrolidine, a small cyclic amine was used (Table 2, entry 1). Worryingly, when piperidine was employed in the reaction (Table 2, entry 2), a moderate yield of 64% was achieved. As the ring size of the amine was increased, *i.e.* a 5-membered ring vs. a 6-membered ring, the yield of this reaction drops significantly. The selectivity of the reaction was probed using commercially available diamines; *N*-methyl-1,3-diaminopropane (163, Table 2, entry 3) and 1,2-diaminopropane (116, Table 2, entry 4), which resulted in moderate isolated yields of 51% and 63% respectively. *N*-Methyl-1,3-diaminopropane (163) was chosen to challenge the ability of the substrate to cope with an acyclic amine and to investigate the capability of the substrate to distinguish between a primary and secondary amine. Gratifyingly, 178 formed the corresponding amide at the least hindered primary amine with 100% selectivity. 1,2-Diaminopropane (116), which contains two primary amines in sterically different environments, was utilised to further test the
selectivity of 178. Pleasingly, it was observed that 178 also furnished the corresponding amide with 100% selectively at the least hindered nitrogen atom. This is an interesting observation, as 116 was the only diamine previously evaluated by Dr. Vikas Kumar that did not furnish amides, derived from benzil (70), with 100% selectivity (Scheme 52).

Scheme 52  NHC-mediated oxidative amidation between 70 and 116 carried out by Dr Vikas Kumar

It was postulated that the steric sensitivity of this reaction (in comparison to the analogous reaction with 70: cf. Table 2, entry 4 and Scheme 52) is influenced by the introduction of the o-substituted silyl-protected alcohol on 178. This modification to 178 means that only the least sterically hindered nitrogen atom of a diamine can attack the sterically congested tetrahedral intermediate 192 (Figure 17). It is assumed that the remainder of 178 (that does not undergo amidation) forms a DBU-carboxylate salt 193, arising from reaction of the Breslow intermediate\(^{51}\) with trace amounts of oxygen in the reaction flask, likely through an ‘oxygenative’ pathway (see Section 1.4.3).\(^{74}\)

Figure 17  Tetrahedral intermediate 192 and DBU-carboxylate salt 193

Substrate 178 represents a solution to the selectivity problem (which was observed when benzil (70) was utilised in the reaction, Scheme 52) and (partially) the deprotection problem. However, this methodology was not yet efficient enough as an acylation protocol due to the low amide yields obtained when diamines were employed in the reaction (Table 2)
2.3.4 Attempts to optimise the NHC-catalysed oxidative amidation of 178

Modifications of the reaction conditions were carried out to try to increase the yield of the NHC-catalysed oxidative amidation reaction between 178 and piperidine (Scheme 53).

Scheme 53 Modifications to the oxidative amidation reaction conditions

When the amidation reaction was carried out in the absence of phenazine (53), condition set B, Scheme 53), a decreased yield of 43% was observed, in comparison to the moderate yield obtained when phenazine was present in the reaction (64%, condition set A, Scheme 53). This implied that the external oxidant was necessary to furnish amide 194 in higher yields. The influence of the reaction concentration was also investigated. The optimal reaction conditions for these amidations (Scheme 32) requires THF as a solvent at a concentration of 0.4 M. These catalytic reactions were generally carried out on a small scale (0.1 mmol), which results in a small volume of solvent (approximately 250 µL) being used. The amidation reaction between 178 and piperidine was carried out at dilute concentrations of 0.1 M and 0.04 M (condition set C and D, Scheme 53), in order to increase the volume of solvent in the reaction flask. In the case of the reaction carried out at a concentration of 0.1 M, a poor isolated yield of 14% of 194 was obtained. When a 0.04 M concentration was employed in the reaction, amide 194 was not observed at all (observation by analysis of 1H NMR spectroscopic methods). Further variations of solvent and reaction concentrations have not been undertaken at present. The amidation reaction was carried out with a glass stopper (condition set E, Scheme 53) in the place of a septum and argon balloon due to the postulate that any traces of molecular oxygen in the reaction flask oxidises the Breslow intermediate via an ‘oxygenative’ pathway. It was thought that flushing the reaction flask with argon and sealing it with a glass stopper would maintain an argon atmosphere throughout the reaction, as it provides a better seal than a rubber septum. However, it was observed that the reaction occurred in a low yield of 40% when the stopper was used, as opposed to a 64% yield of amide 194 when an argon-filled balloon and septum were used (condition set A, Scheme 53).
The low yields observed when larger cyclic amines and acyclic diamines were used in this reaction (Table 2, entries 2-4) mandated modification of 178. Altering the silyl protecting group used was one possible modification that could have been undertaken, however, it was not expected that the yield would increase significantly by doing this, as most stable silyl ether protecting groups are bulky in nature. Attempts to synthesise the 3,4-substituted pyridine derivative 195 (Figure 18) were undertaken. This substrate was of particular interest as it moved the bulky silyl-protected alcohol to the meta position, thus making the crucial intermediate (analogous to 192) less congested. However, synthesis of 195 was difficult to carry out due to the decreased reactivity at the C-3 and C-4 positions of the pyridil core and subsequently. The synthesis of 195 has not been pursued any further at present.

Figure 18 3,4-Substituted pyridil derivative 195

2.4 Substrate redesign

Although selectivity in the preliminary amidation reactions using 178 was as desired, the yields obtained were unsatisfactory. This led to the acylating agent being redesigned in an effort to maintain chemoselectivity, while increasing the yield of the protection reaction. As there was little scope for modification of 178 without encountering numerous synthetic challenges, it was decided to move away from using the pyridil core. For the second-generation substrate, a benzil-core was opted for and an sp²-hybridised electron withdrawing group was included in the redesign, for deprotection, as opposed to an sp³-hybridised analogue, such as the primary alcohol in 178. The rationale behind this decision was that a flat sp²-hybridised substituent would occupy less space, thus minimising steric hindrance in the reaction, while activating the adjacent carbonyl electrophile, leading to increased potency of the acylating agent. An amide was the sp²-hybridised substituent chosen. In 1991, Weigel et al. disclosed that amines can be deprotected under acidic conditions using a similar o-pyrrolidinocarbonylbenzamide (OPCB) protecting group 196 (Scheme 54). Protecting group 196, containing a secondary amine, can reversibly form phthalamide (197) and in doing so release pyrrolidine.
Scheme 54  Weigel’s deprotection of pyrrolidine under acidic conditions

The core benzil structure, substituted with electron withdrawing groups (necessary to activate the substrate towards nucleophilic attack, see Section 2.3) was maintained on the second-generation substrate (Figure 19). It was envisaged that there would be additional modifications available using this second-generation protecting group strategy that were not possible when using substrates such as 178, due to the challenges with its synthesis.

Figure 19  Model compound for second-generation substrate design

2.4.1 Synthetic route towards the second-generation substrate

The initial substrate synthesised contained a simple benzil-core with an ortho-substituted amide group with N-methylbenzyl substituents. The first of this new class of substrates synthesised was 198 (Figure 20). As 198 was a prototype substrate, it did not have any other electron-withdrawing substituents on the aromatic ring. The electron-withdrawing groups were omitted on 198 to investigate if the amide substituent was sufficiently electron-withdrawing to allow the NHC-catalysed amidation reaction to proceed. Consideration was given to the fact that it would likely be challenging to cleave the benzyl substituent of 198 for deprotection purposes, however, 198 was still synthesised and evaluated to ensure that the introduction of an amide group in the o-position resulted in it being a competent substrate for amidation.
The synthetic route towards 198 is shown in Scheme 55. The first step in the synthesis of 198 was to ring-open commercially available phthalide (199) with N-methylbenzylamine (200) in the presence of a Lewis acid, aluminium trichloride (201, AlCl₃), to form alcohol 202. Upon oxidation to aldehyde 203, a benzoin condensation furnished the benzoin derivative 204, which could be oxidised with MnO₂ to benzil 198.

Scheme 55  Synthesis route to substrate 198
2.4.2 Substrate scope of the second-generation protecting group 198

Having synthesised 198, its efficiency and selectivity in the NHC-catalysed oxidative amidation reaction with amines and diamines was evaluated (Table 3).

**Table 3** NHC-mediated oxidative amidations between substrate 198 and various amines

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>yield (%)$^a$</th>
<th>selectivity$^b$</th>
<th>1$^a$ amine:2$^a$ amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyrrolidine</td>
<td>99</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>piperidine</td>
<td>79</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$\text{H}_2\text{N} \text{H} \text{N}$</td>
<td>41</td>
<td>100:0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$\text{C} \text{N} \text{H}_2$</td>
<td>53</td>
<td>100:0</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Isolated yield. $^b$Refers to the acylation at the least hindered amine compared to the more hindered N-atom.

When the amidation reaction was carried out with pyrrolidine, a high yield (99%) of the corresponding amide was obtained (Table 3, entry 1). Gratifyingly, when piperidine was employed in this reaction, the amidation proceeded with an adequate yield of 79% (Table 3, entry 2). This result is an improvement on the yield obtained in the same reaction with piperidine and 178 (64%, Table 2, entry 2). However, when diamines were employed in this reaction the yield was reduced to 41% when 163 (Table 3, entry 3) and 53% with 162 (Table 3, entry 4) were used. Although the yields of these reactions were not satisfactory,
encouragingly, all amidations occurred with 100% selectivity, with acylation occurring exclusively at the least hindered nitrogen atom.

2.4.3 Developing a modified second-generation substrate
As exhibited in the amidation of o-tolualdehyde-derived benzil 170 (Scheme 49), electron withdrawing groups on the benzil moiety were necessary to partially compensate for the steric hindrance imposed by ortho-substitution. Thus, attempts were made to synthesise derivatives of 198 with electron-withdrawing groups on the benzil moiety. The library of substrates, the synthesis of which were attempted, are shown in Figure 21.

![Figure 21](image_url)

In order to vary the electronic properties of the benzil core, a new synthetic strategy had to be devised, as the necessary substituted phthalides were not commercially available. The syntheses of tetrahalo-substituted substrates 205 and 206, are outlined in Scheme 56.
Starting by reacting the appropriate, commercially available, tetrafluoro- or tetrachloro-substituted phthalic anhydride (208) or (209) with 200, the corresponding carboxylic acids were furnished in excellent yields. Esterification of the resulting carboxylic acids and subsequent reduction of the resulting methyl esters yielded alcohols 214 and 215, respectively (Scheme 56). Disappointingly aldehyde 216 was not obtained after oxidation of alcohol 214. With the tetra-fluoro derivatives, the yields of each reaction decreased from step-to-step, which was likely attributed to the instability of the heavily electron-withdrawing substituted-aryl ring towards nucleophilic aromatic substitution. Due to the instability of the intermediates in the synthesis of 205 to relatively mild reaction conditions, it was postulated that it would not likely withstand the NHC-catalysed oxidative amidation reaction, thus no further attempts at its synthesis were attempted.

Conversely, the tetrachloro derivatives better tolerated the synthesis of 206. However, 206 was not obtained, as the benzoin condensation of aldehyde 217 in the presence of catalyst 27, was too slow to be synthetically viable (16% conversion in 7 days, as determined by analysis of the $^1$H NMR spectrum of the crude reaction mixture). The sluggish benzoin condensation of 217 was likely caused by the steric hindrance introduced by the tetrachloro groups retarding the rate of reaction. As the benzoin condensation of 217 was not successful, it was deduced that benzil 206, if synthesised (through a different synthetic route other than
a benzoin condensation), it would not be an efficient substrate for the NHC-catalysed selective oxidative amidation reactions.

As the tetrachloro-substituted benzil 206 was too sterically encumbered to undergo either of the NHC-catalysed reactions it was required for, the bis-chloro derivative 207 (Figure 21) was proposed as an alternative solution. This acylating agent retains activating (from an electrophilicity standpoint) chlorine atoms on the aromatic ring of the benzil moiety, but is devoid of a sterically encumbering chloro-substituent adjacent to the carbonyl moiety which must be attacked by the carbene catalyst (and later, the amine nucleophile). Attempts at synthesising 207 were carried out in a similar fashion to that associated with 205 and 206 (Scheme 57).

Scheme 57  Attempted synthesis of 207

Commercially available, 4,5-dichlorophthalic anhydride (218) was converted to the corresponding carboxylic acid 219 via ring-opening with amine 200, in almost quantitative yield. Esterification of 219 and subsequent reduction furnished alcohol 221 which was oxidised to aldehyde 222 using MnO2. Disappointingly, 222 did not tolerate the benzoin condensation to furnish benzil 207. Aldehyde 222 was destroyed in the benzoin condensation with no trace of the product being observed in either the 1H NMR spectroscopy or TLC analysis of the reaction mixture. Due to the instability of such chloro- and fluoro-substituted intermediates and their intolerance to withstand NHC catalysis, this design strategy was abandoned.
2.4.4 Attempts to cleave the second-generation protecting group

The second class of novel amine protecting groups containing an amide substituent was targeted as it was postulated that there would be a wider range of deprotection strategies available. Substrate 198 was a prototype substrate; it had been noted that there were likely going to be difficulties associated with removing the benzyl group under mild conditions. In 2007, Kuang et al. reported the debenzylation of N-benzylcarboxamides of type 223, using N-bromosuccinimide (NBS) and catalytic N-methylacetylamide (NMA) at room temperature in moderate to good yields (Scheme 58).^{171}

Scheme 58  Debenzylation of N-benzylcarboxamides reported by Kuang et al.

Unfortunately, when the reaction was carried out with amide 225 (derived from the acylation of pyrrolidine by 198, Table 3, entry 1, Section 2.4.2) the deenzylated product 226 was not observed (Scheme 59). The reaction was carried out in chloroform (as per Kuang’s report) and also dichloromethane, however, no product was detected in the reaction mixture (monitored by both $^1$H NMR spectroscopy and TLC analysis); only unreacted starting material was obtained after stirring the reaction for 24 hours.

Scheme 59  Attempted debenzylation of 225 with NBS and NMA
2.5 Development of a third generation protecting group

The difficulties associated with deprotecting \(N\)-benzylated amides under mild conditions led to the development of a new substrate with a \(p\)-methoxyphenyl (PMP) substituent in place of the benzyl group (substrate 227, Figure 22).

![Figure 22: PMP-substituted substrate 227](image)

In 1984, Sameulsson et al. demonstrated that a \(p\)-methoxyphenyl (PMP) moiety can be cleaved from hydroxyl groups, using ceric(IV) ammonium nitrate (CAN), in an acetonitrile:water solvent system in excellent yields (up to 95% yield, Scheme 60).

![Scheme 60: PMP deprotection carried out by Sameulsson et al.](image)

The rationale behind designing substrate 227 was that the PMP group present in the protected amine, such as in 230, could be cleaved using CAN (at low pHs, in aqueous media) to form the corresponding secondary amide, 231, which could close upon the protected amine and in doing so, release it (Scheme 61).

![Scheme 61: Proposed deprotection of the protected amine 230 with CAN](image)
2.5.1 Substrate scope of the third generation protecting group 227

Substrate 227 was synthesised via ring-opening phthalide (199) with 4-methoxy-N-methylaniline (232) to form alcohol 233 facilitated by the addition of Lewis acid, AlCl₃ (Scheme 62). Subsequent oxidation of 233 furnished aldehyde 234 which was employed in a benzoin condensation. Oxidation of benzoin intermediate 235 furnished benzil 227 in a relatively low yield (Scheme 62).

![Scheme 62: Synthesis of benzil 227](image)

Upon synthesis of 227, it was employed in the NHC-catalysed oxidative amidation reaction in order to evaluate its efficiency as a protecting group precursor (Scheme 63).

![Scheme 63: NHC-mediated oxidative amidations between substrate 227 and cyclic amines](image)
When pyrrolidine was utilised as the amine in the NHC-catalysed oxidative amidation, a moderate yield of amide 236 was obtained (Scheme 63). However, when compared to the reaction between pyrrolidine and the first-generation substrate 178 (Table 2, entry 1) and the second-generation substrate 198 (Table 3, entry 1), 227 yielded the pyrrolidine amide in a comparably lower yield. Similarly, the use of piperidine furnished the amide product 237 in a poor yield of 33% (Scheme 63). As benzil 227 produced such disappointing results when employed in the NHC-catalysed oxidative amidation, diamines were not tested in the reaction. Additionally, benzil 227 was abandoned as a potential acylating agent due to its propensity to decompose over time (p-anisidine is known to be light sensitive and this may have contributed to the instability of the amide products).

It became apparent that having a reliable deprotection strategy was of the upmost importance when considering substrate design; as a large amount of time was consumed in synthesising substrates which then did not necessarily work well in the NHC-catalysed oxidative amidation. Accordingly, it was decided to first synthesise the ‘protected amines’ (protected as amides) and investigate potential deprotection strategies before undertaking the synthesis of any further benzils. Thereby if a deprotection strategy was not viable, no further effort would be directed towards that endeavour.

2.6 Evaluating deprotection strategies for protected amines

As the benzil substrates evaluated so far as protecting groups were not successful in furnishing protected amines in high yields and providing an efficient deprotection route, alternative solutions were necessary. When evaluating other potential protecting group strategies, one substrate which had not been considered until this point had been a benzil incorporating a secondary amide unit in its structure (238, Figure 23). Having a secondary amide in the benzil structure would mean that it would not be necessary to cleave an amide substituent (such as the benzyl group on substrate 198 or the PMP unit on 227) in order to carry out ring-closure on the protected amine and release it.

![Figure 23](Benzil containing secondary amide)
However, attempts to synthesise 238 via a benzoin condensation was not successful. This was likely due to the reactive nature of the secondary amide. Other synthetic routes towards the synthesis of 238 were not attempted and its synthesis was not pursued any further.

As discussed in Section 2.5.1, having spent a considerable amount of time synthesising benzils which proved inadequate in either the NHC-catalysed oxidative amidation, amine deprotection or both, it was decided to acquire the amines in their protected forms (synthesised stoichiometrically) and attempt to deprotect them, prior to any benzils being synthesised. By taking this approach, no further time or effort was spent pursuing substrates and deprotection strategies that were not functional. The protected amines (pyrrolidine in this case) that were synthesised and evaluated, contained an allyl substituent 239 and a Weinreb amide 240 (Figure 24).

**Figure 24** Protected amines 239 and 240

The synthesis of 239 and 240 was carried out in the same fashion and was relatively straightforward. These protected amines were synthesised via reaction of phthalic anhydride (241) with pyrrolidine to form carboxylic acid 242. Following an EDC-mediated coupling with the appropriate amine (N-allylmethyl amine (243) in the case of 239 and Weinreb amine (244) in the case of 240) to yield the desired products in moderate yields (Scheme 64).
Deprotection through cleavage of the allyl substituent of 239 was attempted using both palladium on carbon (in alcoholic and acidic media) and with palladium-tetrakis(triphenylphosphine)\textsuperscript{172,173}. Using these conditions promotes migration of the allyl double bond to form an enamine, which can be cleaved upon hydrolysis. However, all attempts to cleave the allyl substituent proved ineffective; analysis of the crude reaction mixture by \textsuperscript{1}H NMR spectroscopic methods and TLC analysis showed no product formation, only unreacted starting material. Although there is literature precedent that shows the cleavage of allyl groups from secondary amides is possible using other transition metals (such as ruthenium\textsuperscript{174} and nickel\textsuperscript{175}) these routes, along with the use of palladium catalysts, were not deemed viable as they were not in keeping with an organocatalytic process and so this deprotection protocol was not investigated any further.
Scheme 65  Conditions for attempted deprotection of the allyl substituent of 239

The Weinreb amide was chosen as a cleavable substituent as it has been shown that such alkoxy groups can be reduced from tertiary amines, using activated zinc and acetic acid, to furnish the corresponding secondary amine.\(^\text{176}\) Although this example used amines and not amides, the protocol was nevertheless attempted. Disappointingly, when this reaction was carried out on 240, cleavage of the methoxy group was not achieved (Scheme 66). Using excess zinc (up to 40 equivalents) and varying the ratio of aqueous to acidic media (condition sets A to C, Scheme 66) failed to promote any reaction; in all cases, only starting material was observed in analysis of the crude reaction mixture. Other alkoxy substituents were not screened at this stage, as modifying the alkyl substituent on the oxygen atom would result in increased steric bulk being introduced into an already stericly sensitive system (as discussed in Section 2.3.3).

Scheme 66  Attempted deprotection of the methoxy group on 240 via a zinc-mediated reduction

While all the efforts thus far towards the development of a facile deprotection strategy proved unsuccessful, gratifyingly, changing the amide unit ortho to the protected amine to a nitrile yielded more promising results. The potential advantages associated with the inclusion of a nitrile substituent as the handle for deprotection were three-fold. Firstly, it is possible to reduce aromatic nitriles to the corresponding primary amines via hydrogenolysis.
at atmospheric pressure.\textsuperscript{177} When this reaction was carried out on protected amine 245, the corresponding amine 246 was produced in a respectable yield (Scheme 67).

![Scheme 67 Aromatic nitrile reduction](image)

It was envisaged that primary amine 246, the product of the nitrile reduction, could close upon the protected amide under base-catalysed conditions to form lactam 247 and release the protected amine (Scheme 68).

![Scheme 68 Base-catalysed ring-closure and amine release](image)

Simultaneously, the nitrile would serve as an electron withdrawing group, activating the C-2 position towards nucleophilic attack and potentially increasing the yield of the NHC-catalysed oxidative amidation. Also, in terms of minimising steric hinderances in the substrate, a nitrile group is also one of the smallest possible electron withdrawing groups, again potentially increasing the yield of the subsequent catalysis reaction.

With a potential deprotection strategy in hand, it was necessary to synthesise benzil 248 (Figure 25) which would contain nitrile groups \textit{ortho} to the benzil carbonyls.

![Figure 25 Ortho-nitrile substituted benzil 248](image)
The initial strategy towards the synthesis of 248 was to carry out a benzoin condensation on commercially available 2-cyanobenzaldehyde (249) to form benzoin 250 followed by subsequent oxidation to form benzil 248 (Scheme 69, route A). Disappointingly, due to the reactive nature of the nitrile group, this reaction was not successful. As only a decomposition product was obtained from the benzoin condensation at room temperature, the reaction was carried out at lower temperatures. Initially the reaction temperature was set at -78 °C and the reaction monitored by 1H NMR spectroscopy. After 5 days stirring at -78 °C with no conversion to the benzoin product, the temperature was slowly increased to -60 °C followed by -20 °C and -10 °C. Unfortunately, at all temperatures and after 8 days of monitoring the reaction, 74% of aldehyde 249 remained (determined by 1H NMR spectroscopic analysis of the reaction mixture) and 250 was not observed (Scheme 69 A).

Another coupling reaction that was attempted to synthesise 248 (via diol 251), was a pinacol coupling with 249, mediated by aluminium under basic conditions (Scheme 69, route B). It was envisaged that diol 251 could then be oxidised to 248. This reaction was carried out using a relatively mild set of reaction conditions (the equivalents of aluminium and base used were kept to a minimum). Unfortunately, although the coupling was possible, 251 was not obtained, instead the nitrile groups were hydrolysed to the corresponding carboxylic acid to form 252 (likely assisted by the coordination of aluminium between the diol oxygen and the nitrile, followed by hydrolysis by potassium hydroxide).

![Scheme 69 Attempted synthesis of 248 using coupling reactions](image)

An alternative route that was investigated was to install the diketone moiety in 248 via epoxide ring-opening. This was carried out by first synthesising the phosphonium salt 254 of 2-(bromomethyl)benzonitrile 253 (by treatment with triphenylphosshine) (Scheme 70,
route C). A Wittig reaction was carried out between salt 254 and 249 to produce olefin 255 (Scheme 70, route C). It had been thought that oxidation from alkene 255 towards formation of benzil 248 could be achieved via epoxidation of 255 by meta-chloroperoxybenzoic acid (mCPBA), followed by hydrolysis to form diol 251 and oxidation to 248 (Scheme 70, route C). However, epoxide 256 was not formed (determined upon analysis of the $^1$H NMR spectrum of the reaction mixture). This may be attributed to the electron-deficient nature of 255. Typically, epoxidation reactions using peroxyacids are best achieved with electron-rich, non-sterically encumbered alkenes, thus 255 was not a good candidate for epoxidation in this manner.

The last method explored was to synthesise epoxide 256 via a Johnson-Corey-Chaykovsky reaction$^{178}$ between sulfonium salt 259 and aldehyde 249; providing the desired product in a low conversion of 28% (determinised by $^1$H NMR spectroscopy, Scheme 70, route D). *In situ* hydrolysis of epoxide 256 proved much more difficult than anticipated, likely due to the hydrophilic nature of 251 in combination with the necessity to use aqueous acid or base to achieve this hydrolysis (diol 251 was not recovered from the organic layer at the end of the work-up procedure).

Currently, all efforts towards the synthesis of 248 have proved futile, and even more discouragingly, 249 did not tolerate the benzoin condensation reaction (this is generally an indicator that the corresponding benzil will not withstand the NHC-catalysed oxidative amidation reaction). As a result, it was decided not to pursue the synthesis of 248 any further.
After significant experimentation to develop a selective protecting group methodology for diamines, the methodology that had proved most effective so far was the modified pyridil system (benzil 178, Figure 16). Examination of this structure led to the development of a new deprotection methodology. It was postulated that 2,2-pyridil (258), which is commercially available and unsubstituted at the C-2 position, could be used in the NHC-catalysed oxidative amidation reaction to produce amines protected as amides. Modification of the endocyclic nitrogen atom of the pyridine ring of the subsequent amide would yield an organic salt 259 that, upon manipulation, could close onto the carbonyl of the amide to release the amine 261 and form lactam 260 as a by-product (Scheme 71).
2.7.1 Substrate scope of 2,2-pyridil

With a potential deprotection methodology in hand, evaluating the scope of 258 in the NHC-catalysed oxidative amidation reaction was attempted (Table 4).

The initial set of amines evaluated were primary and secondary amines. Encouragingly, when the cyclic amines pyrrolidine and piperidine were employed in the reaction, excellent yields of the corresponding amides 262 and 263 (Table 4) were achieved. Comparing these results to the other substrates screened (i.e. 178, 198 and 227) and employed in the same reaction so far (Tables 2, 3 and 4), somewhat unsurprisingly, 258 is superior in this reaction.

The superiority of 258 in the amidation reaction is likely due to the electrophilic nature of the benzil carbonyl of 258, assisted by the electron-withdrawing capabilities of the nitrogen of the pyridine ring and the absence of a substituent ortho to the electrophilic carbonyl group. The lack of such substitution in 258 means that the reaction intermediates in the catalytic cycle are less sterically encumbered, thus accounting for increased yields in this amidation reaction. This trend is observed overall for all amides formed and the results are displayed in Table 4.

Scheme 71  Postulated modification of the protected amine to allow deprotection
Table 4  
Substrate scope of 2,2-pyridil (258) and various primary and secondary amines

```
\[
\text{258 (1.0 equiv.)} + \text{R}^1 \text{N} \text{R}^2 \text{H} \rightarrow \text{25 (15 mol\%) \ 53 (1 equiv.) DBU (1.1 equiv.) THF (0.2 M) Ar, rt, 24 h} \\
\text{258 (1.0 equiv.)} \rightarrow \text{R}^1 \text{N} \text{R}^2 \\
\]
```

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>262</td>
<td>93%</td>
</tr>
<tr>
<td>263</td>
<td>94%</td>
</tr>
<tr>
<td>264</td>
<td>93%</td>
</tr>
<tr>
<td>265</td>
<td>83%</td>
</tr>
<tr>
<td>266</td>
<td>65%</td>
</tr>
<tr>
<td>267</td>
<td>99%</td>
</tr>
<tr>
<td>268</td>
<td>83%</td>
</tr>
<tr>
<td>269</td>
<td>79%</td>
</tr>
<tr>
<td>270</td>
<td>68%</td>
</tr>
<tr>
<td>271</td>
<td>91%</td>
</tr>
<tr>
<td>272</td>
<td>81%</td>
</tr>
<tr>
<td>273</td>
<td>66%</td>
</tr>
</tbody>
</table>

The ability of 258 to tolerate steric bulk on the amine substituent was investigated using simple primary amines isobutylamine (274), isopropylamine (275) and secondary amine dipropylamine (276, Table 4). In the case of 274, the steric bulk is situated at the β-carbon and the corresponding amide product 264 was isolated in excellent yield. Comparatively, when the steric bulk on the amine is moved to the α-carbon, as is the case with 275, the yield of the corresponding amide 265 was lower but remains a respectable yield. This result further highlighted the steric sensitivity of this reaction with respect to the amine. While this decrease in efficiency is not dramatic, it is still informative in understanding why other more sterically encumbered benzils previously designed were not suitable for this reaction. When 276, a relatively sterically encumbered secondary amine was screened in this reaction (Table 4, amide 266), a moderate isolated yield was obtained. This result was not surprising due to the now clear effect of steric bulk in this sensitive system.
Next, amines that contained some alkene and alkyne functionality were evaluated to see if they were tolerated in the NHC-catalysed oxidative amidation reaction. Use of (E)-3-phenylprop-2-en-1-amine (277) produced the corresponding amide 267 in an almost quantitative yield (Table 4). Amine 277 was synthesised by carrying out a Mitsunobu reaction between cinnamyl alcohol (278) and phthalimide (279) to form 280 (Scheme 72). Imide 280 was subsequently deprotected using excess hydrazine hydrate (281) to render amine 277 in a relatively low yield (Scheme 72).

\[
\text{Ph} \quad \text{OH} \quad \text{PPh}_3 \text{ (1.3 equiv.)} \quad \text{MeOH (0.06 M)} \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O (4 equiv.)} \\
\text{278} \quad \text{279 (1.5 equiv.)} \quad \text{280 (60%)} \quad \text{281 (4 equiv.)} \quad \text{277 (44%)}
\]

Scheme 72 Synthesis of amine 277

When allylamine (282) was evaluated in the reaction, a good isolated yield of amide 268 was obtained, while its alkynyl counterpart, propargyl amine (283) furnished amide 269 in a satisfactory yield (Table 4). The lower yield of 268 and 269 may be related to the volatility of allylamine (282, b.p. 54 °C) and propargyl amine (283, b.p. 83 °C) at s.t.p.; since the solid cinnamylamine 277 produced 267 in near quantitative yield.

Piperidine-4-carbonitrile (284), a cyclic secondary amine containing an electron withdrawing group at the 4-position, was employed in this reaction and produced amide 270 in a somewhat diminished yield (relative to the use of piperidine itself, Table 4). However, these results were pleasing as they demonstrated that 258 could undergo the NHC-catalysed amidation reaction with varying steric bulk and functionality in the amine nucleophile (i.e. yielding amides 267-270).

The reaction was carried out with varying substitution around a benzylamine core; further probing steric bulk in the amine nucleophile. Benzylamine (285), α-methylbenzylamine (286) and N-methylbenzylamine (200) were utilised in the amidation reaction. The amidation reaction carried out with 286 furnished amide 271 in an excellent yield. The addition of a methyl group at the α-position (amine 286) furnished amide 272 in a high yield; albeit a 10% yield decrease when compared to the use of 285 as the amine. This result highlighted again how sterically sensitive this reaction is; the introduction of a single methyl group one carbon away from the reactive nitrogen atom will result in a reduction in the
efficiency of the reaction (in terms of yield). Thus, it was unsurprising that amide 273 derived from 200 was furnished in a moderate yield of 66% (Table 4).

After investigating the influence of amine structure in the amidation reaction, a small library of diamines was selected for screening in the NHC-catalysed acylation by 258 to observe if the acylation reaction occurs chemoselectively (Table 5).

**Table 5** Substrate scope of 258 and various diamines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>287</td>
<td>94%</td>
</tr>
<tr>
<td>288</td>
<td>98%</td>
</tr>
<tr>
<td>289</td>
<td>98%</td>
</tr>
<tr>
<td>290</td>
<td>94%</td>
</tr>
<tr>
<td>291</td>
<td>98%</td>
</tr>
<tr>
<td>292</td>
<td>77%</td>
</tr>
</tbody>
</table>

*0.5 equivalents of 258 utilised*

With regard to the reactions involving diamines (Table 5), both the yield of the reaction and the selectivity with regards to the amine being acylated was examined. As it was demonstrated that sterically hindered amines (both primary and secondary) were not tolerated as well as those that are not sterically encumbered. In a system in which a diamine contains two nitrogen atoms in slightly different steric environments, the least hindered nitrogen atom should be acylated first. Also, by altering the number of equivalents of 258 used in the reaction, no acylation should be detected at the free amino terminus (*i.e.* no bis-acylation of the diamine should occur).

Initially, the reaction between 258 and some commercially available diamines was investigated. The first diamine tested in this reaction was 2-(aminomethyl)piperidine (162). This diamine incorporates both a primary amine and a cyclic secondary amino unit. As was
postulated, the acylation of 162 occurred chemoselectively to furnish amide 287 in an excellent isolated yield.

The next amine that was evaluated in this system was 3-(methylamino)propylamine (163), an aliphatic amine with both a primary and secondary amine terminus. The steric differences between the amino moieties in this diamine are less pronounced than with 162, but it was still anticipated that acylation would occur at the less hindered primary amine. Gratifyingly, acylation was achieved with 100% selectivity at the primary amine to produce amide 288 in an almost quantitative yield. In order to probe the selectivity of this reaction further, it was decided to evaluate 1,2-diaminopropane (116). Again, the system was capable of selecting between the two primary amines in 116, distinguished only by an α-methyl group, to produce amide 289 in an excellent isolated yield (Table 5).

The next challenge posed to this selective amidation reaction, was to distinguish between two different secondary amino groups on the same molecule. The diamines selected for testing, 120 and 164 were not commercially available and had to be synthesised as outlined in Scheme 73.

Scheme 73  Synthetical route towards diamines 120 and 164

Protection of commercially available 3-methylamino-1-propanol (293) with di-tert-butyl dicarbonate furnished protected amine 294. Tosylation of the free alcohol of 294 to form bis-protected 295 was carried out in a poor yield of 35%. Substitution of the tosyl group with the appropriate amine, ethyl amine in the case of 296 and isopropyl amine in the case of 297 was subsequently carried out. Removal of the Boc protecting group of 296 and 297 was
carried out under acidic conditions using TFA. The resulting TFA salts of the amines were treated with K₂CO₃ to furnish the desired products 120 and 164.

With the diamines of interest in hand, the NHC-catalysed oxidative amidation reaction was carried out. Gratifyingly, amine 164 produced amide 290 unambiguously, achieving 100% selectivity towards amidation at the methylamine terminus in an excellent isolated yield (Table 5). Amine 120 was designed to test the limits of the steric selectivity of this reaction. It contains two secondary amino units, one substituted with a methyl group and the other with an ethyl group. Structurally this difference should be so insignificant that the system should not able to distinguish between them but astonishingly, acylation occurred chemoselectively at the methyl amine terminus to furnish amide 291 in an almost quantitative yield. This result further highlights the remarkable selectivity associated with this reaction.

As none of the reactions with diamines outlined so far produced any bis-acylated products, it was decided to provide a significant challenge in this context. When (±)-trans-1,2-diaminocyclohexane (298) was utilised in this reaction (Table 5), monoacylated amide 292 was formed in a reduced, yet appreciable, yield of 77%; with the remainder obtained being bisacylated product. Amine 298 is particularly useful as it is a core structure in several asymmetric catalysts¹⁸¹,¹⁸²,¹⁸³ (e.g. 299 - 301, Figure 26) and its need to be mono-acylated is of great synthetic interest in catalyst synthesis.

![Figure 26](image)

**Figure 26** Examples of (±)-trans-1,2-diaminocyclohexane (298) cores in asymmetric catalysts

Preparations of mono-acylated 298 have been achieved in the literature however, they require the use of excess 298, which is undesirable due to its considerable expense. Lee et al. reported the mono-Boc protection of 298 in an 80% yield using just one equivalent of the amine and one equivalent of di-tert-butyl dicarbonate, however HCl gas is used to achieve this transformation, which is impractical to use on an industrial scale (Scheme 74).¹³⁰
Scheme 74  Mono Boc-protection of 298 reported by Lee et al.

2.7.2 Competition experiments to investigate possible intramolecular hydrogen bonding

It was considered that intramolecular hydrogen bonding may be facilitating such exquisite selectivity obtained in the experiments outlined in Table 5. Accordingly, competition reactions were carried out to investigate this. In such competition reactions, 258 was reacted with two different amines (1 equivalent of each) containing varying steric bulk, to observe if either amine would be acylated preferentially in the NHC-catalysed amidation. The first reaction performed was between benzylamine (285) and N-methylbenzylamine (200). The less sterically hindered benzylamine-derived amide 271 was furnished in a 79% yield while no trace of amide 273 was detected (Scheme 75).

Scheme 75  Competition between 285 and 200 for reaction with 258 in the presence of 25

A similar competition experiment was carried out between benzylamine (200) and α-methylbenzylamine (286, Scheme 76). Once again, amide 271 was formed exclusively in an excellent isolated yield, while acylation of the more sterically encumbered amine 286 was not observed. From the results obtained in Schemes 75 and 76 it can be deduced that the ability of the system to acylate the least hindered nitrogen atom in a diamine is related to steric sensitivity of the process and not through formation of intramolecular hydrogen bonds between the termini of either the substrates or products.
Scheme 76 Competition between amines 285 and 286

While benzylamine was consumed in both of these reactions (Schemes 75 and 76, detected by $^1$H NMR spectroscopy using $p$-iodoanisole as an internal standard) and none of the more sterically hindered amide was detected in either case, it is assumed that the remainder of 258 used in the reaction is not regenerated in the catalytic cycle and becomes oxidised to the DBU-carboxylate salt (303, Figure 27; this by-product was not readily detected by NMR spectroscopy or mass spectrometry analysis in this project, however it has been detected in previous NHC-catalysed oxidative amidation reactions).88

![Scheme 76](image)

Figure 27 2,2-Pyridil-derived DBU-carboxylate salt 303

With a successful acylation protocol of both amines and diamines having been developed, it was next necessary to develop a facile deprotection strategy to cleave the pyridil unit from the protected amines.

2.8 Development of a strategy to cleave pyridil unit from protected amines

The basis of this cleavage strategy, as shown in Scheme 71 (Section 2.7), was to react the nitrogen atom of the pyridoyl-protected amine with an electrophile that upon manipulation can close to release the protected amine; a similar principle to all the previous deprotection strategies. The problem anticipated with this deprotection method was that the pyridine nitrogen atom would not be sufficiently nucleophilic to attack the electrophile necessary for deprotection. Although the pyridine nitrogen atom can be alkylated with electrophiles (often Lewis acids) to form the corresponding pyridinium salts,184–186 the added steric bulk of the C-2 amide in these pyridoyl-protected amines was predicted to pull electron density away from the nitrogen atom, thus reducing its nucleophilicity. As a result, when deciding on
electrophiles for this system, it was imperative that their electrophilicity be primed for alkylation by the pyridoyl nitrogen atom. The library of electrophiles screened for use in this deprotection strategy are shown in Figure 28.

![Figure 28](image)

**Figure 28** Library of electrophiles tested to promote the cleavage of the pyridoyl moiety

### 2.8.1 Electrophile screen to promote pyridil cleavage

The initial electrophiles screened contained an ester functionality of general structure 314, the premise being that upon alkylation, the resulting ester 315 could be reduced to alcohol 316 which can attack the carbonyl of the amide, releasing amine 318 (Scheme 77).

![Scheme 77](image)

**Scheme 77** Proposed pyridil cleavage using an ester-containing electrophile

When methyl bromoacetate (304) was employed as the electrophile, no reaction between it and the model pyridoyl-protected amine 262 was observed (Scheme 78). The same result was observed when phenyl bromoacetate (305) and 2-bromoacetamide (306) were utilised (Scheme 78). Heating the reaction mixture under reflux and the addition of tetrabutylammonium iodide (TBAI, added to convert the alkyl chloride to the more
electrophilic alkyl iodides, via the Finkelstein reaction$^{187}$ still failed to promote alkylation in each case. Attempts were not made to further optimise this reaction.

Another electrophile that was screened was 2-(bromomethyl)benzonitrile (307). It was postulated that upon alkylation, the nitrile in 320 could be reduced to the corresponding primary amine 321 which could close (possibly facilitated by basic conditions). Reaction of 307 with 262 furnished the corresponding pyridinium salt 320 in a moderate yield, however heating the reaction mixture under reflux and the addition of TBAI was required to achieve this (Scheme 79). Attempts to reduce 320 to 321 (using the conditions outlined previously in Scheme 67, Section 2.6) proved unsuccessful. The crude reaction mixture was analysed by TLC and $^1$H NMR spectroscopy and was found to contain multiple compounds, none of which were determined to be the desired product.

Substituted aromatic benzyl bromide derivative 308 was also evaluated in this alkylation reaction. Incorporating a Boc-protected primary amine ortho to the electrophilic site, it was envisaged that once alkylated, removal of the Boc group would render it possible for the primary amine to close upon the pyridoyl amide and allow for deprotection. Synthesis of 308 was carried out by first protecting the primary amine of 2-aminobenzyl alcohol (322) with di-tert-butyl dicarbonate to form protected amino alcohol 323 in near quantitative yield.
Alcohol 323 was transformed to benzyl bromide 308 via a subsequent Appel reaction (Scheme 80).

Scheme 80  Synthesis of electrophile 308

While alkylation of 262 with 308 was possible, albeit in a moderate yield (Scheme 81), problems arose upon deprotection of the Boc group to reveal the primary amine. The use of TFA (a standard deprotection method for removal of Boc groups, see Section 1.6.1.1) to carry out the Boc deprotection of 324 resulted in cleavage of the previously installed electrophile and regeneration of 262 and 308 (Scheme 81).

Scheme 81  Attempted use of 308 as an electrophile for pyridoyl cleavage

2.8.2 Development of 2-iodoethanol derivatives as electrophiles

Optimisation of the routes outlined in Schemes 78-81 (Section 2.8.1) was not carried out as, in the interim, alkylation of 262 with 309 was carried out with initial moderate success. Excess TBS-protected 2-iodoethanol 309 was initially installed to 262 via heating in a sealed tube at an elevated temperature of 120 °C using acetonitrile as the solvent (the boiling point of acetonitrile is 82 °C at s.t.p., thus the necessity to use a sealed tube). This furnished the organic salt 326 in 73% yield (Scheme 82).
Prototype amide 262 used for the deprotection studies up until this point, was changed to 273; as the methylbenzyl motif possesses more distinct signals in the $^1$H NMR spectrum which allows the reactions to be easily monitored by $^1$H NMR spectroscopy. $N$-methylbenzyl amine (200) is also not as volatile as pyrrolidine so it can be trapped at the end of the deprotection reaction if care is taken. The yield of salt 327, the product when 273 was alkylated with 309 was increased to 87% by changing the concentration of acetonitrile from 0.4 M to 1.0 M (c.f.73% yield in Scheme 82); this also allowed for the equivalents of electrophile used to be lowered from five to four (Scheme 83). Other electrophiles were evaluated in this reaction to try increase the yield above 87%; the leaving group component of the electrophile was modified to those considered more electrophilic than iodide in an attempt to achieve this. Electrophiles 310, 311 and 312, depicted in Figure 28 (Section 2.8) were screened and their performance in this reaction is shown in Scheme 83.

![Scheme 83 Evaluation of electrophiles in the alkylation of 273](image)

When the tosyl-protected electrophile 310 was used as the alkylating agent, salt 328 was obtained in an excellent yield. The yield of 329 was somewhat diminished when 311, the analogous mesyl-protected derivative was employed (Scheme 83). Somewhat surprisingly, when the most electrophilic of this suite of electrophiles was employed in this reaction, triflate-protected 312, a disappointing 22% yield of salt 330 was obtained. This observation is likely attributed to the increased reactivity of 311 and 312; these electrophiles were found to decompose over time (even while being stored in the freezer), thus decreasing the amount of viable electrophile available in the reaction mixture for alkylation. Taking these results into consideration, 309 and 310 were chosen for further reaction optimisation.

With an alkylation strategy in hand, albeit unoptimised, studies into ring-closure to facilitate amine deprotection were undertaken. Organic iodide salt 327 was first evaluated in the ring-
closure; facilitated under acidic conditions. Consideration was taken to choose an organic acid when devising conditions for this reaction; the use of an aqueous acid may have complicated the work-up step, as both the lactone by-product 331 and the de-protected amine salt 332, would likely proved difficult to extract from an aqueous layer due to their hydrophilic nature. The organic acids chosen initially were $p$-toluenesulfonic acid (PTSA) and camphorsulfonic acid (CSA). While PTSA did promote the ring-closure with moderate efficiency (24 hours, 65% conversion of 327 to 331, determined by $^1$H NMR spectroscopic analysis), CSA was superior in this reaction (Scheme 84), facilitating deprotection in 18 hours at 70 °C with 100% of 327 being converted to salt 331 (determined by analysis of the $^1$H NMR spectrum) and 92% of amine salt 332 was recovered.

**Scheme 84** Deprotection of $N$-methylbenzyl amine (200) from 327 mediated by CSA

An unexpected observation with this reaction was that when it was carried out using CHCl$_3$ as the solvent, the by-product, lactone salt 331 precipitated from solution. This facilitated a simple purification procedure for this reaction; filtration of 331 and concentration of the filtrate yielded 332. When this reaction was attempted with tosylate derivative 328 the reaction proceeded and salt 333 was obtained, as was a mixture of both $N$-methylbenzyl amine (200) and its CSA salt 332 (Scheme 85).

**Scheme 85** Deprotection of 200 from 328 using CSA

Disappointingly, 333 is soluble in CHCl$_3$ and so separation of it from 200 and 323 was more cumbersome and required careful extractions. Other solvents were screened in this reaction (CH$_2$Cl$_2$, toluene, DMF, CH$_3$CN) but yields were highest when CHCl$_3$ was used. Although tosylate salt 328 underwent deprotection efficiently (96% total yield of amine salt and free
base) it was not investigated further as its purification was more complicated than that of iodide salt 327.

2.8.3 Optimisation of the alkylation strategy using 2-iodoethanol derivatives

While the ring-closure/pyridil cleavage worked well with 327 (Scheme 84), attempts to optimise the alkylation reaction (Scheme 83) by altering the solvent used were undertaken. This solvent screen was carried out in order to investigate if the use of other solvents could reduce the reaction time and reaction temperature required for alkylation. The criteria for choosing potential solvents for this alkylation reaction were threefold. The solvent should be one that typically favours SN2 reactions, i.e. polar aprotic solvents. It should be polar enough to dissolve both the nucleophile and electrophile; and it should not undergo intermolecular hydrogen-bonding with the nucleophile. With this in mind, the solvents screened were CH₃CN, acetone, DMF, DMSO respectively and the results are summarised in Table 6.

Table 6 Solvent screen to carry out 327 alkylation optimisation

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temperature</th>
<th>yield⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>120</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>acetone</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>120</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>120</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

⁺Isolated yield determined after flash column chromatography

Entry 1 of Table 6 is the same result as outlined in Scheme 83, when the reaction was carried out in acetonitrile (87 % yield). When acetone was used in this reaction, a low yield of 20% was obtained after 18 hours with heating at 60 °C (Table 6, entry 2), comparatively acetone was much slower at promoting this reaction; a higher yield is likely had the reaction been allowed to proceed past 18 hours. When DMF was used in this reaction (Table 6, entry 3) at
120 °C (boiling point of DMF: 153 °C at s.t.p.), the reaction mixture was complicated to analyse by both TLC analysis and ¹H NMR spectroscopy as many products were observed and it was difficult to identify any discernible amounts of 327. While DMSO did facilitate alkylation of 273 (68% conversion as determined by ¹H NMR spectroscopy using p-iodoanisole as the internal standard) it was not trivial to extract salt 318 from the final reaction mixture, consequently making DMSO an unsuitable choice of solvent for this reaction. Following the solvent screen, a more efficient protocol for alkylation was still required for the deprotection methodology. This led to the electrophile being re-examined. While the leaving group had been investigated previously, in an effort to improve the yield of the reaction (Scheme 83), the alcohol protecting group component had not been considered. The alcohol moiety of 309 was protected as a silyl ether as it was envisaged that the free alcohol would close upon itself to form an oxirane, under the reaction conditions, rendering itself unusable in the alkylation. Alkylation of 273 with unprotected 2-iodoethanol (334) was carried out using only 1.5 equivalents of the electrophile, to furnish organic salt 335 in almost quantitative yield (Scheme 86). Purification of 335 was carried out by concentrating the reaction mixture in vacuo and passing the residue through a short plug of silica to remove any excess electrophile and internal standard (included to monitor the reaction progress by ¹H NMR spectroscopy). The pyridil unit of 335 was then cleaved using CSA, furnishing the CSA salt of N-benzylmethyl amine 332 and heterocyclic lactone salt 331 as the by-product.

Scheme 86 Alkylation of 273 and subsequent deprotection of 200 as CSA salt 332
This methodology could be extended to other tertiary amides such as pyrrolidine amide 262 (Scheme 87). Again, alkylation was carried out in an excellent yield and ring-closure was successful with 100% of salt 336 being converted to lactone 331 and the pyrrolidine CSA salt 337 being recovered (as determined by analysis of the ¹H NMR spectrum of the reaction
mixture using \( p \)-iodoanisole as the internal standard). An accurate isolated yield of \( 339 \) was not determined due to its low molecular weight and resulting volatility.

**Scheme 87**  Alkylation of \( 262 \) and subsequent deprotection of pyrrolidine

Amides which were the products of the chemoselective acylation such as amide \( 291 \) which contains a free amino group, were deprotected using a similar methodology, however, the amino group was first Boc-protected to prevent its possible acylation by \( 334 \) (Scheme 88). A one-pot Boc-protection and alkylation afforded salt \( 338 \) in an excellent isolated yield. Salt \( 338 \) was purified by passing the final reaction mixture through a short plug of silica and upon purification was lactonised using CSA to furnish \( 331 \) and render the deprotected amine \( 120 \) as its CSA salt \( 339 \), in 100% conversion (as determined by \(^1\)H NMR spectroscopy using \( p \)-iodoanisole as the internal standard). Isolated yields of pyrrolidine and amine \( 120 \) have not been obtained at present due to the volatile nature of these amines. As it was clear that this methodology works due to observation of salt \( 331 \) and amine salts \( 337 \) and \( 339 \) by \(^1\)H NMR spectroscopic analysis, it was decided that the isolation of these amines was not necessary at present.

**Scheme 88**  Deprotection of tertiary amides incorporating a free secondary amide
2.8.4 Extending the methodology to amides incorporating free amino groups

When this methodology was extended to secondary amides or tertiary amides incorporating free amino groups, complications arose. Attempts to alkylate secondary amide 271 with either unprotected 334 or its TBS-protected counterpart 309 failed to produce significant quantities of 340 in either case, even after a prolonged reaction time of 48 hours (Scheme 89).

Scheme 89 Attempted alkylation of secondary amide 271

A potential reason for this alkylation reaction either not occurring at all, or being very sluggish, is that the proton of the secondary amide could undergo intramolecular hydrogen bonding with the pyridoyl nitrogen atom and in doing so, reducing its nucleophilicity towards alkylation with either 309 or 334 (depicted in Scheme 89). As 334 is more electrophilic than the protected analogue 309, the reaction does proceed, albeit very slowly (30% conv. was observed after 48 hours, Scheme 89). Similarly, when amide 288 was used (a secondary amide with a free amino group) alkylated product 341 was not observed when using electrophile 334 (Scheme 90). Again, intramolecular hydrogen bonding between the amino groups and the pyridoyl nitrogen atom is likely responsible for preventing the alkylation from occurring.

Scheme 90 Attempted alkylation of 288
A means to overcome this problem was to protect the free amido unit of 271 with a Boc group and then carry out the alkylation reaction as depicted in Scheme 89A. However, Boc-protection of 271 to furnish 342 did not allow for alkylation to proceed with 334, presumably due to the additional steric bulk of the Boc group hindering alkylation from occurring. At this juncture, it was clear that an alternative solution was necessary to pyridil cleavage from such secondary amides. In 2002, Monteiro et al. reported the reductive cleavage of tert-butyl acylcarbamates using NaBH₄ on this exact substrate, amide 271 (Scheme 91B).\(^{188}\) The reductive cleavage would proceed by an initial hydride transfer from NaBH₄ to Boc-protected 342 to produce the corresponding 2-pyridinecarboxaldehyde (343) and deprotect the amine as Boc-protected 344. The resulting aldehyde by-product 343 is then readily reduced to 2-pyridinemethanol (345) which is easily separated from 344 during the work-up procedure.

Scheme 91  Methods attempted to deprotect secondary amides

The same methodology was extended to the challenging secondary amides with free secondary amines such as 288. Boc-protection of the two amino groups of 288 produced bis-protected 346 in an excellent yield (Scheme 92). It is worth noting that the Boc-protection of pyridoyl C-2 secondary amides is not trivial\(^{188}\) and in the case of both 271 (Scheme 91) and 288 (Scheme 92), relatively large numbers of equivalents of di-tert-butyl dicarbonate were required to carry out this protection. Gratifyingly, reductive cleavage of 346 was
carried out in a good yield in only two hours, to furnish the desired Boc-protected amine 347.

Scheme 92  Deprotection of secondary amides with free secondary amines

2.9 Conclusions: Chapter 2

Having previously carried out the NHC-catalysed acylation of diamines using benzil (70, Scheme 47), it was observed that this reaction occurred with unprecedented levels of chemoselectivity; the least hindered amine in the system being acylated preferentially. This unexpected result can be explained by the sterically hindered reaction intermediates in the catalytic cycle of this reaction. Following this observation, it was decided to exploit this chemoselectivity to design a new amine protecting group, containing a benzil core. This protecting group would be installed via an NHC-catalysed oxidative amidation, in doing so the amine is protected as an amide. Following a first- and second-generation protecting group design, it was decided that simple 2,2-pyridil (258) would be used as the acylating agent of choice.

Pyridil (258) was demonstrated to be an unconventional acylating agent, capable of the chemoselective acylation of a range of primary and secondary amines in the presence of an NHC catalyst. In the examples outlined in this chapter, exquisite levels of chemoselectivity were observed using this methodology. The system can easily discriminate between amines in a diamine – always acylating the least hindered N-atom, producing amides in high yields. This methodology allowed for the acylation of a range of primary and secondary amides. Primary amines were acylated exclusively over secondary amines in diamines and in the case of diamines containing two secondary amines, impressively, the system can distinguish between them based only on subtly steric differences; an N-Me substituted amine can be exclusively acylated in the presence of an N-Et substituted unit.
Alkylation of the nitrogen atom of the subsequent pyridoyl amides allowed for the deprotection of the amines. A novel set of conditions was developed to deprotect the monoacylated pyridoyl amines, without requiring the harsh acidic and basic hydrolytic conditions associated with cleaving benzoyl units from amines. This methodology can thereby be employed as a highly chemoselective protection group strategy for amino groups.

A summary of the novel deprotection methodologies developed which allow the resulting monoacylated pyridoyl amides to be cleaved is shown in Scheme 93. These conditions cleave the pyridoyl unit without requiring the harsh acidic and basic hydrolytic conditions associated with benzoyl protection of aliphatic amines; thereby allowing this methodology to potentially serve as a highly chemoselective protection group strategy for amino groups.
Scheme 93  Summary of pyridoyl-amide cleavage
Chapter 3 DKR of azlactones via aminolysis

As discussed in Section 1.8.3, a robust methodology that employs the aminolysis of azlactones under DKR conditions, to provide the corresponding amides, is lacking in the literature. Additionally, a methodology that allows the aminolysis of azlactones by amino acids or peptides, producing not only diastereomERICally pure products, but also carrying out a peptide coupling step in situ (forming orthogonally-protected di- and tripeptides) would be both novel and highly beneficial to the field. Thus, the aim of this project was to develop such a methodology that would produce not only enantioenriched amides derived from azlactones, but in doing so, develop a method of peptide coupling that does not require an S,N-acyl transfer as with NCL or an O,N-acyl transfer as reported by Connon and co-workers in 2015.156

3.1 Initial studies: fluorinolysis of azlactones

Connon and co-workers recently reported the enantioselective desymmetrisation of meso-anhydrides by a fluoride ion, mediated by phase-transfer catalysis (PTC).189 This study prompted the use of a fluoride ion to facilitate azlactone aminolysis. As discussed in Section 1.8.3, the aminolysis of azlactones is difficult due to the highly nucleophilic and basic nature of amines and their propensity to racemise azlactones and add to them uncatalysed. For this reason, it was envisaged that fluorinolysis of an azlactone to produce an acyl fluoride intermediate, which could be quenched with an amine, would furnish the desired amide product. It was proposed that if a fluoride ion could be generated in a chiral environment, it could be possible to gain enantiocontrol over the fluoride-catalysed ring-opening step.

The initial work on this concept was carried out by Ms. Sarah Cronin. Development of this methodology was largely inspired by a 2015 publication by Seidel et al., who reported a dual-catalysis anion binding approach, for asymmetric acyl transfer reactions (Scheme 94).190

![Scheme 94](image)

Seidel’s anion-binding concept for asymmetric acyl transfer reactions190
This chiral acylating agent is generated \textit{in situ} via an interaction between three components: DMAP (348), an achiral acylating reagent and a chiral anion receptor/hydrogen bond-donating catalyst.\textsuperscript{190} When DMAP and various acylating agents are combined they are known to exist in equilibrium with their acyl pyridinium salts (349, ion pair 1, Scheme 94). Achiral ion pair 1 349 can be made chiral by interaction with a chiral anion receptor, such as a thiourea-based hydrogen bonding catalyst to render ion pair 2 350. Ion pair 2 exhibits enhanced electrophilicity/solubility relative to the acyl pyridinium salt 349, and so it acts as a chiral acyl transfer reagent in Seidel’s work. The chiral anion receptor (hydrogen bond donating catalyst) pushed the equilibrium between DMAP and the acylating agent in favour of forming 349 which can go on to form ion pair 2, 350, the active chiral acyl transfer reagent.

Seidel and co-workers employed this strategy in a range of acyl transfer reactions including: the Steglich rearrangement of O-acylated azlactones; the desymmetrisation of \textit{meso}-diamines and the kinetic resolution of various amines.\textsuperscript{190} In each case, this novel form of catalysis was carried out utilising ion pair 2, 350. This novel study prompted the use of a similar chiral ion pair as a nucleophilic catalyst in the aminolysis of azlactones.

Using benzoyl fluoride (351) as the electrophilic agent, along with 348, Ms. Cronin attempted to generate the chiral ion pair 353 (Scheme 95A), which could open azlactone 354, (Scheme 95B) producing acid fluoride 355 which, upon addition of a protected amino acid nucleophile 356, would result in the formation of peptide 357. Enantioenrichment was envisaged in the acyl fluoride product 355 by means of DKR, using the chiral fluoride ion 353 with concomitant regeneration of 348, accounting for catalytic turnover.

\begin{center}
\textbf{Scheme 95} \hspace{1cm} Aminolysis strategy carried out by Ms. Sarah Cronin
\end{center}
However, after many attempts to optimise the reaction conditions, including varying the nucleophilic catalyst, the anion receptor, the acylating agent, the solvent, reaction concentration, catalyst loading and temperature, Ms. Cronin failed to carry out this aminolysis via the DKR of azlactone 354. While it was demonstrated that the achiral ion pair 352, generated from benzyol fluoride and catalytic DMAP could effectively open azlactone 354 to afford the desired acid fluoride product 355, an unprecedented hydrogen fluoride-elimination across the acyl centre of 355 was observed and in doing so, ketene 358 was formed (Scheme 96). Attack of ketene 358 by amine nucleophile 356 resulted in collapse of 358 to form the desired amide product 357 (Scheme 96). However, formation of ketene 358 (observed by 1H, 13C NMR spectroscopic analysis and mass spectrometry) resulted in the loss of any potential stereochemical information installed in the reaction intermediate due to the destruction of the chiral centre in 355, thus this reaction could not be carried out enantioselectively. Further optimisation of this process has not been carried out at present.

\[
\begin{align*}
\text{355} & \xrightarrow{-\text{HF}} \text{358} \\
\text{358} & \xrightarrow{R^1, R^2} \text{357}
\end{align*}
\]

Scheme 96  Elimination of hydrofluoric acid to form ketene 358

3.2 Racemic aminolysis of azlactones using phase-transfer conditions

Following on from Ms. Cronin’s preliminary experiments into the aminolysis of azlactones by a fluoride anion, the work which will be outlined in this thesis was commenced. The initial concept of this project was to again use a fluoride anion, generated from benzoyl fluoride (351) to ring-open an azlactone and in doing so, generate an acid fluoride intermediate, which could be quenched by an amine to generate an amide product. This work differed from that carried out by Ms. Cronin in that, instead of using an anion-binding catalysis approach to carry out this reaction enantioselectively, it was envisaged that a phase-transfer catalyst (PTC), with a bound fluoride ion, could carry out the DKR process. Prior to attempting this reaction enantioselectively, the reaction was first attempted racemically, using tetra-n-butylammonium fluoride (TBAF) as the PTC of choice.

The azlactone used in this racemic study was derived from DL-phenylalanine (359). Acylation of the amino group of 359 using benzoyl chloride (173), under basic conditions,
produced N-benzoyl amide 360. Intramolecular ring-closure of 360 was carried out using 

\[ \text{N,N'-dicyclohexylcarbodiimide (DCC)} \]

(Scheme 97).

![Scheme 97](image)

**Scheme 97**  Synthesis of azlactone 354 derived from DL-phenylalanine (359)

The first set of reaction conditions utilised in the fluoride-mediated aminolysis of 354 was the use TBAF (catalytically) and benzoyl fluoride (351, stoichiometrically); using CH$_2$Cl$_2$ as the solvent and with the addition of molecular sieves, to maintain strictly anhydrous conditions (Scheme 98).

![Scheme 98](image)

**Scheme 98**  Initial attempted aminolysis of 354 using PTC conditions

The reaction was carried out at room temperature for 18 hours after which time 100% of 354 was consumed (determined by $^1$H NMR spectroscopy using p-iodoanisole as the internal standard). Upon addition of the amine nucleophile, benzyl amine (285, added in excess, 1.5 equivalents, in order to quench any remaining benzoyl fluoride), the major product of the reaction was mono-acylated 361, isolated in 47% yield. Contrary to the results obtained by Ms. Cronin, imide 362 was not observed. While 361 was the major product of this reaction, several other products were observed in the $^1$H NMR spectrum of the crude reaction mixture, however, due to the number of other compounds observed, they have not been isolated and characterised at this time. However, analysis of the $^1$H NMR spectrum of the crude reaction mixture prior to quenching confirmed that, in keeping with Ms. Cronin’s findings, the racemic reaction using TBAF and 351 also undergoes hydrogen fluoride elimination across the acyl fluoride intermediate 363 to form ketene 364 (Scheme 99). The ketene intermediate, tentatively assigned as mono-acylated 364 was quenched by the addition of benzyl amine to form the mono-acylated product 361. Ketene formation again signified that this reaction cannot be carried out enantioselectively using this method.
Scheme 99  Elimination of HF from mono-acylated intermediate 363 to form ketene 364

Modification of the azlactone structure was carried out to observe if ketene formation could be suppressed. Azlactone 367, derived from 2-methylalanine (365) was synthesised as shown in Scheme 100. N-acylation of 365 with 173 under basic conditions was followed by cyclisation of 366 to render 367, mediated by DCC.

Scheme 100  Synthesis of 2-methylalanine-derived azlactone 367

Although ketene formation is not possible with 367 as it lacks an α-proton, nevertheless this was an interesting experiment to observe the effect of the α-proton on azlactone ring-opening. However, when the conditions outlined in Scheme 98 were employed in this reaction, no conversion of 367 to product was observed after 24 hours. The fluoride anion failed to open 367 under either catalytic (both 20 and 50 mol% TBAF was employed in this reaction) or stoichiometric (1 equivalent) conditions (Scheme 101).

Scheme 101  Attempted fluoride mediated ring-opening of 367

From this result, it was ascertained that the α-proton of such azlactones is required to facilitate ring-opening. It is postulated that the carbonyl centre of 367 cannot be accessed by the fluoride anion nucleophile due to the considerable steric bulk of the adjacent geminal dimethyl group. At present, the fluorinolysis of azlactones has not been investigated further.
3.3 Investigation into other anions capable of facilitating azlactone aminolysis

As fluoride was ruled out as an anion to carry out azlactone ring-opening, attention was turned to other (less basic) anions that could potentially be used to carry out this transformation. The other anions tested were chloride, as well as carboxylate anions; acetate, benzoate and pivalate.

When chloride was investigated as the anion for azlactone opening, tetra-n-butylammonium chloride (TBACl) and benzoyl chloride (173) were used in order to bring about this transformation (Scheme 102). However, this reaction proceeded far too slowly for it to be practical. After 192 hours, only 21% of azlactone 354 had been consumed. A potential explanation for the slow conversion is the reversibility of this reaction. The amido group of 369 can attack the adjacent electrophilic acyl chloride unit to reform azlactone 354. Due to the prolonged reaction time to reach only 21% conversion, this reaction was not allowed to progress to completion. The product of this reaction has not been ascertained, but the postulated product is the amido acid chloride 369.

Scheme 102  Attempted ring-opening of 354 using chloride

Carboxylate anions were next screened in this reaction; a general mechanism for this reaction is depicted in Scheme 103. It was postulated that opening azlactone 354 with a carboxylate anion (provided in this reaction as its corresponding tetra-n-butylammonium salt 370), would result in mixed anhydride salt 371, which could be protonated by the parent carboxylic acid 372 of salt 370. Deprotonation of 372 would allow for the carboxylate anion to be regenerated and it would be free to enter another catalytic cycle. Subsequent treatment of the now protonated mixed anhydride 373, with an amine nucleophile 356 would furnish the aminolysis product amide 374. It was envisaged that if careful consideration was given to the steric bulk of the carboxylate anion which adds to the azlactone, amine nucleophile 356 would be forced to add preferentially to carbonyl A of mixed anhydride 373. In doing so, aminolysis of the azlactone would be achieved. If the carboxylate anion was not sufficiently sterically encumbered, it was thought that 356 could add indiscriminately to carbonyl A and carbonyl B (provided in the structure through azlactone opening by the carboxylate anion).
Scheme 103  Mechanism of the carboxylate ring-opening of azlactones

The first carboxylate anion used in this reaction was an acetate ion. Initially, tetra-\(n\)-butylammonium acetate (TBAOAc) and acetic anhydride (375) were employed in this reaction (Scheme 104A). This led to a complex \(^1\)H NMR spectrum of the crude reaction mixture; as there were many products formed. Due to the non-trivial isolation of each of these products by flash column chromatography, isolation and characterisation of each product was not carried out. However, one attempt at product isolation resulted in mixed anhydride 376 being isolated (via flash column chromatography) in a very low yield. The expected \(\text{bis-acylated product } 377\) was not isolated after purification; this does not necessarily indicate that 377 was not formed but rather that it was not possible to isolate it. In order to overcome the lack of chemoselectivity associated with this reaction, a buffer-type system was put in place. It was hypothesised that the nitrogen-centred anion of mixed anhydride intermediate 371 (Scheme 103) could be involved in many other deprotonation events (possibly deprotonating other molecules of azlactone or other reaction intermediates; there are many possibilities of side-reactions that could occur) in the absence of a proton source. This led to acetic acid (378) being used in the place of 375 (Scheme 104B).
When acetic acid (378) was used in the place of 375, 71% of 354 was consumed after 39 hours, however, analysis of the $^1$H NMR spectrum of the crude reaction mixture showed that while 354 was being consumed, again, many products were being formed. Mixed anhydride 376 was tentatively assigned as being formed in 24% yield (determined by analysis of the $^1$H NMR spectrum using $p$-iodoanisole as the internal standard). However, this reaction was not purified and the products isolated; thus, this was only a tentative assignment, based on comparison between the crude reaction mixture $^1$H NMR spectrum and that of isolated 376. Long reaction times coupled with this reaction not proceeding cleanly meant that the use of the acetate anion was not pursued any further.

A tetra-$n$-butylammonium benzoate (TBAOBz)/benzoic anhydride (379) and a TBAOBz/benzoic acid (380) system were also evaluated as potential anions to facilitate the aminolysis of 354. Again, long reaction times and complex crude reaction mixtures meant that both systems were not investigated further.

At this stage of the project, it was decided to change from using the phenylalanine derived azlactone 354 to a TCIC-substituted azlactone 381 (again derived from phenylalanine). The decision to use azlactone 381 was undertaken because, as previously discussed in Section 1.8.2.4, the use of such azlactones in an aminolysis process will render an orthogonally protected peptide which is of great synthetic utility. There are also few other modifications that can be made to amide product of 354 once it is formed.

Azlactone 381 was synthesised as per the 2015 Connon and co-workers report (Scheme 105). Tetrachlorophthalic anhydride (382) was treated with isopropanol, under basic conditions, to furnish carboxylic acid 383. Concurrently, DL-phenylalanine (359) was protected as tert-butyl ester 384 using tert-butyl acetate (385) and perchloric acid (386).
Subsequent coupling of 383 and 384 using DCC furnished 387 in a moderate yield. Cleavage of the tert-butyl ester of 387 was achieved using TFA to form carboxylic acid 388. Trifluoroacetic anhydride (TFAA) was used to facilitate intramolecular ring-closure to produce azlactone 381, which was purified quickly via flash column chromatography.

Scheme 105  Synthetic route towards azlactone 381

3.4  Aminolysis of azlactone 381 via anionic ring-opening

Azlactone 381 was first employed in the TBAOAc/acetic acid ring-opening system (the mechanism for which is the same as depicted in Section 3.3, Scheme 103). As 381 was consumed (48 hours, 75% consumption of azlactone) again, several products were observed in the $^1$H NMR spectrum of the crude reaction mixture; the TBAOAc/acetic acid conditions were not investigated further. In addition to this reaction not progressing chemoselectively, it was also postulated that the acetate group would not be sterically bulky enough to direct the amine nucleophile 356 to attack the carbonyl A of mixed anhydride 389 (which is derived from the addition of acetate to azlactone 381 (carbonyl A, Figure 29) to achieve selective aminolysis.
Gratifyingly, when azlactone 381 was ring-opened using a benzoate ion (using a TBAOBz/benzoic acid system), more promising results were obtained. Using TBAOBz (catalytically) as the source of benzoate ion and benzoic acid (stoichiometrically) in CH₂Cl₂ (the optimal solvent from Ms. Cronin’s earlier experiments) and with the addition of molecular sieves (to maintain anhydrous conditions throughout the reaction) 72% of azlactone 381 was converted to mixed anhydride 390 (open form) and 391 (closed form) after 120 hours (Scheme 106A). After this time, the reaction was quenched with benzylamine (285, 1.5 equivalents) at room temperature. The products obtained from this reaction are shown in Scheme 106. As the reaction was quenched with benzylamine (at 72% conversion); amide 392 was obtained from the ring-opening of unreacted 391 with benzylamine (a background reaction between 391 and benzylamine was carried out previously which showed that 391 is readily opened by benzylamine in near quantitative yield in less than 1 hour, Scheme 106B). Another product of this reaction was phthalimide 393 which was synthesised in a poor yield, either by aminolysis of mixed anhydride 390 followed by subsequent ring-closure or via direct amine addition to anhydride 391. Although 393 was produced in a low yield, this was an exciting result as it demonstrated that aminolysis and ring-closure to produce orthogonally protected phthalimide 393 can be carried out in one step. The major product of this reaction however was N-benzylbenzamide (394) which was produced as the by-product of the aminolysis of either anhydride 390 or 391 at the benzoate carbonyl as opposed to the azlactone carbonyl (analogous to the acetate mixed anhydride amine addition in Figure 29). Although this result was not the desired outcome, it was still a promising observation, demonstrating that TBAOBz could ring-open azlactone 381 to produce orthogonally protected bis-amide 393, albeit in a low yield. While amine addition was not controlled in this example, it was envisaged that more careful manipulation of the steric bulk of the carboxylate ion nucleophile could direct amine addition to the desired side of the mixed anhydride, to achieve aminolysis. Carboxylic acids 395 and 396, produced as a result of aminolysis at the benzoate carbonyl of 390 and 391 respectively, have not been
isolated. The products of this reaction were separated by flash column chromatography and prior to purification consideration was not given to the formation of carboxylic acid products. This resulted in the retention of carboxylic acids 395 and 396 on silica gel during column chromatography.

**Scheme 106**  Azlactone 381 ring-opening by tetra-n-butylammonium benzoate

It is posited that ring-closure to produce 393 occurred *via* either an acid- or base-catalysed system present in the reaction mixture. Although Connon and co-workers required the addition of an external base (DABCO, 20 mol%) to bring about this ring-closure, as there is both acid and base present (benzoic acid and a benzoate anion) in this system, it is not possible to determine which is facilitating this ring-closure. The control reaction carried out between 381 and 285 exclusively furnished open bisamide 392 (Scheme 106B). Allowing the reaction to stir at room temperature for a prolonged reaction time (up to 18 hours) still failed to produce phthalimide 393. This observation indicates that the conditions outlined in
Scheme 106A are necessary to bring about ring-closure to furnish tetrachlorophthalimide-protected 393.

It was apparent that redesign of the carboxylate anion catalyst was necessary to promote amine addition to the azlactone-derived carbonyl of the mixed anhydride produced after azlactone ring-opening. In order to control amine addition (towards the required carbonyl of the mixed anhydride) it was decided to employ a pivalate anion in the system to investigate the effects this bulkier anion would have. It was envisaged that the bulky tert-butyl group of the pivalate anion would hinder amine addition to its carbonyl (carbonyl B, Figure 30) in mixed anhydride 397 (formed from the addition of a pivalate anion to azlactone 381) and promote addition of the nucleophilic amine to carbonyl A in order to achieve aminolysis (Figure 30).

![Figure 30](image-url)

**Figure 30** Proposed mixed anhydride 397 which is formed after pivalate anion ring-opening of 381

While this pivalate anion system appeared to be a solution to the challenge of controlling amine addition to mixed anhydrides such as 397, several problems arose when this methodology was put in place. As tetrabutylammonium pivalate (399) is not commercially available, it was generated *in situ* using 398 and TBAB. When catalytic sodium pivalate (398) was employed in the ring-opening of TCIC-substituted azlactone 381, with TBAB and stoichiometric pivalic acid (400) using CH₂Cl₂ as the solvent (as had been used in previous ring-opening protocols, Schemes 104 and 106), the reaction proceeded very slowly (Scheme 107). When the reaction was carried out, only 81% of the 381 was consumed after 5 days stirring at room temperature. This reaction was not quenched as it had not proceeded to completion; quenching the reaction mixture before it reaches 100% conversion in such azlactone ring-opening reactions results in the amine adding to unreacted azlactone (see Scheme 106B) making it impossible to distinguish if the amide product was generated as a result of the pivalate anion system or through quenching unreacted 381 with the amine.
Attempts were made to decrease this reaction time; the concentration of CH$_2$Cl$_2$ used was increased (0.2 and 0.4 M were screened) and other solvents were tested (THF, CH$_3$CN, EtOAc, toluene, CHCl$_3$, MTBE). Disappointingly, all efforts failed to promote faster azlactone ring-opening by the pivalate anion (in all cases, the reactions failed to reach above 85% consumption after 7 days). When these reactions were stirred for longer periods of time, a fine white precipitate was observed in the reaction flask. When filtered, this precipitate was determined to be carboxylic acid 396. It is speculated that mixed anhydride 397 (Figure 30) is not stable to hydrolysis over long periods of time (as discussed, this reaction was left to proceed for up to 7 days in an effort to achieve 100% conversion) and so any adventitious water present in the system may have hydrolysed 397, resulting in the formation of acid 396 (2% yield). Efforts were taken to eliminate trace amounts of moisture in the reaction (using anhydrous solvent, use of molecular sieves, purification of all reagent prior to use, generating sodium pivalate in situ in the reaction flask), however, each of these endeavours failed to either decrease the reaction time or stop formation of acid 396.

### 3.5 Evaluation of phenolate-derived anions to achieve azlactone aminolysis

As the carboxylate anion/carboxylic acid system to carry out aminolysis of azlactones up until this point were unsuccessful, other anions were explored in the aminolysis of azlactones. It was decided to investigate phenolate and phenolate-derived ions in this system. This endeavour was undertaken as it was speculated that the phenolate anion used would be sufficiently nucleophilic to ring-open 381 with ease; and the ester or thioester (if a
thiophenolate system was employed) generated would be the only site susceptible to aminolysis by an amine nucleophile (unlike the mixed anhydride examples in which there was more than one viable electrophilic carbonyl for amine addition, Figure 29 and 30).

### 3.5.1 Examination of thiophenolate anions to carry out azlactone aminolysis

Due to their reduced basicity and increased nucleophilicity in comparison to their phenolate counterparts, thiophenol was first evaluated as a potential method to ring open 381. Connon and co-workers have previously carried out the DKR of azlactones via thiolysis, these protocols utilised benzyl mercaptan (401), 4-tert-butylbenzyl mercaptan (402) and octanethiol (403) as the nucleophilic partners to carry out the azlactone ring-opening. It was envisaged that thiophenolate would readily act as a leaving group upon treatment of the thioester product with an amine to furnish the desired amide product.

In order to investigate the ability of the thiophenolate anion to ring-open 381, it was treated with commercially available sodium thiophenolate (404), TBAB in catalytic quantities (20 mol%) and with stoichiometric thiophenol (405), in THF (Scheme 108). THF was used in the place of CH₂Cl₂ as it was found to promote the rate reaction marginally in the addition of the pivalate anion to 381.

![Scheme 108](image)

**Scheme 108** Thiolysis of 381 using sodium thiophenolate (404)

This reaction proceeded very rapidly - with thioester 406 being produced exclusively, in just 15 minutes. A subsequent control reaction was carried out to investigate if TBAB was in fact necessary to bring about this reaction. Repeating this transformation using 381, 404 (20 mol%) and 405 in THF, again resulted in 406 being furnished in quantitative yield (determined by ¹H NMR spectroscopic analysis) in just 1 hour (Scheme 109).
Scheme 109  Thiolysis control reaction of 381 using 404 and 405

Analysis of the control reaction indicates that the phase-transfer catalyst, TBAB was not required to bring about azlactone ring-opening, thus introduction of a chiral PTC to bring about asymmetric induction would not be possible via this mode of catalysis. As the overall aim of this project was to carry out the aminolysis of azlactones to produce enantioenriched products via DKR, it was envisaged that the anion ring-opening system facilitated by a (chiral) PTC could carry out this transformation. Therefore, it was disappointing when the background reaction (Scheme 109) proceeded efficiently uncatalysed. It is likely that in the reaction can proceed in the absence of TBAB due to the very high intrinsic activity of the thiophenolate ion; meaning that even miniscule amounts of it which are soluble in the reaction solvent are capable of reacting rapidly with 381 and initiating the reaction.

In order to gain control over the addition of 404 to 381 and allow its addition to be mediated by TBAB, the catalytic loading of 404 was lowered and the solvent system used in the reaction was modified. Ideally, 404 would not be soluble in the reaction solvent and would require the PTC to introduce it to the organic solvent and allow the reaction to progress.

Carrying out the thiolysis control reaction at catalyst loadings of 10 mol%, 5 mol%, 2 mol%, 1 mol% and even as low as 0.1 mol% 404, in THF, failed to eliminate the background reaction (Scheme 110). In each case, quantitative yield of thioester 406 was observed in the $^1$H NMR spectrum of the crude reaction mixture.
Scheme 110  Evaluation of the influence of catalyst loading of 404 on the thiolysis of 381

Solvents with varying polarities were also evaluated in the control reaction to observe any change in the solubility of 404. It was postulated that at low catalyst loading and in a relatively non-polar solvent, it may be possible that 404 is insoluble in the reaction mixture and so not be capable of attacking 381 un-catalysed. As depicted in Table 7, all solvents screened (at 5 mol% 404) in this reaction failed to eliminate the background reaction (entries 1-6).

Table 7  Thiolysis background reaction: the influence of solvent

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>MTBE</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>hexanes</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>hexanes: toluene (1:1)</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using p-iodoanisole as the internal standard.
Azlactone 381 was not soluble in hexanes and so no reaction was observed (Table 7, entry 7). A mixture of toluene and hexanes was investigated however, 1:1 hexanes: toluene was required to dissolve 381 and at this solvent ratio, the background reaction was observed (Table 7, entry 8).

Another method investigated to control the thiolysis background reaction was to utilise a different source of thiol, in this case, \textit{p}-nitrothiophenol (407). Thiol 407 has a lower $pK_a$ than 405 and so it was postulated that its anion would be less nucleophilic than 404 resulting in its addition to 381 requiring the influence of a PTC. Attempts at synthesising the sodium salt of 407 using sodium hydride (NaH) under anhydrous conditions failed to render the desired sodium salt pure (Scheme 111). Disulfide 408 was instead observed each time this reaction was carried out.

![Scheme 111 Attempted synthesis of sodium \textit{p}-nitrophenolate 409](image)

Further efforts to synthesise sodium \textit{p}-nitrothiophenolate (409) have not been explored at this time. It was instead decided to attempt this reaction using sodium thiophenolate (404) as the initiator and to employ \textit{p}-nitrophenol (407) in stoichiometric quantities (Scheme 112). Disappointingly, almost quantitative conversion of 381 to thioester 410 was observed after 1 hour at room temperature.

![Scheme 112 The thiolysis of 381 with 404 and 407](image)
While other anionic sources of thiols could have been implemented in this reaction (such as those with steric bulk around the sulfur atom or additional electron withdrawing groups to further lower the $pK_a$), it was decided to turn our attention to phenolate anions; due to their increased $pK_a$ values and their potential to be more controllable in the azlactone ring-opening. Further investigations into the thiolysis of azlactones via this means of catalysis have not been undertaken at present.

### 3.5.2 Aminolysis of azlactone 381 mediated by phenolate anions

Having briefly explored the thiolysis of azlactones as a means of carrying out aminolysis and observing that the background reaction was going to require careful reaction conditions to be eliminated, formal aminolysis via an ester intermediate was next examined. While the alcoholysis of azlactones has been studied at length as a means of synthesising amino acid derivatives (enantioenriched products are formed if this process is carried out by DKR, see Section 1.8.2), alcoholysis using phenol (411) and phenol derivatives have rarely been employed in this type of reaction. It was decided to investigate if a phenolate anion (with a tetra-$n$-butylammonium counterion) could potentially ring-open 381 as it was envisaged that the phenolate ester formed could be quenched with an amine nucleophile to render the aminolysis product.

A sodium phenolate/phenol system was first screened in this reaction. Sodium phenolate (412) was synthesised via reaction of 411 with NaH in anhydrous THF (Scheme 113).

![Scheme 113 Synthesis of sodium phenolate salt 412](image)

As observed with the thiophenolate system previously discussed (Section 3.5.1), it was imperative to first investigate if the phenolate anion took part in a background reaction, *i.e.* if the alcoholysis reaction proceeds in the absence of a phase-transfer catalyst (TBAB). Azlactone 381 was reacted with 412 (catalytic quantity) and 411 (stoichiometric) using THF as the reaction solvent (Scheme 114).
After 1 hour, 34% of 381 had been consumed, but no discernible product resonance signals were observed in the $^1$H NMR spectrum of the crude reaction mixture. The reaction was allowed to continue and was monitored by $^1$H NMR spectroscopic methods. Following 18 hours stirring at room temperature (under an atmosphere of argon) 70% of 381 had been consumed and the $^1$H NMR spectrum now contained new resonance signals; however these signals did not account for 70% of phenolate ester 413 which should have been produced if the reaction was to proceed as envisaged. A potential explanation for the destruction of starting material without observation of product formation is that 412 is highly hygroscopic and resulted in the hydrolysis of azlactone 381 to carboxylic acid 395, which is not easily detectable by $^1$H NMR spectroscopy. As it seemed evident that this reaction was not going to be straightforward to carry out using this sodium phenolate/phenol system, other phenolate anions were next investigated.

The next phenolate anion investigated in this reaction was sodium $p$-nitrophenolate (414). Sodium salt 414 was synthesised analogously to phenolate salt 412 from $p$-nitrophenol (415), again using NaH (Scheme 115).

**Scheme 115** Synthesis of 414 from phenol 415

Salt 414 was first evaluated in the background reaction with azlactone 381 in THF in the absence of a PTC (TBAB). This reaction was carried out at room temperature using sodium
salt 414 in catalytic quantities and the corresponding p-nitrophenol (415) stoichiometrically (Scheme 116). After 1 hour, 100% of 381 had been consumed. Following flash column chromatography of the reaction mixture, phthalimide 416 was determined to be the major product of this reaction. Isopropylester 417 was also retrieved after purification of the reaction mixture in a diminutive yield. The remaining mass balance was tentatively postulated to be the carboxylic acid 395 or 396, formed as a result of hydrolysis of esters 416 and 417. Such carboxylic acids would adhere to the silica gel during column chromatography and so would not be isolated via these means of purification.

Scheme 116  The background reaction between 381 and 414 in THF

As it was evident that this reaction did not require a PTC catalyst to proceed, it was decided to investigate this phenol/phenolate system in other solvents. It was an encouraging result however that 414 was nucleophilic enough to carry out the azlactone ring-opening step and promote subsequent phthalimide formation, with catalytic turnover, to produce N-protected 416. It was envisaged that with careful tuning of the reaction conditions, it may be possible to eliminate the background reaction and allow for a phase-transfer catalyst to control the phenolate addition to 381.

A small selection of solvents was first investigated in the background reaction and the results of which are summarised in Table 8. While most of the solvents screened (entries 1-4) failed
to eliminate the background reaction, the use of toluene (Table 8, entry 5) completely halted the addition of anionic 414 to azlactone 381. This reaction was stirred at room temperature for a further 4 hours (while being monitored by $^1$H NMR spectroscopic methods) and while all other solvents furnished ester 417 in near quantitative yield, the use of toluene did not. This encouraging observation is likely due to salt 414 being insoluble in toluene and so, in the absence of another source of a base to initiate the reaction, it cannot proceed. In order to test this hypothesis, the PTC TBAB (5 mol%) was added to the reaction mixture (added directly to experiment summarised in Table 8, entry 5) and after only 15 minutes, ester 417 (24% conversion) was observed in the $^1$H NMR spectrum of the crude reaction mixture.

Table 8  Studying the effect of solvents in the alcoholysis of 381 by 414

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>MTBE</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$O</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Determined by $^1$H NMR spectroscopy using p-iodoanisole as the internal standard; based on the conversion of 381 to ester 417

As the background reaction had now been eliminated with the use of toluene as the solvent, the phase transfer-catalysed reaction using TBAB was next carried out to determine reaction time and yield of the products formed. As shown in Table 9, when TBAB was used in this azlactone alcoholysis reaction, the initial product formed is isopropyl ester 417 (entries 1 and 2) but as the reaction proceeds over time (entries 3 and 4) ester 417 begins to close to form phthalimide 416, eventually resulting in $N$-protected 416 being formed as the major product (entries 5 and 6). This was an encouraging result as it had now been demonstrated that 414 could carry out the ring-opening of 381 to form not only isopropyl ester 417 but to
undergo the *in situ* ring-closure to form the orthogonally protected 416, under the influence of the achiral PTC TBAB.

**Table 9** TBAB-catalysed alcoholysis of 381 using 414 and 415

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>conversion to 416 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>conversion to 417 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>67</td>
<td>33</td>
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<tr>
<td>5</td>
<td>48</td>
<td>92</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using *p*-iodoanisole as the internal standard.

It was now imperative to demonstrate that the addition of an amine to phenolic ester 416 (or even isopropyl ester 417, which can undergo a simple base-catalysed ring-closure to form the desired amide product) would form the amide coupling product; in doing so aminolysis would be achieved (which was the main aim of this methodology).

The TBAB-catalysed reaction depicted in Table 9 was repeated and upon complete conversion of 381 to phthalimido-protected 416 (determined by <sup>1</sup>H NMR spectroscopy using *p*-iodoanisole as the internal standard), benzyamine (285) was added to the crude reaction mixture (at room temperature) which gratifyingly furnished amide 393, albeit in an unsatisfactory yield (Scheme 117).
Scheme 117  Initial quench of 416 with benzylamine (285)

The moderately low yield of amide 393 was a surprising result, accompanied by the absence of any other product formation in the $^1$H NMR spectrum of the crude reaction mixture; 393 was the only product observed. It is worth noting that 393 is relatively insoluble in many organic solvents (CHCl$_3$ and THF being exceptions). In order to overcome this challenge, an additional solvent, one in which the product amide 393 would be readily soluble in, was added to the reaction mixture prior to quenching, to investigate if the yield of 393 formation would be improved (Scheme 118). It was also decided to quench the alcoholysis reaction upon complete formation of isopropyl ester 417 as opposed to allowing phthalimide 416 to form exclusively; which required a long reaction time (up to 48 hours).

Scheme 118  Optimised amine addition to 417 to achieve aminolysis

The alcoholysis reaction was quenched after 20 hours (upon complete conversion to 417 as determined by $^1$H NMR spectroscopy) by the addition of THF to the reaction mixture, a few minutes before the addition of benzylamine. With these improved, although unusual reaction conditions in hand, N-protected 416 was now produced in a shorter reaction time and in an excellent isolated yield, with the remaining product formed being the open amide 392 (Scheme 118).
3.6 Attempted DKR of azlactone 381 *via* alcoholysis by a phenolate anion

As the aminolysis of azlactone 381, *via* an ester intermediate, had now been carried out racemically (using TBAB as the PTC) the next endeavour was to attempt to carry out DKR of 381 enantioselectively. It was envisaged that either bifunctional or phase-transfer catalysts could be used to carry out this transformation. It should be noted that the catalysts screened in the azlactone DKR reaction were those available in the research group, at present no catalysts have been synthesised specifically for this reaction.

3.6.1 Evaluation of bifunctional organocatalysts in the DKR of 381

Bifunctional *cinchona* alkaloid-derived organocatalysts were first evaluated in the DKR of azlactone 381. For the initial study of such bifunctional catalysts, the simple urea-based *cinchona* alkaloid-derived catalyst 418 (a dehydrogenated derivative of the catalyst previously used by Connon and co-workers to carry out the alcoholysis and thiolysis of azlactones in 2008)\(^\text{153}\) was first utilised. Through use of this catalyst, it was not necessary to add a catalytic quantity of phenolate 414 as there is a basic *motif* incorporated in the catalyst’s structure which can initiate the catalytic cycle. The aminolysis reaction catalysed by 418 is shown in Scheme 119.

![Scheme 119](image)

**Scheme 119** Evaluation of bifunctional catalyst 418 in the DKR 381

Catalyst 418 was capable of promoting the alcoholysis of azlactone 381 using 415 as the alcoholic nucleophile. Aminolysis of ester intermediate 417 was carried out with a respectable yield of the open amide product 392 achieved (24 hours after quenching the reaction, 392 did not close *in situ* to form 393 under these reaction conditions). Disappointingly when amide 392 was analysed by CSP-HPLC, the chromatogram only indicated marginal product enantioenrichment (2% *ee*, Scheme 119). As this was the first reaction in which an asymmetric reaction had been employed, it was decided to investigate if amine 285 added to quench the reaction mixture was capable of racemising the
stereocentre in ester intermediate 417. In order to investigate this possibility, the reaction in Scheme 119 was repeated without quenching. Ester 417, the product of the alcoholysis reaction was analysed by CSP-HPLC and again, the ee obtained was negligible. This result indicates that amine 285 was not racemising amide 417 but rather that catalyst 418 was an ineffective promoter of the DKR of 381.

Next, a set of experiments were carried out, in parallel, to observe if the quinoline ring of 418 was capable of promoting the alcoholysis reaction. If this were the case, the reaction may not be taking place in the chiral pocket of catalyst 418 which would account for absence of enantioselectivity observed in Scheme 119.

In the first experiment, catalyst 418 was replaced with 6-methoxyquinoline (419), which did not result in the formation any product, even when the reaction was left to proceed for up to 24 hours (Scheme 120). In a concurrent reaction, 2-chloro-6-methoxyquinoline (420) was employed as the catalyst. Catalyst 420 was employed in this reaction to investigate if the addition of a 2-chloro group would hinder the quinoline nitrogen atom from promoting this reaction. As with 419, substituted 420, unsurprisingly failed to facilitate the alcoholysis of 381 (Scheme 120). The results of these reactions indicated that the quinoline nitrogen atom of catalyst 418 was not responsible for the poor ee observed in Scheme 119.

![Scheme 120](image)

**Scheme 120** Investigations into quinoline as a potential catalyst to promote the alcoholysis of 381

The next organocatalyst evaluated in this reaction, was Song’s C2-symmetric squaramide catalyst 151. This catalyst has set a literature benchmark in the organocatalytic DKR of azlactones via alcoholysis, being used by both Song and more recently Connon and co-workers to achieve enantioenriched products in both excellent yields and enantioselectivities. Although catalyst 151 performed very well in other alcoholysis
reactions, when evaluated in this reaction using 381, disappointingly only a marginal enantiomeric excess was detected upon analysis of amide product 393 by CSP-HPLC (Scheme 121). A longer reaction time was also necessary to obtain complete conversion of 381 to ester intermediate 417 when this catalyst was utilised.

Scheme 121  Evaluation of Song’s C2-symmetric urea-based catalyst 151 in the aminolysis of 381

At present other bifunctional organocatalysts have not been evaluated in the DKR of azlactone 381 using this phenolate protocol.

3.6.2 Evaluation of chiral phase-transfer catalysts in the DKR of azlactone 381
Considering the inability of bifunctional organocatalysts to promote the DKR of azlactones using this methodology, phase-transfer catalysts were next evaluated. It had been postulated previously that phase-transfer catalysts (PTCs) would outperform bifunctional catalysts in this reaction. It was envisaged that sodium phenolate salt could undergo a counterion exchange with the chiral PTC salt to generate a chiral ammonium phenolate in situ.

As discussed in Section 3.5.2, no reaction was observed between phenolate salt 414 and azlactone 381 in toluene, most likely due to the insolubility of the sodium salt. However, when a (chiral) PTC is introduced to the system (TBAB in the racemic case) counterion exchange can occur between the PTC and 414 which results in anion 414 entering the organic solvent and attacking 381. It was envisaged that the use of a chiral PTC could facilitate the
addition of 414 to 381 in a chiral environment to form ester intermediate 417, which would be quenched with an amine to form the formal aminolysis product, N-protected 393.

The first PTC screened in this reaction was Maruoka’s binaphthyl catalyst 421 incorporating flexible straight-chain alkyl groups. Maruoka utilised these catalysts to alkylate amino acid derivatives in excellent yields and enantioselectivities with very low catalyst loadings (as low as 0.1 mol%). When catalyst 421 was employed in this reaction however (Scheme 122), no enantiocontrol was observed in amide product, with a racemic mixture of 393 observed by analysis of the chiral HPLC chromatogram.

Scheme 122 Attempted DKR of 381 using Maruoka’s PTC 421

As Marouka’s PTC failed to induce any enantiocontrol, the next class of PTCs evaluated in this DKR reaction were chiral, quinine-based, quaternary ammonium salts. The first example of such salts being used as PTCs was in the epoxidation of chalcones by Wynberg et al. in 1976. Less than ten years later, Dolling et al. reported the first example of cinchona-derived ammonium salts facilitating the alkylation of active methylene compounds in excellent product yields and enantioselectivities (Scheme 123).

Scheme 123 Asymmetric phase-transfer catalysed alkylation of 422

124
This report outlined a rationale to explain the enantiocontrol catalyst 423 exhibits over the methylation of indanone derivative 422 to induce such high levels of enantioselectivities in the product. Dolling et al. proposed that the enolate formed from 422 associates with the catalyst via ionic interactions. The positively charged nitrogen atom of catalyst 423 is proposed to bind to the negatively charged oxygen atom of the enolate ion of 422 (Figure 31). The authors also propose that π-stacking interactions occur between the aromatic systems of the catalyst and substrate as well as hydrogen bond interaction between the hydroxyl group of catalyst 423 and the oxygen atom of the enolate. This forms a pre-transition state assembly where the Si-face of the enolate is blocked by the catalyst resulting in addition of MeCl will occur at the Re-face exclusively. This accounts for the high levels of enantiocontrol observed in the alkylation reaction depicted in Scheme 123.

![Figure 31](image-url)  
Pre-transition state assembly for asymmetric PTC alkylation proposed by Dolling et. al.

The cinchona-derived ammonium salts screened in this reaction are outlined in Table 10. It was envisaged that similarly to Dolling co-workers report, this class of catalyst possesses the same core functionality that produced excellent product enantioselectivities in their publication. Such catalyst structures (Table 10) contain all the necessary elements for transferral of stereochemical information: an alcohol moiety to provide hydrogen bond interactions between the catalyst and azlactone, chiral carbons C-8 and C-9 to impart chiral information and a tuneable benzyl unit to introduce steric bulk and possible π-stacking interactions.

The first catalyst evaluated in the DKR of 381 by 414 was the unsubstituted catalyst from Dolling’s report, catalyst 424 (Table 10, entry 1). Although N-protected phthalimide 393 was furnished in excellent yield when catalyst 424 was employed in this the reaction, the use of this catalyst failed to result in any enantiocontrol with respect to product formation. The same trend was observed when catalyst 426 - incorporating a bulky N-anthracenylmethyl group was utilised in this reaction (Table 10, entry 2). The use of the Corey and Lygo’s catalyst195,196 427 (Table 10, entry 3, the hydrogen bond donating unit on catalyst 427 is
eliminated via allylation of the hydroxyl group) unsurprisingly failed to promote any enantiocontrol over the product formed.

Table 10 Catalyst screen of cinchona-derived ammonium PTC salts 424-429

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>424</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>426</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>427</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>428</td>
<td>92</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>429</td>
<td>94</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using <i>p</i>-iodoanisole as the internal standard. Determined by CSP-HPLC analysis after isolation by column chromatography.

Catalyst 428 - bearing an <i>N</i>-benzyl unit substituted with electron-withdrawing groups in the <i>meta</i> positions - furnished 393 in excellent yield and with a significant increase in enantiomeric excess (Table 10, entry 4). Replacing the electron-withdrawing groups on 428 with bulky tert-butyl groups resulted in a slight increase in <i>ee</i> when catalyst 429 was utilised (Table 10, entry 5). Although the <i>ee</i> values may have been very low, obtaining even low levels of enantiocontrol was an exciting result. This was the first example of azlactones
undergoing DKR via formal aminolysis to produce orthogonally protected amino acid products enantioselectively.

The next set of catalysts screened were *cinchona* alkaloid-derived bifunctional PTCs. This class of catalyst combines a phase-transfer functionality (due to the *N*-alkylated quinine ring) with a hydrogen-bond donating unit (thio)urea or squaramide catalysts were screened in this reaction, see Section 1.8.2.4). This type of catalyst was first employed in 2010 by Lassaletta *et al.* to carry out the asymmetric cyanosilylation of nitroalkenes (Scheme 124).\(^{197}\) The hydrogen bond donating moiety of the bifunctional PTC 430 utilised by Lassaletta and co-workers had a dual purpose; firstly, nitroalkene 431 was activated towards nucleophilic attack by a cyanide ion *via* hydrogen bond donation and furthermore, the nucleophilic cyanide anion was present to carry out this attack due to an ionic interaction, facilitated by the *N*-alkylated quinuclidine ring serving as the required phase-transfer *motif*.

![Scheme 124](image)

**Scheme 124** 1,4-Addition of cyanide to nitroalkanes catalysed by bifunctional PTC 430\(^{197}\)

It was proposed that a similar mode of catalysis could be utilised in the DKR of azlactone 381. Using a chiral bifunctional PTC, 381 could be activated towards nucleophilic attack by the *p*-nitrophenolate anion, which would be bound to the catalyst through ionic interactions, as per Lassaletta’s report.\(^{197}\) This reaction would take place in the chiral environment provided by the catalyst, which should result in enantiomeric excess being observed in the products.

Due to time constraints, the selection of catalysts screened in this reaction were limited to those which were readily available and were not necessary to synthesise. The results of the catalyst screen of *cinchona* alkaloid-derived bifunctional PTC in this DKR protocol are outlined in Table 11. As is apparent from analysis of the data in Table 11, drastic changes to the catalyst structure failed to bring about significant changes in the level of enantioselectivities observed in the product.
Table 11  Catalyst screen of *cinchona* alkaloid-based bifunctional PTCs
<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>435</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>436</td>
<td>94</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>437</td>
<td>99</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
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<td>439</td>
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</tr>
<tr>
<td>8</td>
<td>442</td>
<td>100</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by ³H NMR spectroscopy using p-iodoanisole as the internal standard. <sup>b</sup>Determined by CSP-HPLC analysis after isolation by column chromatography.

The first bifunctional PTC screened, 435 contained a urea hydrogen-donating unit with an N-benzyl moiety on the quinine nitrogen atom. The N-benzyl moiety provides the phase-transfer functionality as well as additional steric bulk which was envisaged to aid in directing the selective addition of the nucleophilic counteranion to 381. Utilising catalyst 435 in this reaction produced only marginal ee in the amide product (Table 11, entry 1). Addition of a phenyl unit to the C-2 position of the quinoline ring to incorporate further steric bulk in the catalyst structure, i.e. catalyst 436, resulted in an increase in ee of only 1% (Table 11, entry 2). This result indicated that steric bulk at the C-2 position was most likely not necessary to produce products with high enantioselectivity.

Catalyst 437 - which maintains substitution at the C-2 position with the addition of steric bulk to the N-benzyl unit in the form of bis tert-butyl groups at the meta - positions, produced amide 393 again, in an excellent yield and did result in a moderate increase in product ee (Table 11, entry 3). This result however should be compared to catalyst 429 (Table 10, entry 5) which does not include a urea hydrogen bond donating unit. Catalyst 429 was capable of promoting the reaction in excellent yield and with a marginally higher enantioselectivity, albeit with a more simplistic catalyst structure. Replacing the sterically encumbered di-tert-butyl groups with an electron-withdrawing pentafluoro-substituted N-benzyl moiety, i.e. catalyst 438, again resulted in only a marginal increase in ee (Table 11, entry 4). The highest ee value obtained in this preliminary catalyst screen was when catalyst 439 was utilised (Table 11, entry 5). A urea-based PTC, bearing an electron-withdrawing and relatively sterically bulky iodine atom at the 2-position of the N-benzyl substituent, 439 promoted the formation of 393 in excellent yield and with 23% ee. This result was a slight improvement.
on the results obtained with the other hydrogen bond donating, bifunctional PTCs but still only slightly higher than the use of catalyst 429 (Table 10, entry 5), which again has a more simplistic catalyst design (and synthesis). Catalyst 440, which incorporates additional steric bulk to the N-benzyl moiety in the form of \textit{m}-terphenyl groups at the 3 and 5 positions, resulted in a marked decrease in enantioselectivity (Table 11, entry 6). Following a similar trend, catalyst 441 which contains bulky substituents at the N-benzyl moiety and, in particular, at the C-2 position of quinoline ring again resulted in very poor enantiocontrol being observed (Table 11, entry 7). The final catalyst tested, catalyst 442, differed from the others evaluated as it contained a squaramide hydrogen bond donating \textit{motif}. In this structure the \textit{N}-benzyl unit contained a chlorine atom at the 2-position for additional electron-withdrawing capability on the aromatic ring, as well as a degree of steric bulk. Squaramide catalyst 424 also catalysed the formation of 393 in almost negligible \textit{ee} (Table 11, entry 8). Thiourea catalysts have not been evaluated in this reaction at present as there was no access to thiourea-derived bifunctional PTCs at the time of testing.

As it was evident that making major changes to the catalyst structure failed to cause significant increases in enantioselectivity in this azlactone aminolysis reaction, it was decided to evaluate other nitro-substitutions on the phenolate anion to observe if any increase in \textit{ee} would occur. Both \textit{o}-nitrophenolate (443) and \textit{m}-nitrophenolate (444) were synthesised by treating the appropriate phenol with NaH, under strictly anhydrous conditions (Scheme 125).

![Scheme 125](image)

\textbf{Scheme 125}  Synthesis of salts 443 and 444

Encouragingly, when 443 was screened in the initial background reaction with 381, in toluene, in the absence of a PTC (either achiral TBAB or an asymmetric PTC), 443 failed to add to azlactone 381 to produce ester 447 (Scheme 126).
The background reaction between 381 and o-nitrophenolate anion 443

Although addition of TBAB to the reaction mixture did result in the reaction proceeding and phenolate ester 417 being formed, this reaction occurred very slowly relative to the p-nitrophenolate/phenol system. After 48 hours, only 77% of azlactone 381 had been converted to ester 417 (Scheme 127).

Evaluation of o-nitrophenolate salt 443 in the alcoholsysis of 381

At present, this reaction has not been carried out with an asymmetric PTC as the prolonged reaction time would result in the reaction being left to proceed for an extended time period to reach 100% conversion. It is necessary to allow these reactions to reach completion before quenching with an amine nucleophile to prevent the amine ring-opening unreacted racemic azlactone which would result in inaccurate data being obtained after analysis of the chiral HPLC chromatogram (such a chromatogram would contain a HPLC trace of the amide derived from quenched racemic azlactone).

Conversely, when m-nitrophenolate (444) was employed in the background reaction (in the absence of TBAB), the addition of 444 to azlactone 381 occurred with 100% conversion (determined by examination of the 1H NMR spectrum of the reaction mixture) in under 1
hour to furnish ester 448 (Scheme 128). Changing the solvent from toluene to a mixture of toluene and hexanes (1:1, which previously inhibited the rapid thiolyis reaction between 381 and sodium thiophenolate (404)) also failed to eliminate the background reaction.

![Scheme 128](image)

**Scheme 128** Evaluation of m-nitrophenolate salt 444 in the alcoholysis of 381

Owing to the decreased activity of 443 (likely attributed to the added steric bulk situated ortho to the nucleophilic oxygen atom) and the increased nucleophilicity of 445 (and the inability to control the associated background reaction), these phenolates have not been examined further.

Current experimental studies are underway within the research group, along with computational analysis of the reaction, in an attempt to determine the optimal combination of nucleophilic anion and catalyst binding which will result in this DKR protocol of azlactones to be carried out in high levels of enantioselectivity.

### 3.7 Development of a chemical ligation protocol via the aminolysis of azlactones

As it had now been demonstrated that it is possible to carry out the aminolysis of azlactones (*via* formation of an ester intermediate using a substituted phenolate anion) under the control of phase-transfer catalysis, to furnish products with a small degree of enantioselectivity. Attention was next turned towards the scope of the aminolysis step.

One of the primary aims of this project was to carry out the formal aminolysis of azlactones using an amino acid to furnish an orthogonally-protected dipeptide in one-pot. This novel chemical ligation strategy has never been achieved in one-step due to the reactive nature of the amine nucleophile and the difficulties associated with controlling its addition to azlactones (see Section 1.8.3).

In order to investigate if it was possible to use this methodology to produce an orthogonally protected dipeptide, a simple chiral amino acid, L-alanine (449) was chosen to test this
hypothesis. It was necessary to protect the carboxylic acid functionality of 449 (as an ester) to ensure that the N-terminus reacted smoothly with the ester intermediate 417 formed using the phenolate alcoholysis reaction. The non-enantioselective reaction using TBAB as the PTC was first carried out in order to produce the reaction racemates which would be used to compare with the products of enantioselective reaction (when a chiral PTC would be employed in the reaction).

Following synthesis of the racemates, the alcoholysis of 381 using phenolate 414 and 415 was facilitated by PTC 429 (one of the most successful catalysts employed in the DKR reaction section 3.6.2, Table 10, entry 5). Ester intermediate 417 formed from the alcoholysis reaction was quenched with protected amino acid 450 to produce orthogonally protected dipeptide 451 in a moderate yield (Scheme 129). Ester 416 was also obtained in a low yield following purification.

![Scheme 129](image)

**Scheme 129** Synthesis of dipeptide 451 via azlactone aminolysis

Attempts were made to record the diastereomeric ratio of 451 using CSP-HPLC analysis and compare the trace obtained with that of the racemates, however, carrying this out was not trivial and currently has not been achieved using the CSP-HPLC columns and solvent systems available. Optimisation of this process is ongoing within in the research group.

In order to observe the diastereomeric ratio (d.r.) between the two diastereomers of 451, $^1$H NMR spectroscopic techniques were employed. To carry this out, it was first necessary to deprotect the N-protected phtalimido group of 451, which was carried out using ethylene diamine at low temperature to produce amino ester 452 in a moderate yield (Scheme 130).
Scheme 130  Deprotection of orthogonally protected 451 to form dipeptide 452

As the amino acid nucleophile 450 utilised in the aminolysis reaction was chiral and azlactone 381 was derived from a racemic mixture of phenylalanine (359) it was possible to compare the $^1$H NMR spectrum of deprotected dipeptide 452 against a literature $^1$H NMR spectrum of L-phenylalanine L-alanine methyl ester (453). Through analysis of the $^1$H NMR spectrum, the d.r. was determined to be 3:2, which was in agreement with the ee value obtained when catalyst 429 was utilised in the aminolysis reaction (Section 3.6.2, Table 10, entry 5).

3.8 Conclusion: Chapter 3

The aminolysis of azlactones under DKR conditions to synthesise orthogonally-protected peptides has remained elusive in the literature. This is in short due to the difficulties associated with controlling the addition of amines to azlactones under catalyst influence. In this project, a novel methodology was developed that utilises a phenolate anion to carry out the alcoholysis of azlactones, under PTC conditions, to furnish phenolate esters which are readily reacted with amine nucleophiles to furnish orthogonally protected amides and dipeptides. Although this reaction produces the amide products in excellent product yields, the current lack of understanding of how the catalyst influences the reaction means that the products are formed with low levels of enantioselectivity. Although further experimentation and computational studies are required to gain control over the DKR process and produce products with high levels of enantioselectivity, this methodology is, to our knowledge, the first example of racemic azlactones being used to carry out peptide coupling without requiring a $S,N$-acyl transfer as with NCL or an $O,N$-acyl transfer as previously reported in the literature to achieve chemical ligation.
Chapter 4   Experimental procedures and data

4.1 General
Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent CDCl$_3$, DMSO-d$_6$ or CH$_3$OD and referenced relative to residual CHCl$_3$ ($\delta = 7.26$ ppm) DMSO ($\delta = 2.50$ ppm) or CH$_3$OH ($\delta = 3.31$ ppm). Chemical shifts are reported in ppm and coupling constants ($J$) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and EXSY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides and visualized by UV irradiation, KMnO$_4$ and ninhydrin staining. Anhydrous acetonitrile (CH$_3$CN), dichloromethane (CH$_2$Cl$_2$), tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Unless otherwise noted, all commercially available compounds were used as provided, without any further purification. DMF, DBU, NEt$_3$ and all other amines were distilled over calcium hydride under argon before use. Commercially available anhydrous methanol (CH$_3$OH), methyl-tert-butyl ether (MTBE) and toluene were used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns. Prior to CSP-HPLC analysis of the enantioselective product, the compound was synthesised in its racemic form, which allowed for determination of retention time and ideal separation between the two enantiomers. For clarity the numbering system associated with the assignment of the $^1$H NMR peaks did not follow the IUPAC nomenclature system.
4.2 Experimental data for Chapter 2

N-(3-benzamidopropyl)-N-methylbenzamide (174)

To an oven-dried 10 mL round-bottomed flask, containing a magnetic stirring bar, under an argon atmosphere was charged with benzoyl chloride (173, 120 µL, 1 mmol), NEt$_3$ (175 µL, 1.25 mmol) and THF (2.5 mL). N-methyl-1,3-propanediamine (163, 125 µL, 1.2 mmol) was added dropwise to the stirring solution at room temperature. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo and purified via flash column chromatography (CH$_2$Cl$_2$:MeOH, 100:2.5) to afford 174 as a white solid (145.2 mg, 49%). M.p. 122-125°C.

$\delta$H (400 MHz, CDCl$_3$): 7.98 (2 H, d, $J$ 7.1, H-1), 7.53-7.44 (8 H, m, H-2, H-3, H-9, H-10, H-11), 3.74 (2 H, t, $J$ 5.7, H-5a, H-5b), 3.54 (2 H, t, $J$ 5.7, H-7a, H-7b), 3.00 (3 H, s, H-4), 1.98-1.88 (2 H, m, H-6).

$\delta$C (100 MHz, CDCl$_3$): 172.8 (C=O), 167.1 (C=O), 136.0 (q), 134.5 (q), 131.3, 129.8, 128.6, 128.5, 127.1, 126.7, 44.2, 37.3, 35.5, 26.2.

$\nu$$_{max}$ (neat)/cm$^{-1}$: 3306 (NH), 2918, 2850, 1646 (C=O), 1618 (C=O), 1539, 1503, 1478, 1411, 1371, 1309, 1297, 1251, 1167, 1099, 1072, 926, 807, 789, 742, 697, 634, 584.

HRMS (m/z - ESI): Found: 297.1605 (M+H)$^+$ C$_{18}$H$_{21}$N$_2$O$_2$ Requires: 297.1598.

Synthesis of 4-Ethyl-1-methyl-1H-1,2,4-triazol-4-ium iodide (25)

1-Methyl-1H-1,2,4-triazole (454)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged methanol (80 mL) and sodium (3.30 g). The solution was stirred for 5 minutes before 1,2,4-triazole (115, 10 g, 155.0 mmol) was charged to the reaction mixture and it was stirred at room temperature until the observed solids had dissolved. The vessel was then placed under a protective atmosphere of argon and cooled to 0°C in a H$_2$O/ice bath. Iodomethane...
(9.04 mL, 20.61 g, 155.0 mmol) was added dropwise via syringe. Stirring was continued for 5 minutes at 0 °C before warming to room temperature. The reaction mixture was stirred for a further 2 h under argon before equipping a reflux condenser to the flask and heating it to 60 °C for 20 h. Upon cooling, the solvent was removed in vacuo and H₂O (60 mL) was added. The product was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to yield the title product 454 as a yellow liquid (4.67 g, 39%) that was dried under vacuum for several hours.

Spectral data for this compound were consistent with those in the literature.⁷⁶

\[ \delta_H (400 \text{ MHz, CDCl}_3): \] 7.93 (1 H, s, H-2), 7.78 (1 H, s, H-3), 3.80 (3 H, s, H-1).

HRMS \((m/z - \text{ESI})\): Found: 84.0564 (M+H)+  C₃H₆N₃ Requires: 84.0562.

4-Ethyl-1-methyl-1H-1,2,4-triazol-4-ium iodide (25)

\[
\begin{array}{c}
\text{I} \\
\text{N} \\
\text{N} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{5}
\end{array}
\]

To an oven-dried 50 mL round-bottomed flask, equipped with a magnetic stirring bar, septum seal and argon-filled balloon, was charged 1-methyl-1H-1,2,4-triazole (454, 4.2 g, 50.5 mmol). The vessel was placed under an atmosphere of argon and ethyl iodide (17.3 g, 8.9 mL, 111 mmol) was added via syringe. The flask was covered with aluminium foil and the reaction mixture stirred for 96 h at room temperature under argon. The resulting precipitate was filtered, washed with Et₂O (3 x 20 mL) and recrystallised from 1% MeOH in Et₂O to yield the title product as a white crystalline solid (3.07g, 23%).

Spectral data for this compound were consistent with those in the literature.⁷⁶

\[ \delta_H (400 \text{ MHz, DMSO-d}_6): \] 10.03 (1 H, s, H-2), 9.18 (1 H, s, H-3), 4.2 (2 H, q, J 7.3, H-4), 4.03 (3 H, s, H-1), 1.41 (3 H, t, J 7.3, H-5).

HRMS \((m/z - \text{ESI})\): Found: 112.0874 (M)+  C₅H₁₀N₃ Requires: 112.0875.
1,2-di-o-tolylethane-1,2-dione (175)

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged sequentially Rb$_2$CO$_3$ (1.21 g, 5.22 mmol), 4-ethyl-1-methyl-1H-1,2,4-triazol-4-ium iodide (25, 1.14 g, 4.77 mmol), o-tolualdehyde (176, 3.0 mL, 25.9 mmol) and THF (15 mL). The flask was fitted with a septum seal and argon-filled balloon. The mixture was stirred at room temperature and the progress of the reaction monitored by TLC analysis. Upon complete consumption of 176 (determined by TLC analysis of the crude reaction mixture) the solvent was removed in vacuo and the resulting residue dissolved in CH$_2$Cl$_2$ (70 mL). MnO$_2$ (13.5 g, 152.1 mmol) was charged to the flask and the resulting suspension was stirred until complete oxidation of the benzoin derivative to the benzil product was achieved. The oxidation reaction was monitored by TLC analysis of the crude reaction mixture. The suspension was filtered over a pad of celite and eluted with CH$_2$Cl$_2$ until no trace of product could be detected in the eluent (monitored by TLC analysis). The filtrate was concentrated in vacuo to furnish a residue that was purified via flash column chromatography (9:1 hexanes:EtOAc) to yield the title product 175 as a yellow solid (1.51 g, 25%). M.p. 97-98 °C (lit.,$^{199}$ M.p. 95-96 °C).

Spectral data for this compound were consistent with those in the literature.$^{199}$

$\delta$H (400 MHz, CDCl$_3$): 7.65 (1 H, dd, $J$ 7.8, 0.8, H-1), 7.47 (1 H, td, $J$ 7.5, 0.8, H-3), 7.33 (1 H, app. t, H-2), 7.28-7.25 (1 H, m, H-4), 2.69 (3 H, s, H-5).

Synthesis of first-generation substrate for selective amine protections

Dimethyl 2,3-pyridinedicarboxylate (184)

An oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with 2,3-pyridinedicarboxylic acid (183, 10.01 g, 59.91
mmol) and anhydrous methanol (40 mL). Sulfuric acid (4 mL) was added dropwise to the stirring suspension, under ice cooling. The flask was fitted with a reflux condenser and the mixture was heated under reflux for 18 h. After cooling, the reaction mixture was quenched with a saturated solution of NaHCO₃ (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (25 mL), dried over MgSO₄, filtered and concentrated in vacuo to afford 184 as a pale yellow solid (8.61 g, 74%). M.p. 55-57 °C (lit.200 m.p., 55-56 °C).

Spectral data for this compound were consistent with those in the literature.¹⁶⁸

δ_H (400 MHz, CDCl₃): 8.75 (1 H, dd, J 4.8, 1.6, H-1), 8.15 (1 H, dd, J 8.1, 1.6, H-3), 7.47 (1 H, dd, J 8.1, 4.8, H-2), 3.97 (3 H, s, H-4), 3.91 (3 H, s, H-5).

**Pyridine-2,3-diylibis(methylene) diacetate (185)**

![image](image-url)

To an oven-dried 250 mL round-bottomed flask containing a magnetic stirring bar, under an argon atmosphere, was charged with dimethyl 2,3-pyridinecarboxylate (184, 7.32 g, 40.40 mmol) and ethanol (100 mL). Sodium borohydride (7.72 g, 202.0 mmol) was added portion wise to the stirring solution under ice cooling. The flask was fitted with a reflux condenser and the mixture was heated under reflux for 24 h. The reaction was cooled to room temperature and concentrated under reduced pressure; the crude oil obtained was dissolved in CH₂Cl₂ (40 mL). DMAP (1.02 g, 8.08 mmol) was charged to the stirring mixture followed by triethylamine (45 mL). Acetic anhydride (31 mL) was charged to the flask under ice cooling. The reaction mixture was allowed to stir for 7 days after which time the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (75 mL) and water (75 mL), dried over MgSO₄, filtered, concentrated under reduced pressure and purified via flash column chromatography (CH₂Cl₂:methanol, 100:1) to yield 185 as an orange oil (3.73 g, 41%).

δ_H (400 MHz, CDCl₃): 8.60 (1 H, dd, J 4.8, 1.4, H-1), 7.75 (1 H, dd, J 7.7, 1.1, H-3), 7.31 (1 H, dd, J 7.7, 4.8, H-2), 5.31 (2 H, s, H-5), 5.23 (2 H, s, H-4), 2.15 (3 H, s, H-7), 2.12 (3 H, s, H-6).
$\delta_C$ (100 MHz, CDCl$_3$): 170.7 (C=O), 170.5 (C=O), 153.8 (q), 149.3, 137.6, 130.4 (q), 123.4, 65.1, 62.7, 20.9.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2960, 1738 (C=O), 1579, 1443, 1378, 1222, 1028, 968, 921, 796, 606.

HRMS ($m/z$ - ESI): Found: 246.0312 (M+Na)$^+$  C$_{11}$H$_{13}$NNaO$_4$ Requires: 246.0737.

**2,3-Bis(hydroxymethyl)pyridine (186)**

![Diagram of 2,3-Bis(hydroxymethyl)pyridine (186)](image)

To a stirred solution of 185 (3.73 g, 16.7 mmol) in anhydrous MeOH (70 mL) at 0 °C, under an argon atmosphere, in a 250 mL round-bottomed flask equipped with a magnetic stirring bar, sodium methoxide (2.73 g, 50.5 mmol) was added portion wise. The reaction mixture was warmed to room temperature and stirred for 48 h, after which time Dowex® 50WX8 hydrogen form was added portion wise with stirring to quench the reaction mixture. The reaction mixture was filtered, concentrated *in vacuo* and purified *via* flash column chromatography (CH$_2$Cl$_2$:MeOH, 9:1) to yield the title compound 186 as an orange solid (1.65 g, 71%). M.p. 56-59 °C (lit.$^{168}$ m.p., 56-58 °C).

Spectral data for this compound were consistent with those in the literature.$^{168}$

$\delta_H$ (400 MHz, CDCl$_3$): 8.45 (1 H, d, $J$ 3.8, H-1), 7.74 (1 H, d, $J$ 7.4, H-3), 7.24 (1 H, dd, $J$ 7.4, 3.8, H-2), 4.76 (3 H, s, H-5), 4.68 (3 H, s, H-4).

* The protic signals H-7 and H-8 are not visible in CDCl$_3$.
(3-(tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)methanol (187)

To a stirred solution of diol 186 (1.45 g, 10.4 mmol), imidazole (0.89 g, 13.1 mmol) and DMAP (140 mg, 1.1 mmol) in CH$_2$Cl$_2$ (75 mL), at 0 °C, under an argon atmosphere, in a 100 mL round-bottomed flask equipped with a magnetic stirring bar, was added tert-butyldimethylsilyl chloride (1.64 g, 10.4 mmol) portion wise. The resultant mixture was warmed to room temperature and stirred for 16 h. The solvent was then removed in vacuo and the residue was purified via flash column chromatography (CH$_2$Cl$_2$:EtOAc, 15:1) to furnish 187 as a colourless oil (1.34 g, 51%).

δ$_H$ (400 MHz, CDCl$_3$): 8.48 (1 H, d, $J$ 4.8, H-1), 7.78 (1 H, d, $J$ 7.5, H-3), 7.26 (1 H, dd, $J$ 7.5, 4.8, H-2), 4.72 (2 H, s, H-7), 4.67 (2 H, s, H-4), 0.95 (9 H, s, H-6), 0.13 (6 H, s, H-5).

* The protic signal (H-8) is not visible in CDCl$_3$.

δ$_C$ (100 MHz, CDCl$_3$): 155.2 (q), 146.2, 134.6, 132.9 (q), 122.3, 61.2, 60.9, 25.9, 18.3 (q), -5.4.

ν$_{max}$ (neat)/cm$^{-1}$: 3365, 2954, 2930, 2885, 2856, 1583, 1462, 1410, 1254, 1119, 1079 1054, 834, 775, 721, 669, 619.

HRMS (m/z - APCI): Found: 254.1569 (M+H)$^+$ C$_{13}$H$_{24}$NO$_2$Si Requires: 254.1571.

3-(tert-butyldimethylsilyl)oxy)methyl)picolinaldehyde (188)

To a stirred solution of 187 (0.857 g, 3.38 mmol) in CH$_2$Cl$_2$ (15 mL), under an argon atmosphere in a 25 mL round-bottomed flask equipped with a magnetic stirring bar, was
charged MnO₂ (5.89 g, 67.6 mmol). The resultant suspension was stirred at room temperature for 24 h. The reaction mixture was filtered over a pad of celite and eluted with CH₂Cl₂ until no trace of product could be detected in the eluent (monitored by TLC analysis of the eluent). The filtrate was concentrated *in vacuo* to furnish 188 as a colourless oil (612 mg, 72 %).

δ_H (400 MHz, CDCl₃): 10.19 (1 H, s, H-7), 8.72 (1 H, d, J 4.4, H-1), 8.27 (1 H, d, J 7.9, H-3), 7.57 (1 H, dd, J 7.9, 4.4, H-2), 5.19 (2 H, s, H-4), 0.99 (9 H, s, H-6), 0.16 (6 H, s, H-5).

δ_C (100 MHz, CDCl₃): 195.8 (C=O), 147.9 (q), 147.8, 140.5 (q), 134.7, 127.3, 61.2, 25.9, 18.4 (q), -5.4.

ν_max (neat)/cm⁻¹: 2954, 2930, 2857, 1707 (C=O), 1568, 1463, 1255, 1122, 1077, 835, 776, 663.

HRMS (m/z - APCI): Found: 252.1411 (M+H)⁺ C₁₅H₂₂NO₂Si Requires: 252.1414.

**General procedure I: Preparation of substituted benzils 178, 198, 227**

To an oven-dried 5 mL round bottom flask, equipped with a magnetic stirrer bar, Rb₂CO₃ (99.995% anhydrous, 0.2 mmol, 20 mol%, 46.19 mg) that had been ground finely with a mortar and pestle, was added. The reaction vessel was put under vacuum and heated with a heat gun for several minutes. Upon cooling, the appropriate catalyst (0.2 mmol, 20 mol %) was added to the flask and the reaction vessel was evacuated under vacuum and put under an atmosphere of argon. The flask was fitted with septum seal and argon-filled balloon. Anhydrous THF (1.1 M) was charged to the reaction flask, followed by the relevant aldehyde (1 mmol). The reaction was stirred at room temperature for 48 h after which time the reaction was filtered through a short pad of silica, washed with CH₂Cl₂ and concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ (4 mL) followed by the addition of MnO₂ (20 equiv.) and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered over a pad of celite and eluted with CH₂Cl₂ until no trace of product could be detected in the eluent (monitored by TLC analysis of the eluent). The filtrate was concentrated *in vacuo* to furnish a residue that was purified *via* flash column chromatography.
**1,2-bis(3-(tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)ethane-1,2-dione (178)**

![Chemical Structure](image)

Prepared according to general procedure I using THF (0.9 mL), Rb₂CO₃ (46.2 mg, 0.2 mmol), catalyst 27 (72.6 mg, 0.2 mmol) and aldehyde 188 (251 mg, 1 mmol). Purified by flash column chromatography (hexanes:EtOAc, 6:4) to afford 178 as a pale yellow solid (186 mg, 75%). M.p. 210-211 °C.

δ_H (400 MHz, CDCl₃): 8.44 (1 H, dd, J 4.6, 1.2, H-1), 8.30 (1 H, dd, J 8.1, 1.2, H-3), 7.49 (1 H, dd, J 8.1, 4.6, H-2), 5.37 (2 H, s, H-4), 1.03 (9 H, s, H-6), 0.2 (6 H, s, H-5).

δ_C (100 MHz, CDCl₃): 198.8 (C=O), 146.9 (q), 146.8, 141.1 (q), 137.7, 127.1, 61.4, 26.0, 18.4 (q), -5.1.

ν_max (neat)/cm⁻¹: 2974, 1744 (C=O), 1708 (C=O), 1567, 1463, 1257, 1120, 1077, 837, 772, 648.

HRMS (m/z - ESI): Found: 501.2599 (M+H)⁺ C_{26}H_{41}N_{2}O_{4}Si₂ Requires: 501.2599.

**Synthesis of second-generation substrate**

*N*-benzyl-2-(hydroxymethyl)-*N*-methylbenzamide (202)

![Chemical Structure](image)

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged AlCl₃ (6.46 g, 48.5 mmol) followed by anhydrous dichloroethane (25 mL). The
vessel was placed under a protective atmosphere of argon and cooled to 0 °C in a H₂O/ice bath. The flask was fitted with a septum seal and argon balloon. *N*-methylbenzylamine (200, 12 mL, 93.2 mmol) was added to the flask, the reaction mixture was maintained at 0 °C and stirred for 30 minutes after which time phthalide (199, 5.03 g, 37.3 mmol) was added portion wise to the stirring solution. The reaction mixture was stirred for a further 2 h at room temperature following which, ice and water were added to the flask carefully and an emulsion was observed. This emulsion was filtered over a pad of celite and the filtrate was extracted into CH₂Cl₂ (3 x 25 mL). The combined organic extract was washed with brine (2 x 25 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 6:4) to yield 202 as a colourless oil (8.18 g, 82%).

Spectral data for this compound were consistent with those in the literature.201

*A non-degenerate mix of rotamers is observed in the ¹H NMR spectrum of this compound.

δH (400 MHz, CDCl₃): Major rotamer: 7.47-7.39 (8 H, m, H-1, H-3, H-4, H-8, H-9, H-10), 7.11 (1 H, d, J 7.2, H-2), 4.78 (2 H, s, H-7), 4.56 (2 H, s, H-5), 2.82 (3 H, s, H-6).

Minor rotamer: 7.47-7.39 (8 H, m, H-1, H-3, H-4, H-8, H-9, H-10), 7.11 (1 H, d, J 7.2, H-2), 4.56 (2 H, s, H-7), 4.48 (2 H, s, H-5), 3.06 (3 H, s, H-6).

* The protic signal (H-11) is not visible in CDCl₃.

HRMS (m/z - ESI): Found: 256.1333 (M+H)⁺ C₁₆H₁₈NO₂ Requires: 256.1333.

*N-benzyl-2-formyl-N-methylbenzamide (203)

![Chemical Structure](image)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged *N*-benzyl-2-(hydroxymethyl)-N-methylbenzamide (202, 4.4g, 17.4 mmol). The vessel was placed under a protective atmosphere of argon and CH₂Cl₂ (70 mL) was charged
to the flask followed by MnO$_2$ (30.3g, 348 mmol). The reaction mixture was stirred at room temperature until complete consumption of the starting material was observed (monitored by TLC analysis). The resulting suspension was filtered over a pad of celite and the filter cake washed with CH$_2$Cl$_2$ until no further product was detected in the eluent (monitored by TLC analysis). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (hexanes:EtOAc, 6:4) to afford 203 as a colourless oil (3.45g, 77%).

Spectral data for this compound were consistent with those in the literature.$^{202}$

*A non-degenerate mix of rotamers is observed in the $^1$H NMR spectrum of this compound.*

$^{1}$H NMR (400 MHz, CDCl$_3$):  
Major rotamer: 10.07 (1 H, s, H-10), 7.95-7.90 (1 H, m, H-4), 7.69-7.55 (2 H, m, H-1, H-3), 7.45-7.26 (5 H, m, H-7, H-8, H-9), 7.10 (1 H, d, $J$ 7.1, H-2), 4.82 (2H, s, H-6), 2.68 (3 H, s, H-5).

Minor rotamer: 10.08 (1 H, s, H-10), 7.95-7.90 (1 H, m, H-4), 7.69-7.55 (2 H, m, H-1, H-3), 7.45-7.26 (5 H, m, H-7, H-8, H-9), 7.10 (1 H, d, $J$ 7.1, H-2), 4.30 (2H, s, H-6), 3.09 (3 H, s, H-5).

HRMS ($m/z$ - ESI): Found: 276.0996 (M+Na)$^+$ C$_{16}$H$_{15}$NNaO$_2$ Requires: 276.0995.

**2,2’-oxalylbis(N-benzyl-N-methylbenzamide) (198)**

![Image of 2,2'-oxalylbis(N-benzyl-N-methylbenzamide) (198)]

Prepared according to general procedure I using THF (0.9 mL), Rb$_2$CO$_3$ (46.2 mg, 0.2 mmol), catalyst 27 (47.8 mg, 0.2 mmol) and aldehyde 203 (253 mg, 1 mmol). Purified by flash column chromatography (CH$_2$Cl$_2$:MeOH, 20:1) to afford 198 as a pale yellow solid (179 mg, 71%). M.p. 66-68 °C.
Note: The NMR spectra associated with this compound are unexpectedly complex due to the presence of four apparently degenerate rotameric species.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
8.02 (4 H, d, \( J = 7.8 \), H-1, 4 rotamers), 7.67 (2 H, t, \( J = 7.5 \), H-3, 2 rotamers), 7.63-7.50 (6 H, m), 7.48-7.27 (20 H, m), 7.25 (4 H, d, \( J = 7.3 \) H-5, 2 rotamers), 4.77 (2H, s, H-8, 1 rotamer), 4.74 (2 H, s, H-8, 1 rotamer), 4.44 (4 H, s, H-8, 2 rotamers), 3.01 (3 H, s, H-9, 1 rotamer), 2.98 (3 H, s, H-9, 1 rotamer), 2.80 (3 H, s, H-9, 1 rotamer), 2.79 (3 H, s, H-9, 1 rotamer).

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]
192.6 (C=O), 192.5 (C=O), 192.4 (C=O), 192.3 (C=O), 171.0 (C=O), 170.9 (C=O), 170.6 (C=O), 138.4 (q), 138.4. (q), 138.2 (q), 138.1 (q), 136.8 (q), 136.8 (q), 136.3 (q), 136.3 (q), 133.8, 133.7, 133.7, 132.7, 132.7, 132.6, 132.5, 131.6 (q), 131.4 (q), 131.3 (q), 131.1 (q), 129.5, 129.4, 129.3, 129.3, 128.9, 128.6, 128.4, 128.4, 127.7, 127.7, 127.5, 127.5, 127.4, 127.3, 127.1, 127.1, 127.0, 126.9, 54.8, 54.8, 50.4, 36.2, 36.1, 32.8.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1} \):
2967, 1745 (C=O), 1554, 1358, 1231, 1217, 877.

HRMS \((m/z \text{- ESI})\): Found: 505.2138 (M+H)\(^+\) \( C_{32}H_{29}N_2O_4 \) Requires: 505.2127.

Synthesis of other substituted-benzils evaluated as substrates for selective amine protection

2-(benzyl(methyl)carbamoyl)-3,4,5,6-tetrachlorobenzoic acid (211)

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged tetrachlorophthalic anhydride (209, 1.51 g, 5.2 mmol) followed by THF (20 mL). The vessel was then placed under a protective atmosphere of argon. The flask was fitted with a septum seal and argon balloon. \textit{N}-methybenzylamine (200, 0.8 mL, 6.3 mmol) was added to the flask and the reaction mixture was stirred for 16 h following which, the solvent was concentrated \textit{in vacuo}. The corresponding residue was extracted into CH\(_2\)Cl\(_2\) (3 x 25 mL)
and the organic extract was washed with brine (2 x 25 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting residue solidified upon trituration with hexanes to yield **211** as a white solid (1.84 g, 87%). M.p. 140-143 °C.

*A non-degenerate mix of rotamers is observed in the ¹H and ¹³C NMR spectra of this compound.*

**δ**<sub>H</sub> (400 MHz, CDCl₃):  
Major rotamer: 8.57 (1 H, br s, H-1), 7.47-7.19 (5 H, m, H-4, H-5, H-6), 4.40 (2 H, d, J 14.8, H-3), 2.81 (3 H, s, H-2).

Minor rotamer: 8.57 (1 H, br s, H-1), 7.47-7.19 (5 H, m, H-4, H-5, H-6), 5.03 (2 H, d, J 14.8, H-3), 2.91 (3 H, s, H-2).

**δ**<sub>C</sub> (100 MHz, CDCl₃):  
Major rotamer: 167.1 (C=O), 166.5 (C=O), 135.5 (q), 134.4 (q), 133.8 (q), 133.4 (q), 130.3 (q), 129.7, 128.8 (q), 128.2, 127.8, 55.2, 35.6.

Minor rotamer: 167.5 (C=O), 167.3 (C=O), 134.7 (q), 134.6 (q), 134.3 (q), 133.9 (q), 133.2 (q), 129.4 (q), 128.9, 128.6 (q), 128.4, 128.0, 50.9, 32.3.

**ν<sub>max</sub>** (neat)/cm⁻¹:  
2480, 1769, 1739 (C=O), 1603 (C=O), 1531, 1454, 1415, 1349, 1249, 1235, 1180, 1142, 903, 821, 735, 696, 644, 600.

**HRMS (m/z - APCI):** Found: 405.9571 (M+H)<sup>+</sup> C<sub>16</sub>H<sub>12</sub>NO<sub>3</sub>Cl<sub>4</sub> Requires: 405.9566.

**Methyl-2-(benzyl(methyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (213)**

![Methyl-2-(benzyl(methyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (213)](image)

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged 2-(benzyl(methyl)carbamoyl)-3,4,5,6-tetrachlorobenzoic acid (**211**, 2.48 g, 6.11 mmol), DMF (25 mL) and K₂CO₃ (5.1 g, 36.7 mmol). The reaction vessel was placed under a protective atmosphere of argon and was cooled to 0 °C in a H₂O/ice bath. The flask was fitted with a septum seal and argon balloon. Methyl iodide (3.8 mL, 61.1 mmol) was added
to the flask dropwise at 0 °C. The reaction mixture was warmed slowly to room temperature and was stirred overnight after which time water (25 mL) was added to the flask and the mixture was extracted into EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes:EtOAc, 6:4) to afford **213** as a colourless oil (2.06 g, 80%).

\[\delta_H (400 \text{ MHz, CDCl}_3):\]
- Major rotamer: 7.38-7.25 (5 H, m, H-4, H-5, H-6), 4.70 (2 H, d, J 4.8, H-3), 3.81 (3 H, s, H-1), 2.77 (3 H, s, H-2).
- Minor rotamer: 7.38-7.25 (5 H, m, H-4, H-5, H-6), 4.34 (2 H, d, J 1.1, H-3), 3.94 (3 H, s, H-1), 2.91 (3 H, s, H-2).

\[\delta_C (100 \text{ MHz, CDCl}_3):\]
- Major rotamer: 164.6 (C=O), 164.3 (C=O), 135.9 (q), 135.4 (q), 135.2 (q), 134.8 (q), 134.3 (q), 131.1 (q), 130.7 (q), 128.7, 128.6, 127.8, 53.3, 50.6, 35.2.
- Minor rotamer: 164.9 (C=O), 164.6 (C=O), 135.5 (q), 135.1 (q), 134.5 (q), 131.6 (q), 130.8 (q), 129.5 (q), 129.1 (q), 128.8, 128.2, 128.1, 54.8, 53.4, 32.0.

\[\nu_{\text{max}} (\text{neat})/\text{cm}^{-1}:\]
- 3029, 2954, 1733 (C=O), 1643 (C=O), 1532, 1452, 1352, 1256, 1134, 1082, 972, 890, 739, 701, 652, 603, 591.

HRMS (m/z - ESI): Found: 419.9719 (M+H){+} C_{17}H_{14}Cl_{4}NO_{3} Requires: 419.9722.

**N-benzyl-2,3,4,5-tetrachloro-6-formyl-N-methylbenzamide (217)**

An oven-dried 100 mL round-bottomed flask was equipped with a magnetic stirring bar and was flushed with argon. An argon balloon and septum were fitted to the flask following which, LiBH₄ (0.20 g, 9.1 mmol) was added. The flask was cooled to 0 °C in a H₂O/ice bath and anhydrous Et₂O (26 mL) was charged to the reaction flask. In an oven-dried 25 mL round-bottomed flask methyl-2-(benzyl(methyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (213, 3.2 g, 7.57 mmol) was dissolved in THF (10 mL) under an atmosphere of argon.
(septum and balloon). The ester/THF solution was added dropwise to the stirring LiBH₄/Et₂O suspension at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight after which time water (25 mL) was added to the reaction flask at 0 °C and the mixture was extracted into Et₂O (3 x 30 mL). The combined organic layer were dried over MgSO₄ and concentrated under reduced pressure. The crude product was placed under a protective atmosphere of argon and CH₂Cl₂ (40 mL) was charged to the flask followed by MnO₂ (8.76 g, 101 mmol). The reaction mixture stirred at room temperature until complete consumption of the starting material was observed (monitored by TLC analysis of the crude reaction mixture). The resulting suspension was filtered over a pad of celite and the filter cake washed with CH₂Cl₂ until no further product was detected in the eluent (monitored by TLC analysis). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes:EtOAc, 6:4) to afford 217 as a colourless oil (1.05 g, 62%).

*A non-degenerate mix of rotamers is observed in the ¹H NMR and ¹³C spectra of this compound.

δH (400 MHz, CDCl₃): Major rotamer: 10.46 (1 H, s, H-1), 7.50 (2 H, app. d, H-5), 7.42 (1 H, app. t, H-6), 7.36 (2 H, d, H-4), 5.32 (2 H, s, H-3), 2.70 (3 H, s, H-2).

Minor rotamer: 10.45 (1 H, s, H-1), 7.50 (2 H, app. d, H-5), 7.42 (1 H, app. t, H-6), 7.36 (2 H, d, H-4), 5.25 (2 H, s, H-3), 3.07 (3 H, s, H-2).

δC (100 MHz, CDCl₃): Major rotamer: 188.1 (C=O), 165.3 (C=O), 139.2 (q), 136.7 (q), 136.3 (q), 135.9 (q), 134.8 (q), 134.7 (q), 129.4 (q), 128.9, 128.8, 128.7, 50.4, 34.6.

Minor rotamer: 188.0 (C=O), 165.6 (C=O), 139.4 (q), 136.6 (q), 136.4 (q), 136.1 (q), 135.0 (q), 130.7 (q), 129.5 (q), 128.9, 128.8, 128.7, 54.4, 32.2.

νmax (neat)/cm⁻¹: 1767 (C=O), 1698, 1648 (C=O), 1523, 1449, 1344, 1226, 1204, 1169, 1089,967, 843, 777, 695, 576.

HRMS (m/z - ESI): Found: 389.9614 (M+H)⁺ C₁₆H₁₂NO₂Cl₄ Requires: 389.9622.
2-(benzyl(methyl)carbamoyl)-4,5-dichlorobenzoic acid (219)

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged 4,5-dichlorophthalic anhydride (218, 2.02 g, 9.2 mmol) followed by THF (17 mL). The vessel was then placed under a protective atmosphere of argon using a septum seal and argon balloon. N-methylbenzylamine (200, 1.5 mL, 11.1 mmol) was charged to the flask and the reaction mixture was stirred for 16 h following which time the solvent was concentrated in vacuo. The corresponding residue was extracted into CH$_2$Cl$_2$ (3 x 25 mL) and the combined organic extracts were washed with brine (2 x 25 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The crude product solidified upon trituration with hexanes to yield 219 as a pale-yellow oil (2.94 g, 95%).

*A non-degenerate mix of rotamers is observed in the $^1$H and $^{13}$C NMR spectra of this compound.

$\delta_H$ (600 MHz, DMSO-d$_6$): Major rotamer: 13.76 (1 H, br s, H-1), 8.09 (1 H, s, H-2), 7.74 (1 H, s, H-3), 7.49-7.24 (5 H, m, H-6, H-7, H-8), 4.66 (2 H, s, H-5), 2.63 (3 H, s, H-4).

Minor rotamer: 13.76 (1 H, br s, H-1), 8.07 (1 H, s, H-2), 7.72 (1 H, s, H-3), 7.49-7.24 (5 H, m, H-6, H-7, H-8), 4.27 (2 H, s, H-5), 2.85 (3 H, s, H-4).

$\delta_C$ (100 MHz, DMSO-d$_6$): Major rotamer: 168.2 (C=O), 165.7 (C=O), 139.2 (q), 137.5 (q), 136.0 (q), 132.3, 131.9 (q), 129.5 (q), 128.9, 128.4, 127.8, 127.6, 49.8, 36.1.

Minor rotamer: 168.3 (C=O), 165.4 (C=O), 139.0 (q), 137.0 (q), 135.8 (q), 132.4, 129.5 (q), 129.3 (q), 129.2, 129.1, 129.0, 127.9, 54.3, 32.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 2472, 1719 (C=O), 1599 (C=O), 1551, 1495, 1402, 1254, 1231, 1106, 1028, 971, 939, 870, 777, 676, 605, 588.
HRMS (m/z - APCI): Found: 338.0353 (M+H)+ C16H14Cl2NO3 Requires: 338.0345.

Methyl 2-(benzyl(methyl)carbamoyl)-4,5-dichlorobenzoate (220)

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged 2-(benzyl(methyl)carbamoyl)-4,5-dichlorobenzoic acid (219, 3.12 g, 9.2 mmol), DMF (13 mL) and K2CO3 (7.65 g, 55.3 mmol). The vessel was placed under a protective atmosphere of argon and was cooled to 0 °C in a H2O/ice bath. The flask was fitted with a septum seal and argon balloon. Methyl iodide (5.8 mL, 92.2 mmol) was charged to the flask dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature after which time water (30 mL) was added to the flask and the mixture was extracted into EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over MgSO4 and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes:EtOAc, 7:3) to afford 220 as a colourless oil (3.07 g, 94%).

* A non-degenerate mix of rotamers is observed in the 1H and 13C NMR spectra of this compound.

δH (600 MHz, DMSO-d6): Major rotamer: 8.11 (1 H, s, H-1), 7.81 (1 H, s, H-2), 7.48-7.21 (5 H, m, H-6, H-7, H-8), 4.66 (2 H, s, H-5), 3.75 (3 H, s, H-3), 2.67 (3 H, s, H-4).

Minor rotamer: 8.10 (1 H, s, H-1), 7.79 (1 H, s, H-2), 7.48-7.21 (5 H, m, H-6, H-7, H-8), 4.29 (2 H, s, H-5), 3.84 (3 H, s, H-3), 2.89 (3 H, s, H-4).

δC (100 MHz, DMSO-d6): Major rotamer: 167.3 (C=O), 164.1 (C=O), 138.4 (q), 136.9 (q), 136.0 (q), 131.8, 131.7 (q), 129.1, 128.5, 128.1, 127.3, 52.8, 49.5, 35.7.
Minor rotamer: 167.4 (C=O), 163.9 (C=O), 138.4 (q), 136.4 (q), 135.9 (q), 131.9, 131.6 (q), 129.1, 128.5, 127.4, 127.2, 53.8, 52.9, 32.2.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3093, 1888, 1783, 1750 (C=O), 1614 (C=O), 1448, 1389, 1349, 1221, 1194, 1174, 997, 926, 884, 767, 647, 561.

HRMS ($m/z$ - APCI): Found: 352.0509 (M+H)$^+$ C$_{17}$H$_{16}$Cl$_2$NO$_3$ Requires: 352.0502.

*N*-benzyl-4,5-dichloro-2-(hydroxymethyl)-*N*-methylbenzamide (221)

An oven-dried 50 mL round-bottomed flask was equipped with a magnetic stirring bar and was flushed with argon. An argon balloon and septum were attached to the flask following which LiBH$_4$ (0.23 g, 10.4 mmol) was added. The flask was cooled to 0 °C in a H$_2$O/ice bath and anhydrous Et$_2$O (30 mL) was charged to the flask. In an oven-dried 25 mL round-bottomed flask methyl 2-(benzyl(methyl)carbamoyl)-4,5-dichlorobenzoate (220, 3.06 g, 8.70 mmol) was dissolved in THF (11 mL) under an atmosphere of argon (septum and balloon). The ester/THF solution was added dropwise to the stirring LiBH$_4$/Et$_2$O suspension at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. Water (25 mL) was added to the reaction flask at 0 °C and the mixture was extracted into Et$_2$O (3 x 30 mL). The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH$_2$Cl$_2$:MeOH, 100:1) to afford 221 as a colourless oil (2.13 g, 76%).

*A non-degenerate mix of rotamers is observed in the $^1$H and $^{13}$C NMR spectra of this compound.*

$\delta_H$ (400 MHz, CDCl$_3$): Major rotamer: 7.59-7.57 (1 H, m, H-1), 7.44-7.30 (5 H, m, H-7, H-8, H-9), 7.14-7.09 (1 H, m, H-2), 4.77 (2 H, s, H-6), 4.54 (2 H, s, H-3), 3.57 (1 H, br s, H-4), 2.84 (3 H, s, H-5).
Minor rotamer: 7.59-7.57 (1 H, m, H-1), 7.44-7.30 (5 H, m, H-7, H-8, H-9), 7.14-7.09 (1 H, m, H-2), 4.77 (2 H, s, H-6), 4.47 (2 H, s, H-3), 3.57 (1 H, br s, H-4), 3.09 (3 H, s, H-5).

δC (100 MHz, CDCl3):

Major rotamer: 169.3 (C=O), 139.0 (q), 136.3 (q), 134.7 (q), 133.8 (q), 131.6 (q), 131.5, 128.3, 128.2, 128.2, 126.9, 62.7, 50.8, 36.7.

Minor rotamer: 169.9 (C=O), 139.3 (q), 135.6 (q), 134.5 (q), 134.0 (q), 131.6, 131.6 (q), 129.1, 129.0, 128.1, 128.0, 62.6, 55.3, 33.4

νmax (neat)/cm⁻¹:

3087, 3030, 3057, 2922, 2854, 1762, 1696, 1628 (C=O), 1583, 1439, 1316, 1224, 1195, 1066, 985, 916, 805, 739, 670, 852, 554.

HRMS (m/z - ESI):

Found: 324.0556 (M+H)⁺ C₁₆H₁₆NO₂Cl₂ Requires: 324.0553.

N-benzyl-4,5-dichloro-2-formyl-N-methylbenzamide (222)

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged N-benzyl-4,5-dichloro-2-(hydroxymethyl)-N-methylbenzamide (221, 2.02 g, 6.24 mmol). The vessel was placed under a protective atmosphere of argon and CH₂Cl₂ (25 mL) was charged to the flask followed by MnO₂ (5.49 g, 62.4 mmol). The reaction mixture was stirred at room temperature until complete consumption of the starting material was observed (monitored by TLC analysis of the crude reaction mixture). The resulting suspension was filtered over a pad of celite and the filter cake washed with CH₂Cl₂ until no further product was detected in the eluent (monitored by TLC analysis). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes:EtOAc, 6:4) to afford 222 as a colourless oil (1.08 g, 54%).
*A non-degenerate mix of rotamers is observed in the $^1$H and $^{13}$C NMR spectra of this compound.

$\delta_H$ (600 MHz, DMSO-d$_6$): Major rotamer: 9.94 (1 H, s, H-1), 8.25 (1 H, s, H-3), 7.88 (1 H, s, H-2), 7.47-7.17 (5 H, m, H-6, H-7, H-8), 4.70 (2 H, s, H-5), 2.66 (3 H, s, H-4).

Minor rotamer: 9.93 (1 H, s, H-1), 8.21 (1 H, s, H-3), 7.84 (1 H, s, H-2), 7.47-7.17 (5 H, m, H-6, H-7, H-8), 4.30 (2 H, s, H-5), 2.95 (3 H, s, H-4).

$\delta_C$ (100 MHz, DMSO-d$_6$): Major rotamer: 189.9 (C=O), 166.5 (C=O), 137.4 (q), 137.2 (q), 136.8 (q), 133.2, 132.4 (q), 132.3 (q), 129.4, 128.5, 127.9, 127.2, 49.6, 35.8.

Minor rotamer: 189.8 (C=O), 166.6 (C=O), 137.4 (q), 137.1 (q), 136.4 (q), 133.2, 132.5 (q), 132.3 (q), 129.3, 128.6, 127.9, 127.3, 53.7, 32.5.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2922, 2853, 1751 (C=O), 1697, 1629 (C=O), 1548, 1439, 1402, 1358, 1287, 1177, 1066, 985, 902, 805, 726, 697, 553.

HRMS ($m/z$ - ESI): Found: 344.0216 (M+Na)$^+$ C$_{16}$H$_{13}$Cl$_2$NNaO$_2$ Requires: 344.0216.

Synthesis of the third-generation substrate for selective amine protections

2-(Hydroxymethyl)-N-(4-methoxyphenyl)-N-methylbenzamide (233)

To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar was charged AlCl$_3$ (0.26 g, 1.90 mmol) followed by anhydrous dichloroethane (1 mL). The vessel was placed under a protective atmosphere of argon and cooled to 0 °C in a H$_2$O/ice bath. The flask was fitted with a septum seal and argon balloon. 4-methoxy-N-methyl aniline (232, 0.50 g, 3.64 mmol) was charged to the flask, the reaction mixture was maintained at 0 °C and stirred for 30 minutes after which time phthalide (199, 0.49 g, 1.46 mmol) was added.
portion wise to the stirring solution. The reaction mixture was stirred for a further 2 h following which, ice and water were added carefully to the flask. An emulsion was observed. This emulsion was filtered over a pad of celite and the filtrate was extracted into CH$_2$Cl$_2$ (3 x 15 mL). The organic extract was washed with brine (2 x 10 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 7:3) to yield 233 as a brown oil (0.29 g, 74%).

$\delta_H$ (400 MHz, CDCl$_3$): 7.31 (1 H, d, $J$ 7.2, H-3), 7.20 (1 H, app. t, H-4), 7.01-6.87 (4 H, m, H-5, H-6, H-8), 6.69 (2 H, d, $J$ 8.6, H-9), 4.64 (2 H, d, $J$ 5.6, H-2), 3.93 (1 H, t, $J$ 5.6, H-1), 3.72 (3 H, s, H-7), 3.49 (3 H, s, H-10).

$\delta_C$ (100 MHz, CDCl$_3$): 171.6 (C=O), 158.1 (q), 139.8 (q), 137.1 (q), 135.7 (q), 129.8, 129.5, 128.7, 127.7, 126.9, 114.4, 64.7, 55.4, 38.1.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3004, 2935, 2837, 1620 (C=O), 1598, 1509, 1431, 1375, 1289, 1245, 1203, 1179, 1108, 1029, 958, 881, 743, 665, 583.

HRMS ($m/z$ - APCI): Found: 272.1289 (M+H)$^+$ C$_{16}$H$_{18}$NO$_3$ Requires: 272.1281.

2-Formyl-N-(4-methoxyphenyl)-N-methylbenzamide (234)

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged 2-(hydroxymethyl)-N-(4-methoxyphenyl)-N-methylbenzamide (233, 2.26 g, 10.4 mmol). The vessel was placed under a protective atmosphere of argon and CH$_2$Cl$_2$ (42 mL) was charged to the flask followed by MnO$_2$ (9.13 g, 103.8 mmol). The reaction mixture stirred at room temperature until complete consumption of the starting material was observed (monitored by TLC analysis of the crude reaction mixture). The resulting suspension was filtered over a pad of celite and the filter cake washed with CH$_2$Cl$_2$ until no further product was detected in the eluent (monitored by TLC analysis). The filtrate was concentrated in
vacuo and the residue was purified by flash column chromatography (hexanes:EtOAc, 1:1) to afford 234 as a brown oil (1.64 g, 59%).

$\delta_H$ (400 MHz, CDCl$_3$): 10.09 (1 H, s, H-1), 7.73 (1 H, d, J 7.5, H-2), 7.44 (1 H, td, J 7.5, 1.2, H-4), 7.37 (1 H, td, J 7.5, 1.2, H-3), 7.29-7.26 (1 H, m, H-5), 6.95 (2H, d, J 8.9, H-7), 6.66 (2 H, d, J 8.9, H-8), 3.71 (3 H, s, H-6), 3.53 (3 H, s, H-9).

$\delta_C$ (100 MHz, CDCl$_3$): 190.9 (C=O), 169.3 (C=O), 158.3 (q), 138.9 (q), 136.3 (q), 133.4, 132.9 (q), 130.3, 128.9, 128.4, 128.3, 114.3, 55.3, 37.6.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2838, 2746, 1698 (C=O), 1637 (C=O), 1511, 1427, 1371, 1244, 1183, 1028, 881, 756, 732, 642, 612, 586.

HRMS ($m/z$ - ESI): Found: 270.1124 (M+H)$^+$ C$_{16}$H$_{16}$NO$_3$ Requires: 270.1125.

### 2,2'-Oxalylbis(N-(4-methoxyphenyl)-N-methylbenzamide) (227)

Prepared according to general procedure I using THF (2 mL), Rb$_2$CO$_3$ (93.3 mg, 0.40 mmol), catalyst 27 (96.6 mg, 0.4 mmol) and aldehyde 234 (544 mg, 2 mmol). Purified by flash column chromatography (hexanes:EtOAc, 7:3) to afford 227 as a pale yellow solid (128 mg, 24%). M.p. 187-190 °C.

$\delta_H$ (400 MHz, CDCl$_3$): 7.83 (1 H, d, J 6.9, H-4), 7.40-7.30 (2 H, m, H-2, H-3), 7.21 (2 H, d, J 8.3, H-6), 7.10 (1 H, d, J 6.9, H-1), 6.74 (2 H, d, J 8.3, H-7), 3.76 (3 H, s, H-5), 3.45 (3 H, s, H-8).

$\delta_C$ (100 MHz, CDCl$_3$): 191.8 (C=O), 169.2 (C=O), 158.2 (q), 138.1 (q), 137.1 (q), 133.5 (q), 132.0, 131.9, 128.9, 128.5, 128.1, 114.3, 55.3, 38.0.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3002, 1691 (C=O), 1615 (C=O), 1510, 1441, 1385, 1246, 1207, 1174, 1030, 837, 814, 758, 616, 581.
**General procedure II:** Substrate evaluation in the NHC-catalysed oxidative amidation between substituted benzils 178, 198, 227 and various amines (Table 2 and Table 3)

An oven dried 5 mL round-bottomed flask, equipped with a magnetic stirring bar was evacuated and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon balloon. The relevant substituted benzil (1 equiv.), phenazine (1 equiv.) and catalyst 27 (15 mol%), were charged to the flask sequentially. The flask was again evacuated and put under an atmosphere of argon repeatedly. The flask was re-fitted with a septum seal and argon balloon. THF (0.4 M) was charged to the flask followed sequentially by freshly distilled DBU (1.1 equiv.) and the relevant freshly distilled amine (1.2 equiv.) in rapid succession. The reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and was purified by flash column chromatography to furnish the desired product.

(3-(Tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)(pyrrolidin-1-yl)methanone (455, Table 2, entry 1)

![Chemical Structure](image)

Prepared according to general procedure II using THF (0.5 mL), 178 (98.8 mg, 0.194 mmol), 53 (35.0 mg, 0.194 mmol) and 25 (6.96 mg, 0.0291 mmol, 15 mol%), DBU (32 µL, 0.213 mmol) and pyrrolidine (20.5 µL, 0.233 mmol). Purified by flash column chromatography (CH₂Cl₂:MeOH, 95:5) to afford 455 as a brown oil (60.5 mg, 97%).

δ_H (400 MHz, CDCl₃): 8.44 (1 H, d, J 4.7, H-1), 7.91 (1 H, d, J 7.8, H-3), 7.31 (1 H, dd, J 7.8, 4.7, H-2), 4.82 (2 H, s, H-4), 3.68 (2 H, t, J 6.9, H-8), 3.39 (2 H, t, J 6.8, H-7), 2.00-1.86 (4 H, m, H-9), 0.94 (9 H, s, H-6), 0.12 (6 H, s, H-5).

δ_C (100 MHz, CDCl₃): 166.5 (C=O), 152.1 (q), 146.9, 135.6, 135.3 (q), 124.1, 61.4, 48.1, 45.8, 26.1, 25.9, 24.3, 18.4 (q), -5.3.
$\nu$\textsubscript{max} (neat)/cm\textsuperscript{-1}:

2954, 2930, 2882, 2857, 1631 (C=O), 1462, 1412 1254, 1116, 1073, 937, 836, 777, 671.

HRMS (m/z - APCI):

Found: 321.1992 (M+H)$^+$. 

C\textsubscript{17}H\textsubscript{29}N\textsubscript{2}O\textsubscript{2}Si Requires: 321.1993.

(3-(Tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)(piperidin-1-yl)methanone  (456, Table 2, entry 2)

Prepared according to general procedure II using THF (0.5 mL), 178 (98.8 mg, 0.194 mmol) 53 (35.0 mg, 0.194 mmol) and 25 (6.96 mg, 0.0291 mmol, 15 mol%), DBU (32 µL, 0.213 mmol) and piperidine (23.0 µL, 0.233 mmol). Purified by flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 95:5) to afford 456 as a brown oil (41.5 mg, 64%).

$\delta$\textsubscript{H}(400 MHz, CDCl\textsubscript{3}):

8.49 (1 H, d, J 4.8, H-1), 7.89 (1 H, d, J 7.9, H-3), 7.29 (1 H, dd, J 7.9, 4.8, H-2), 4.75 (2 H, s, H-4), 3.82-3.68 (2 H, m, H-10), 3.12 (2 H, t, J 5.5, H-7), 1.70-1.60 (4 H, m, H-8), 1.28-1.20 (2 H, m, H-9), 0.92 (9 H, s, H-6), 0.08 (6 H, s, H-5).

$\delta$\textsubscript{C}(100 MHz, CDCl\textsubscript{3}):

166.3 (C=O), 151.4 (q), 146.7, 136.3, 132.5 (q), 124.2, 64.9, 47.3, 44.1, 27.6 (q), 26.5, 25.4, 24.2, 23.7, -2.3.

$\nu$\textsubscript{max} (neat)/cm\textsuperscript{-1}:

2951, 2875, 2823, 1657 (C=O), 1511, 1489, 1456, 1213, 1117, 1025, 978, 921, 855, 729, 683, 606.

HRMS (m/z - ESI):

Found: 335.2155 (M+H)$^+$. 

C\textsubscript{18}H\textsubscript{31}N\textsubscript{2}O\textsubscript{2}Si Requires: 335.2149.
3-(Tert-butyldimethylsilyl)oxy)methyl)-N-(3-(methylamino)propyl)picolinamide (457, Table 2, entry 3)

Prepared according to general procedure II using THF (0.5 mL), 178 (98.8 mg, 0.194 mmol), 53 (35.0 mg, 0.194 mmol) and 25 (6.96 mg, 0.0291 mmol, 15 mol%), DBU (32 µL, 0.213 mmol) and N-methyl-1,3-diaminopropane (163, 24.5 µL, 0.233 mmol). Purified by flash column chromatography (CH₂Cl₂:MeOH:NEt₃, 100:1:1) to afford 457 as a brown oil (35.4 mg, 51%).

δ_H (400 MHz, CDCl₃): 8.55-8.47 (1 H, m, H-7), 8.44 (1 H, dd, J 4.4, 1.3, H-1), 8.27 (1 H, dd, J 7.9, 1.3, H-3), 7.47 (1 H, dd, J 7.9, 4.4, H-2), 5.33 (2 H, s, H-4), 3.53 (2 H, t, J 6.8, H-8), 2.73 (2 H, t, J 6.8, H-10), 2.48 (3 H, s, H-12), 2.03 (1 H, br s, H-11), 1.85 (2 H, quint, J 6.8, H-9), 0.99 (9 H, s, H-6), 0.16 (6 H, s, H-5).

δ_C (100 MHz, CDCl₃): 166.0 (C=O), 145.6, 144.7 (q), 139.7 (q), 135.3, 126.0, 61.8, 49.5, 37.3, 36.2, 29.4, 26.0, 18.4 (q), -5.3.

ν_{max} (neat)/cm⁻¹: 3646 (N-H), 2935, 2856, 2795, 1665 (C=O), 1572, 1518, 1431, 1255, 1188, 1116, 1069, 1006, 835, 776, 676.

HRMS (m/z - APCI): Found: 338.2263 (M+H)⁺ C₁₇H₃₂N₃O₂Si Requires: 338.2258.

N-(2-aminopropyl)-3-(tert-butyldimethylsilyl)oxy)methyl)picolinamide (458, Table 2, entry 4)

Prepared according to general procedure II using THF (0.4 mL), 178 (84.2 mg, 0.168 mmol), 53 (30.3 mg, 0.168 mmol) and 25 (6.02 mg, 0.0252 mmol, 15 mol%), DBU (27 µL, 0.185...
mmol) and 1,2-diaminopropane (116, 17 µL, 0.202 mmol). Purified by flash column chromatography (CH₂Cl₂:MeOH:NEt₃ 100:1:1) to afford 458 as a brown oil (34.5 mg, 63%).

δ_H (400 MHz, CDCl₃): 8.64-8.56 (1 H, m, H-7), 8.42 (1 H, dd, J 4.5, 1.0, H-1), 8.24 (1 H, dd, J 7.8, 1.0, H-3), 7.46 (1 H, dd, J 7.8, 4.5, H-2), 5.28 (2 H, s, H-4), 3.66 (2 H, br s, H-11), 3.58-3.50 (1 H, m, H-8a), 3.41-3.29 (2 H, m, H-8b, H-9), 1.25 (3 H, d, J 6.0, H-10), 0.97 (9 H, s, H-6), 0.14 (6 H, s, H-5).

δ_C (100 MHz, CDCl₃): 166.4 (C=O), 145.7, 144.4 (q), 139.7 (q), 135.4, 126.2, 61.7, 47.3, 46.1, 26.0, 20.4, 18.4 (q), -5.3.

ν_max (neat)/cm⁻¹: 3388 (NH), 3312 (NH), 2955, 2929, 2857, 1666 (C=O), 1575, 1517, 1471, 1431, 1361, 1255, 1117, 1072, 917, 835, 777, 731, 599.

HRMS (m/z - ESI): Found: 324.2112 (M+H)⁺ C₁₆H₃₀N₃O₂Si Requires: 324.2102.

_N-benzyl-N-methyl-2-(pyrrolidine-1-carbonyl)benzamide (459, Table 3, entry 1)_

![Chemical structure](image)

Prepared according to general procedure II using THF (0.5 mL), 198 (98.2 mg, 0.194 mmol), 53 (35.0 mg, 0.194 mmol) and 25 (6.96 mg, 0.0291 mmol, 15 mol%), DBU (32 µL, 0.213 mmol) and pyrrolidine (19.5 µL, 0.233 mmol). Purified by flash column chromatography (CH₂Cl₂:MeOH, 95:5) to afford 459 as a brown oil (74.7 mg, 99%).

*A non-degenerate mix of rotamers is observed in the ^1H and ^13C NMR spectra of this compound.*

δ_H (400 MHz, CDCl₃): Major rotamer: 7.46-7.08 (9 H, m, H-1, H-2, H-3, H-4, H-5, H-6, H-7), 4.70 (2 H, s, H-8), 3.54 (2 H, t, J 6.9, H-11), 3.37-3.31 (2 H, m, H-10), 2.83 (3 H, s, H-9), 1.97-1.79 (4 H, m, H-12).

Minor rotamer: 7.46-7.08 (9 H, m, H-1, H-2, H-3, H-4, H-5, H-6, H-7), 4.44 (2 H, s, H-8), 3.60 (2 H, t, J 6.9, H-11), 3.37-
δC (100 MHz, CDCl₃): Major rotamer: 170.6 (C=O), 168.5 (C=O), 136.9 (q), 136.0 (q), 134.8 (q), 128.9, 128.7, 128.6, 128.0, 127.5, 127.4, 127.2, 50.6, 48.8, 45.5, 36.9, 25.9, 24.5.
Minor rotamer: 171.1 (C=O), 168.7 (C=O), 136.7 (q), 136.2 (q), 134.6 (q), 128.9, 128.7, 128.6, 128.0, 127.5, 127.2, 126.4, 55.3, 48.9, 45.6, 32.6, 26.0, 24.6.

νₘₐₓ (neat)/cm⁻¹: 3503, 2965, 2878, 2237, 1625 (C=O), 1596, 1497, 1448, 1422, 1402, 1254, 1030, 728, 657.

HRMS (m/z - ESI): Found: 345.1576 (M+Na)⁺ C₂₀H₂₂N₂NaO₂ Requires: 345.1573.

_N-benzyl-N-methyl-2-(piperidine-1-carbonyl)benzamide (460, Table 3, entry 2)_

Prepared according to general procedure II using THF (0.4 mL), 198 (76.7 mg, 0.152 mmol), 53 (27.4 mg, 0.152 mmol) and 25 (5.45 mg, 0.0228 mmol, 15 mol%) DBU (25 µL, 0.167 mmol) and piperidine (18.0 µL, 0.182 mmol). Purified by flash column chromatography (CH₂Cl₂:MeOH, 95:5) to afford 460 as a brown oil (40.4 mg, 79%).

*A non-degenerate mix of rotamers is observed in the ¹H and ¹³C NMR spectra of this compound.*

δH (400 MHz, CDCl₃): Major rotamer: 7.41-7.16 (9 H, m, H-1, H-2, H-3, H-4, H-5, H-6, H-7), 4.70 (2 H, s, H-8), 3.77-3.60 (2 H, m, H-11), 3.37-3.23 (2 H, m, H-10), 2.81 (3 H, s, H-9), 1.74-1.61 (4 H, m, H-12), 1.62-1.47 (2 H, m, H-13).
Minor rotamer: 7.41-7.16 (9 H, m, H-1, H-2, H-3, H-4, H-5, H-6, H-7), 4.44 (2 H, s, H-8), 3.77-3.60 (2 H, m, H-11), 3.37-
3.23 (2 H, m, H-10), 2.94 (3 H, s, H-9), 1.74-1.61 (4 H, m, H-12), 1.62-1.47 (2 H, m, H-13).

$\delta_C$ (100 MHz, CDCl$_3$):

Major rotamer: 170.4 (C=O), 168.7 (C=O), 136.9 (q), 135.1 (q), 134.8 (q), 128.8, 128.7, 128.0, 127.5, 127.3, 127.1, 126.4, 50.5, 48.7, 42.8, 36.9, 26.2, 25.5, 24.5.

Minor rotamer: 170.9 (C=O), 168.9 (C=O), 136.7 (q), 135.2 (q), 134.9 (q), 128.9, 128.7, 128.6, 127.5, 127.1, 126.5, 126.4, 55.3, 42.9, 36.7, 32.6, 26.1, 25.6, 24.6.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3067, 2931, 2856, 1628 (C=O), 1595, 1445, 1430, 1400, 1282, 1257, 1062, 1001, 730, 699, 635.

HRMS ($m/z$ - ESI): Found: 359.1739 (M+Na)$^+$ C$_{21}$H$_{24}$N$_2$NaO$_2$ Requires: 359.1729.

$N$-(4-methoxyphenyl)-$N$-methyl-2-(pyrrolidine-1-carbonyl)benzamide (236)

Prepared according to general procedure II using THF (0.27 mL), 227 (58.3 mg, 0.109 mmol), 25 (3.9 mg, 0.0164 mmol, 15 mol%), 53 (19.7 mg, 0.109 mmol), DBU (18.0 µL, 0.120 mmol) and pyrrolidine (11.0 µL, 0.131 mmol). Purified by flash column chromatography (hexanes:EtOAc, 8:2) to afford 236 as a purple solid (28.7 mg, 86%). M.p. 73-76 ºC.

$\delta_H$ (400 MHz, CDCl$_3$):


$\delta_C$ (100 MHz, CDCl$_3$):

169.9 (C=O), 169.6 (C=O), 157.8 (q), 137.5 (q), 137.4 (q), 135.6 (q), 128.3, 128.2, 128.0, 127.7, 126.1, 114.1, 55.3, 49.0, 45.6, 37.7, 26.0, 24.6.
\[\text{Prepared according to general procedure II using THF (0.3 mL), 227 (62.4 mg, 0.116 mmol), 25 (4.2 mg, 0.0174 mmol, 15 mol%), 53 (21.0 mg, 0.116 mmol), DBU (19.0 \mu L, 0.128 mmol) and piperidine (14 \mu L, 0.139 mmol). Purified \textit{via} flash column chromatography (hexanes:EtOAc, 8:2) to afford 237 as a white solid (13.6 mg, 33\%). M.p. 127-130 ^\circ C.}\]

\[\begin{align*}
\delta_H (400 MHz, CDCl_3): & \quad 7.40 \text{ (2 H, d, J 8.5, H-3)}, 7.33 \text{ (2 H, d, J 8.5, H-2)}, 7.21-7.15 \text{ (2 H, m, H-5, H-8)}, 7.04-6.99 \text{ (1 H, m, H-6)}, 6.91 \text{ (1 H, app. d, H-7)}, 3.79-3.68 \text{ (7 H, m, H-4, H-9)}, 3.52 \text{ (3 H, s, H-1)}, 1.78-1.58 \text{ (6 H, m, H-10, H-11)}. \\
\delta_C (100 MHz, CDCl_3): & \quad 170.6 \text{ (C=O)}, 170.0 \text{ (C=O)}, 157.8 \text{ (q)}, 137.7 \text{ (q)}, 136.7, 136.6 \text{ (q)}, 136.1 \text{ (q)}, 128.4, 128.2, 128.0, 127.9, 127.5, 126.0, 55.3, 42.8, 37.7, 26.0, 25.5, 24.7. \\
\nu_{max} \text{ (neat)/cm}^{-1}: & \quad 3056, 1633 \text{ (C=O)}, 1594 \text{ (C=O)}, 1444, 1368, 1286, 1088, 1001, 954, 889, 705, 668. \\
\text{HRMS (m/z - ESI):} & \quad \text{Found: 375.1685 (M+Na)^+ \quad C_{21}H_{24}N_2NaO_3 \quad Requires: 375.1679}. 
\end{align*}\]
Synthesis of protected amines to investigate deprotection methodologies

2-(pyrrolidine-1-carbonyl)benzoic acid (242)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged phthalic anhydride (241, 8.04 g, 54.0 mmol) followed by THF (120 mL). The vessel was placed under a protective atmosphere of argon. The flask was fitted with a septum seal and argon balloon. Pyrrolidine (4 mL, 54.0 mmol) was charged to the flask and the reaction mixture was stirred for 16 h following which, the solvent was concentrated in vacuo. The resulting residue was extracted into CH$_2$Cl$_2$ (3 x 50 mL) and the organic extract was washed with brine (2 x 30 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The resulting residue solidified upon trituration with hexanes to yield 242 as a white solid (10.7 g, 91%). M.p. 132-135 °C (lit., 203 M.p. 132-134 °C).

Spectral data for this compound were consistent with those in the literature. 204

$\delta$H (400 MHz, DMSO-d$_6$): 7.85 (1 H, d, J 7.5, H-2), 7.59 (1 H, app t, H-4), 7.46 (1 H, app t, H-3), 7.28 (1 H, d, J 7.5, H-5), 3.42-3.37 (2 H, m, H-6), 2.98 (2 H, m, H-7), 1.86-1.70 (4 H, m, H-8).

* The protic signal (H-1) is not visible in DMSO-d$_6$.

N-allyl-N-methyl-2-(pyrrolidine-1-carbonyl)benzamide (239)
To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar, under an atmosphere of argon maintained using a balloon and septum, was charged CH₂Cl₂ (76 mL), NEt₃ (0.86 mL, 6.2 mmol), EDC (1.31 g, 6.84 mmol) and N-methyllallyl amine (243, 0.46 mL, 4.8 mmol). The vessel was cooled to 0 °C in a H₂O/ice bath and 2-(pyrrolidine-1-carbonyl)benzoic acid (242, 1.02 g, 4.6 mmol) was added in one portion. The reaction was slowly warmed to room temperature, overnight after which time the mixture was quenched with aqueous sodium chloride solution (saturated, 25 mL) and stirred for 30 minutes. The resulting solution was extracted into EtOAc (3 x 50 mL) and purified via flash column chromatography (CH₂Cl₂:EtOAc, 10:1) to yield the title product 239 as a yellow oil (0.47 g, 38%).

δH (400 MHz, CDCl₃): 7.45-7.29 (4 H, m, H-5, H-6, H-7, H-8), 5.87-5.67 (1 H, m, H-3), 5.25-5.09 (2 H, m, H-4a, H-4b), 4.09 (1 H, d, J 5.6, H-2a), 3.81 (1 H, d, J 5.6, H-2b), 3.55 (2 H, td, J 6.8, 3.2, H-9), 3.32 (2 H, q, J 6.4, H-10), 2.98 (3 H, s, H-1), 1.96-1.78 (4 H, m, H-11).

δC (100 MHz, CDCl₃): 170.8 (C=O), 170.3 (C=O), 136.0 (q), 135.9 (q), 133.4, 128.9, 128.8, 126.4, 126.2, 117.5, 53.8, 45.6, 37.0, 32.0, 25.9, 24.5.

νmax (neat)/cm⁻¹: 3493, 2971, 2878, 1623 (C=O), 1595 (C=O), 1574, 1498, 1473, 1446, 1418, 1399, 1340, 1254, 1228, 1163, 1118, 1063, 930, 914, 872, 780, 744, 634, 561.


N-methoxy-N-methyl-2-(pyrrolidine-1-carbonyl)benzamide (240)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar under an atmosphere of argon maintained using an argon-filled balloon and septum was charged CH₂Cl₂ (150 mL), NEt₃ (1.7 mL, 12.3 mmol), EDC (2.62 g, 13.7 mmol) and Weinreb amine (0.93 g, 9.6 mmol). The vessel was cooled to 0 °C in a H₂O/ice bath and 2-(pyrrolidine-1-
carbonyl)benzoic acid (242, 2.02 g, 9.1 mmol) was added in one portion. The reaction was slowly warmed to room temperature overnight after which time the mixture was quenched with aqueous sodium chloride solution (saturated, 40 mL) and stirred for 30 minutes. The resulting solution was extracted into EtOAc (3 x 75 mL) and purified via flash column chromatography (CH$_2$Cl$_2$:EtOAc, 10:1) to yield the title product 240 as a colourless oil (1.2 g, 49%).

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 7.51-7.34 (4 H, m, H-3, H-4, H-5, H-6), 3.65-3.56 (5 H, m, H-1, H-7), 3.34 (2 H, t, J 6.6, H-8), 3.29 (3 H, s, H-2), 1.99-1.83 (4 H, m, H-9).

$\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 169.0 (C=O), 168.9 (C=O), 137.0 (q), 133.3, 129.3, 128.5, 127.7 (q), 126.3, 61.1, 49.1, 45.6, 33.5, 26.0, 24.6.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3479, 2971, 2877, 1623, 1594, 1574, 1447, 1416, 1380, 1341, 1251, 1214, 1114, 1035, 975, 889, 848, 779, 632.

HRMS (m/z - ESI): Found: 263.1391 (M+H)$^+$ C$_{14}$H$_{19}$N$_2$O$_3$ Requires: 263.1390.

2-(Pyrrolidine-1-carbonyl)benzonitrile (245)

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar under an atmosphere of argon maintained using an argon-filled balloon and septum was charged CH$_2$Cl$_2$ (28 mL), NEt$_3$ (0.27 mL, 1.92 mmol), EDC (0.41 g, mmol) and pyrrolidine (0.12 g, 1.5 mmol). The vessel was cooled to 0 °C in a H$_2$O/ice bath and 2-cyanobenzoic acid (461, 2.2 g, 1.4 mmol) was added in one portion. The reaction was slowly warmed to room temperature overnight after which time the mixture was quenched with aqueous saturated sodium chloride solution (20 mL) and stirred for 30 minutes. The resulting solution was extracted into EtOAc (3 x 25 mL) and purified via flash column chromatography (CH$_2$Cl$_2$:EtOAc, 8:2) to yield the title product 245 as a colourless oil (0.57 g, 20%).

Spectral data for this compound were consistent with those in the literature.$^{205}$
δ_H (400 MHz, CDCl₃): 7.71-7.68 (1 H, m, H-4), 7.62 (1 H, td, J 7.7, 1.2, H-3), 7.51-7.46 (2 H, m, H-1, H-2), 3.69 (2 H, t, J 6.9, H-5), 3.29 (2 H, t, J 6.6, H-6), 2.03-1.87 (4 H, m, H-7).

HRMS (m/z - ESI): Found: 201.1025 (M+H)⁺ C₁₂H₁₃N₂O Requires: 201.1022.

2-(aminomethyl)phenyl)(pyrrolidin-1-yl)methanone (246)

To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar was charged 2-(pyrrolidine-1-carbonyl)benzonitrile (245, 56.9 mg, 0.284 mmol) and MeOH (3 mL). The vessel was placed under a protective atmosphere of argon and the solution was de-gassed with argon. Palladium on carbon (60.4 mg, 0.568 mmol) and HCl (37%, 0.26 mL, 0.852 mmol) were charged to the flask and the reaction mixture was again de-gassed with argon. The progress of the reaction was monitored by TLC analysis of the crude reaction mixture. At the end of the reaction, the resulting suspension was filtered over a pad of celite and the filter cake washed with MeOH. The filtrate was concentrated in vacuo and EtOAc (15 mL) was added to the residue. The organic layer was basified to pH 9 with saturated sodium bicarbonate solution and was concentrated in vacuo to furnish 246 as a colourless oil (44.1 mg, 76%).

δ_H (400 MHz, CDCl₃): 8.11 (2 H, br s, H-1), 7.84 (1 H, d, J 7.7, H-6), 7.60-7.50 (1 H, app t, H-4), 7.48-7.41 (2 H, app d, H-3, H-5), 4.44 (2 H, s, H-2), 3.70-3.66 (2 H, m, H-7), 2.55-2.43 (2 H, m, H-8), 1.85-1.67 (4 H, m, H-9).

δ_C (100 MHz, CDCl₃): 169.4 (C=O), 137.2 (q), 136.8 (q), 128.2, 127.8, 127.5, 127.4, 64.7, 49.7, 46.3, 26.4, 24.5.

ν_max (neat)/cm⁻¹: 3409, 2968, 2875, 1602 (C=O), 1562, 1514, 1425, 1339, 1252, 1018, 905, 840, 761, 669, 630, 573.

Synthesis of amines and diamines: procedures

2-cinnamylisoindoline-1,3-dione (280)

![2-cinnamylisoindoline-1,3-dione](image)

To an oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with THF (12 mL) and cinnamyl alcohol \((278, 0.77 \text{ mL}, 6.0 \text{ mmol})\) under an atmosphere of argon. Triphenylphosphine (2.05 g, 7.8 mmol), and phthalimide \((199, 1.32 \text{ g}, 9.0 \text{ mmol})\) was charged to the reaction mixture at 0 °C. DIAD (1.6 mL, 7.8 mmol) was added to the flask over 10 minutes at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time the flask was warmed to room temperature and stirred overnight. The resulting mixture was concentrated \textit{in vacuo} and the residue was purified by flash column chromatography, eluting in gradient from 100% hexanes to 12:1 EtOAc:hexanes. The residue obtained after the initial flash column chromatography was dissolved in EtOAc (25 mL) and KOH (1 M, 25 mL). The aqueous phase was extracted into EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO\(_4\) and the solvent was removed under reduced pressure to yield 280 as a white solid (0.94 g, 60%). M.p. 152-154 °C (lit.,\(^{180}\) M.p. 154-155 °C).

Spectral data for this compound were consistent with those in the literature.\(^{180}\)

\[
\delta_H (400 \text{ MHz, CDCl}_3) : \\
7.87 (2H, dd, J 5.5, 3.1, H-7), 7.72 (2H, dd, J 5.5, 3.1, H-8), \\
7.37-7.32 (2H, m, H-1), 7.31-7.27 (2H, m, H-2), 7.24-7.21 (1H, m, H-3), 6.66 (1H, d, J 15.8, H-4), 6.26 (1H, dt, J 15.8, 6.5, H-5), 4.45 (2H, dd, J 6.5, 1.1, H-6).
\]

\((E)-3\text{-phenylprop-2-en-1-amine (277)}\)

![\((E)-3\text{-phenylprop-2-en-1-amine (277)}\)](image)

To a solution of 2-cinnamylisoindoline-1,3-dione \((280, 0.94 \text{ g}, 3.6 \text{ mmol})\) in MeOH (60 mL) in an oven-dried 250-mL round bottomed flask equipped with a magnetic stirring bar, was charged hydrazine monohydrate \((281, 0.72 \text{ mL}, 14.4 \text{ mmol})\) at room temperature. The mixture was stirred overnight at room temperature after which time the mixture was
concentrated *in vacuo*. The resulting residue was diluted with CH$_2$Cl$_2$ (30 mL) and KOH (1 M, 30 mL) and the aqueous phase was extracted into EtOAc (3 x 30 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure to yield 277 as a pale-yellow oil (0.21 g, 44%).

Spectral data for this compound were consistent with those in the literature.$^{180}$

$\delta_H$ (400 MHz, CDCl$_3$):  7.42-7.16 (5 H, m, H-1, H-2, H-3), 6.51 (1 H, d, $J$ 15.8, H-4), 6.33 (1 H, dt, $J$ 15.8, 5.8, H-5), 3.49 (2 H, d, $J$ 5.8, H-6), 1.40 (2 H, br s, H-7).

HRMS ($m/\ell$ - ESI):  Found: 134.0956 (M+H)\textsuperscript{+}  C$_9$H$_{12}$N Requires: 134.0970.

tert-butyl (3-hydroxypropyl)(methyl)carbamate (294)

To a 500 mL round-bottomed flask containing a magnetic stirring bar was charged, 3-methylamino-1-propanol (293, 2.20 mL, 22.6 mmol) and NEt$_3$ (3.50 mL, 24.9 mmol) in CH$_2$Cl$_2$ (200 mL), was charged a solution of di-tert-butyl dicarbonate (5.97 g, 27.2 mmol) in CH$_2$Cl$_2$ (25 mL) dropwise at 0 °C, under an atmosphere of argon. After one hour at 0 °C the reaction mixture was warmed to room temperature and was stirred overnight. After this time the solution was washed sequentially with brine (150 mL), a saturated citric acid solution (150 mL), a saturated sodium hydrogen carbonate solution (150 mL) and water (150 mL). The organic extract was dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield 294 as a colourless oil (4.05 g, 94%).

Spectral data for this compound were consistent with those in the literature.$^{206}$

$\delta_H$ (400 MHz, CDCl$_3$):  3.63 (2 H, m, H-4), 3.38 (2 H, t, $J$ 5.9, H-2), 2.83 (3 H, s, H-1), 1.74-1.63 (2 H, m, H-3), 1.45 (9H, s, H-6).

* The protic signal (H-5) is not visible in CDCl$_3$.

HRMS ($m/\ell$ - ESI):  Found: 212.1261 (M+Na)$^+$  C$_9$H$_{19}$NNaO$_3$ Requires: 212.1257.
3-(Tert-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (295)

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with tert-butyl (3-hydroxypropyl)(methyl)carbamate (294, 5.67 g, 30.0 mmol), CH₂Cl₂ (60 mL) and NEt₃ (9.5 mL, 65.9 mmol). The flask was cooled to 0°C followed which tosyl chloride (6.28 g, 33.0 mmol) and DMAP (0.37 g, 3.0 mmol) were charged to the reaction flask. The reaction mixture was warmed to room temperature overnight. The reaction mixture was quenched with a saturated ammonia chloride solution (50 mL) and extracted into CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried over MgSO₄ and the solvent was concentrated in vacuo. The resulting residue was purified by flash column chromatography, eluting in gradient from 100% hexanes to 10% EtOAc in hexanes to yield 295 as a colourless oil (3.6 g, 35%).

Spectral data for this compound were consistent with those in the literature.²⁰⁶

δ_H (400 MHz, CDCl₃): 7.79 (2H, d, J 8.2, H-5), 7.34 (2H, d, J 8.2, H-6), 4.04 (2H, t, J 6.5, H-4), 3.24 (2H, t, J 6.9, H-2), 2.79 (3H, s, H-1), 2.45 (3H, s, H-7), 1.87 (2H, quin., J 6.5, H-3), 1.42 (9H, s, H-8).

HRMS (m/z - ESI): Found: 366.1353 (M+Na)⁺ \text{C}_{16}\text{H}_{25}\text{NNaO}_{5}\text{S} Requires: 366.1346.

Tert-butyl (3-(ethylamino)propyl)(methyl)carbamate (296)

To a 50 mL round-bottomed flask containing a magnetic stirring bar was added 3-((tert-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (295, 3.01 g, 8.78 mmol)
and ethylamine (66% solution in water, 19 mL). The reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC analysis of the crude reaction mixture), the reaction was quenched with a saturated sodium hydrogen carbonate solution (20 mL) and extracted into CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried over MgSO₄ and the solvent was concentrated in vacuo to yield the product 296 as a colourless oil (1.74 g, 91%). The product was used without further purification.

δ_H (400 MHz, DMSO-d₆): 3.19 (2 H, t, J 7.0, H-2), 2.76 (3 H, br s, H-1), 2.58 (2 H, quart., J 7.1, H-6), 2.51-2.48 (2 H, m, H-4), 1.61 (2 H, quint., J 7.0, H-3), 1.39 (9 H, s, H-8), 1.03 (3 H, t, J 7.1, H-7).

* The protic signal (H-5) is not visible in DMSO-d₆.

δ_C (100 MHz, DMSO-d₆): 155.4 (C=O), 78.8 (q), 66.6, 46.9, 46.8, 46.6, 46.3, 46.0, 43.7, 34.3, 28.5, 27.8, 27.2, 14.8.

*There are an unexpected number of carbon signals observed with this compound due to it being a rotameric molecule. Although this is not observed in the ¹H NMR spectrum, it is confirmed by analysis of HSQC and EXSY spectra.

ν_max (neat)/cm⁻¹: 2970, 2930, 1687 (C=O), 1481, 1454, 1392, 1365, 1311, 1251, 1157, 1050, 878, 771, 641.

HRMS (m/z - ESI): Found: 217.1843 (M+H)+ C₁₁H₂₄N₂O₂ Requires: 217.1838

N¹-ethyl-N³-methylpropane-1,3-diamine (120)

To a 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged tert-butyl (3-(ethylamino)propyl)(methyl)carbamate (296, 2.12 g, 9.69 mmol) and CH₂Cl₂ (50 mL). To this stirring solution was added trifluoroacetic acid (15 mL, 96.9 mmol). The reaction mixture was stirred for 4 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was stirred in Et₂O until a white precipitate was observed. This precipitate (2.67 g, 7.75 mmol) was stirred in CH₂Cl₂ and K₂CO₃ (5.22 g, 31.0 mmol) for 2 h (the progress of this reaction was monitored by ¹⁹F NMR
spectroscopy). After complete consumption of starting material, the resulting suspension was filtered, and the precipitate was washed with Et₂O (3 x 10 mL). The filtrate was concentrated in vacuo (care was taken when removing the solvent as diamine 120 produced is volatile) to yield the title compound (0.79 g, 88%) as a colourless oil which was used without further purification.

δ_H (400 MHz, CDCl₃): 2.72-2.61 (6 H, m, H-3, H-5, H-7), 2.44 (3 H, s, H-1), 1.69 (2 H, quin., J 7.0, H-4), 1.31 (2 H, br s, H-2, H-6), 1.11 (3 H, t, J 7.1, H-8).

δ_C (100 MHz, CDCl₃): 50.6, 48.3, 44.2, 36.6, 30.4, 15.3.

ν_max (neat)/cm⁻¹: 3378 (NH), 2965, 2932, 2799, 1449, 1378, 1305, 1117, 1054, 747.


tert-butyl (3-(isopropylamino)propyl)(methyl)carbamate (297)

To a 10 mL round-bottomed flask containing a magnetic stirring bar was added 3-((tert-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (295, 0.55 g, 1.57 mmol), EtOH (2 mL) and isopropylamine (2.7 mL, 31.4 mmol). The reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC of the crude reaction mixture), the reaction was quenched with a saturated sodium hydrogen carbonate solution (20 mL) and extracted into CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed in vacuo to furnish the product 297 as a colourless oil (0.35 g, 97%). The product was used without further purification.

δ_H (400 MHz, DMSO-d₆): 3.19 (2 H, t, J 7.0, H-2), 2.78-2.70 (4 H, m, H-1, H-6), 2.48 (2 H, t, J 7.0, H-4), 1.58 (2 H, quint., J 7.0, H-3), 1.39 (9 H, s, H-8), 0.98 (6 H, d, J 6.2, H-7).
δ_C (100 MHz, DMSO-d_6): 154.6 (C=O), 78.0 (q), 47.9, 43.5, 40.7, 33.5, 27.9, 27.5, 22.1.

*The carbon signal at 40.7 ppm is not observed in the $^{13}$C spectra attached as it is distorted by the DMSO-d_6 signal, however it is observed by analysis of the HSQC spectra.

ν_max (neat)/cm$^{-1}$: 2967, 2932, 1689 (C=O), 1479, 1454, 1392, 1365, 1308, 1223, 1157, 988, 876, 771, 664.

HRMS (m/z - ESI): Found: 231.2073 (M+H)$^+$ C$_{12}$H$_{27}$N$_2$O$_2$ Requires: 231.2067.

$N^1$-isopropyl-$N^3$-methylpropane-1,3-diamine (164)

To a 25 mL round-bottomed flask equipped with a magnetic stirring bar was charged tert-butyl (3-(isopropylamino)propyl)(methyl)carbamate (297, 0.58 g, 2.53 mmol) and CH$_2$Cl$_2$ (12 mL). To this stirring solution was added TFA (2 mL, 25.3 mmol). The reaction mixture was stirred for 4 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was stirred in Et$_2$O until a white precipitate was observed. This precipitate (0.60 g, 1.67 mmol) was stirred in CH$_2$Cl$_2$ and K$_2$CO$_3$ (0.97 g, 6.68 mmol) for 2 h (the progress of this reaction was monitored by $^{19}$F NMR spectroscopy). After complete consumption of the starting material, the suspension was filtered, and the precipitate was washed with Et$_2$O (3 x 10 mL). The filtrate was concentrated in vacuo (care was taken when removing the solvent as the diamine produced is volatile) to yield the title compound 164 (0.16 g, 72%) as a colourless oil, which was used without further purification.

δ_H (400 MHz, CDCl$_3$): 2.78 (1 H, sept., $J$ 6.2, H-7), 2.69-2.59 (4 H, m, H-3, H-5), 2.43 (3 H, s, H-1), 1.67 (2 H, quint., $J$ 7.2, H-4), 1.55 (2 H, br s, H-2, H-6), 1.05 (6 H, d, $J$ 6.2, H-8).

δ_C (100 MHz, CDCl$_3$): 50.7, 48.8, 45.9, 36.4, 30.1, 22.8.

ν_max (neat)/cm$^{-1}$: 3299 (NH), 3107, 3069, 2962, 2933, 2852, 2796, 1745, 1691, 162, 1547, 1472, 1447, 1363, 1169, 1126, 818, 704.

HRMS (m/z - APCI): Found: 131.1549 (M+H)$^+$ C$_7$H$_{19}$N$_2$ Requires: 131.1543.
Table 4: Experimental data

**General procedure III: Substrate evaluation in the NHC-catalysed oxidative amidation between 2,2’-pyridil and various primary and secondary amines (Table 4).**

An oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was evacuated and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon-filled balloon. 2,2’-pyridil (258, 212.2 mg, 1 mmol), 53 (180.2 mg, 1 mmol) and 25 (35.9 mg, 15 mol%, 0.15 mmol), were charged to the flask sequentially. The flask was again evacuated and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon-filled balloon. THF (0.4 M) was charged to the flask followed sequentially by freshly distilled DBU (165 µL, 1.1 mmol) and the relevant freshly distilled amine (1 mmol) in rapid succession. The reaction was stirred at room temperature for 24 h. The residue obtained was purified by flash column chromatography to furnish the desired product

**Pyridin-2-yl(pyrrolidin-1-yl) methanone (262)**

![Pyridin-2-yl(pyrrolidin-1-yl) methanone (262)](image)

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and pyrrolidine (84 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 1% MeOH to 10% MeOH in CH2Cl2) to produce 262 as a brown oil (176.4 mg, 93%).

Spectral data for this compound were consistent with those in the literature.207

δH (400 MHz, CDCl3): 8.57 (1 H, d, J 4.0, H-1), 7.86-7.74 (2 H, m, H-3, H-4), 7.36-7.30 (1 H, m, H-2), 3.77-3.64 (4 H, m, H-5), 1.98-1.86 (4 H, m, H-6).

Piperidin-1-yl(pyridin-2-yl)methanone (263)

Prepared according to general procedure III using 258 (212.3 mg, 1 mmol) and piperidine (99 μL, 1 mmol). Purified by flash chromatography (eluting in gradient from 1% MeOH to 10% MeOH in CH₂Cl₂), to produce 263 as a brown oil (166.3 mg, 94%).

Spectral data for this compound were consistent with those in the literature.²⁰⁸

δ_H (400 MHz, CDCl₃): 8.59 (1 H, d, J 4.0, H-1), 7.81-7.75 (1 H, m, H-4), 7.57 (1 H, d, J 7.8, H-3), 7.35-7.29 (1 H, m, H-2), 3.78-3.71 (2 H, m, H-5), 3.43 (2 H, t, J 5.6, H-9), 1.73-1.64 (4 H, m, H-6, H-8), 1.61-1.52 (2 H, m, H-7).

HRMS (m/z - ESI): Found: 213.1010 (M+Na)^+ C_{11}H_{14}N_{2}NaO Requires: 213.0998.

N-isobutylpicolinamide (264)

Prepared according to general procedure III using 258 (212.3 mg, 1 mmol) and isobutyl amine (100 μL, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to produce 265 as a brown oil (165.1 mg, 93%).

Spectral data for this compound were consistent with those in the literature.²⁰⁹

δ_H (400 MHz, CDCl₃): 8.55 (1 H, d, J 4.7, H-1), 8.20 (1 H, d, J 7.8, H-4), 8.13 (1 H, br s, H-5), 7.84 (1 H, app. t, H-3), 7.44-7.39 (1 H, m, H-2), 3.31 (2 H, d, J 6.6, H-6), 1.92-1.89 (1 H, m, H-7), 0.99 (6 H, d, J 6.7, H-8).

HRMS (m/z - APCI): Found: 179.1179 (M+H)^+ C_{10}H_{15}N_{2}O Requires: 179.1179.
N-isopropylpicolinamide (265)

Prepared according to general procedure III using 258 (212.1 mg, 1 mmol) and isopropyl amine (100 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate 265 as a brown oil (136.2 mg, 83%).

Spectral data for this compound were consistent with those in the literature.210

δH (400 MHz, CDCl3): 8.53 (1 H, d, J 4.7, H-1), 8.20 (1 H, d, J 7.8, H-4), 7.91-7.81 (1 H, m, H-3, H-5), 7.43-7.38 (1 H, m, H-2), 4.34-4.21 (1 H, m, H-6), 1.29 (6 H, d, J 6.6, H-7).

HRMS (m/z - APCI): Found: 165.1018 (M+H)+ C9H13N2O Requires: 165.1022.

N,N-dipropylpicolinamide (266)

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and dipropyl amine (137 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 10:1 to 1:1, CH2Cl2:EtOAc) to isolate 266 as a pale-yellow oil (135.0 mg, 65%).

δH (400 MHz, CDCl3): 8.59 (1 H, d, J 4.8, H-1), 7.78 (1 H, td, J 7.7, 1.7, H-3), 7.57 (1 H, d, J 7.7, H-4), 7.34-7.30 (1 H, m H-2), 3.49 (2 H, t, J 7.6, H-5), 3.33 (2 H, t, J 7.6, H-8), 1.74 (2 H, sex., J 7.6, H-6), 1.58 (2 H, sex., J 7.6, H-9), 1.00 (3 H, t, J 7.4, H-7), 0.75 (3 H, t, J 7.4, H-10).

δC (100 MHz, CDCl3): 169.0 (C=O), 155.4 (q), 148.3, 136.8, 124.0, 123.2, 50.4, 47.4, 22.1, 20.8, 11.5, 11.1.

νmax (neat)/cm⁻¹: 2964, 2933, 2875, 1628 (C=O), 1484, 1458, 1437, 1114, 809, 748, 618.
HRMS (m/z - ESI):  Found: 207.1484 (M+H)+ C12H19N2O  Requires: 207.1492.

**N-cinnamylpicolinamide (267)**

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and (E)-3-phenylprop-2-en-1-amine (277, 159.7 mg, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate 267 as a colourless oil (237.3 mg, 99%).

δH (400 MHz, CDCl3): 8.58 (1 H, d, J 4.3, H-1), 8.25 (1 H, d, J 7.7, H-4), 7.89 (1 H, td, J 7.7, 1.2, H-3), 7.45 (1 H, ddd, J 7.7, 4.3, 1.2, H-2), 7.42-7.36 (2 H, m, H-9), 7.36-7.30 (2 H, m, H-10), 7.28-7.23 (1 H, m, H-11), 6.64 (1 H, d, J 15.8, H-8), 6.33 (1 H, dt J 15.8, 6.2, H-7), 4.30 (2 H, td, J 6.2, 1.5, H-6).

* The protic signal (H-5) is not visible in CDCl3.

δC (100 MHz, CDCl3): 164.2 (C=O), 149.8 (q), 148.1, 137.4, 136.6 (q), 132.2, 128.6, 127.7, 126.4, 126.3, 125.4, 122.4, 41.5.

νmax (neat)/cm⁻¹: 3384, 3057, 3026, 2921, 1668 (C=O), 1515, 1434, 1161, 964, 745, 692, 620.

HRMS (m/z - ESI):  Found: 239.1187 (M+H)+ C15H15N2O  Requires: 239.1179.

**N-allylpicolinamide (268)**

Prepared according to general procedure III using 258 (212.3 mg, 1 mmol) and allyl amine (75 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate 268 as a brown oil (136.2 mg, 83%).
Spectral data for this compound were consistent with those in the literature.\textsuperscript{211}

$\delta_H (400 \text{ MHz, CDCl}_3)$: 8.55 (1 H, d, $J$ 4.8, H-1), 8.20 (1 H, d, $J$ 7.8, H-4), 8.14 (1 H, br s, H-5), 7.86 (1 H, td, $J$ 7.6, 1.7, H-3), 7.42 (1 H, ddd, $J$ 7.6, 4.8, 1.7, H-2), 5.95 (1H, ddd, $J$ 17.1, 10.3, 5.5, H-7), 5.31-5.24 (1 H, m, H-8a), 5.20-5.15 (1 H, m, H-8b), 4.14-4.08 (2 H, m, H-6).

HRMS (m/z - APCI): Found: 163.0865 (M+H)$^+$ C$_9$H$_{11}$N$_2$O Requires: 163.0866.

\textbf{N-(prop-2-yn-1-yl)picolinamide (269)}

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and propargyl amine (64 $\mu$L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100\% hexanes to 10:1 hexanes:EtOAc) to isolate 269 as an off-white solid (127.1 mg, 79\%).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{212}

$\delta_H (400 \text{ MHz, CDCl}_3)$: 8.55 (1 H, d, $J$ 4.7, H-1), 8.27-8.16 (2 H, m, H-4, H-5), 7.87-7.81 (1 H, m, H-3), 7.45-7.40 (1 H, m, H-2), 4.26 (2 H, dd, $J$ 5.6, 2.4, H-6), 2.26 (1H, t, $J$ 2.4, H-7).

HRMS (m/z - APCI): Found: 161.0712 (M+H)$^+$ C$_9$H$_9$N$_2$O Requires: 161.0709.

\textbf{1-Picolinoylpiperidine-4-carbonitrile (270)}

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and piperidine-4-carbonitrile (112 $\mu$L, 1 mmol). Purified by flash chromatography (eluting in gradient from 1\% MeOH to 10\% MeOH in CH$_2$Cl$_2$) to isolate 270 as a colourless oil (147.3 mg, 68\%).
\(\delta_H(400\text{ MHz},\text{ CDCl}_3):\) 8.55 (1 H, d, \(J\) 4.8, H-1), 7.82 (1 H, td, \(J\) 7.7, 1.7, H-4), 7.67 (1 H, d, \(J\) 7.7, H-3), 7.37 (1H, dd, \(J\) 7.7, 4.8, H-2), 4.04-3.95 (1 H, m, H-5a), 3.84-3.74 (2 H, m, H-5b, H-6a), 3.62-3.53 (1 H, m, H-6b), 2.99-2.94 (1 H, m, H-9), 2.10-1.88 (4 H, m, H-7, H-8).

\(\delta_C(100\text{ MHz},\text{ CDCl}_3):\) 167.5 (C=O), 153.7 (q), 148.3, 137.2, 124.8, 124.0, 120.9 (CN), 45.3, 40.5, 29.1, 28.3, 26.5.

\(\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}:\) 2962, 925, 2236 (CN), 1639 (C=O), 1577, 1308, 1047, 806, 760, 719, 655, 618.

HRMS (\(m/z\) - ESI): Found: 216.1129 (M+H)\(^{+}\) \(\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}\) Requires: 216.1131.

N-benzylpicolinamide (271)

![N-benzylpicolinamide](image)

Prepared according to general procedure III using 258 (212.2 mg, 1 mmol) and benzylamine (110 \(\mu\)L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100\% hexanes to 30\% EtOAc in hexanes) to isolate 271 as a pale yellow solid (194.0 mg, 91\%). M.p. 86-89 °C (lit.,\(^{213}\) M.p. 85-87 °C).

Spectral data for this compound were consistent with those in the literature.\(^{213}\)

\(\delta_H(400\text{ MHz},\text{ CDCl}_3):\) 8.53 (1 H, d, \(J\) 4.6, H-1), 8.38 (1 H, br s, H-5), 8.24 (1 H, d, \(J\) 7.8, H-4), 7.86 (1 H, td, \(J\) 7.8, 1.6, H-3), 7.45-7.41 (1 H, m, H-2), 7.40-7.32 (4H, m, H-7, H-8), 7.31-7.28 (1 H, m, H-9), 4.68 (2 H, d, \(J\) 6.1, H-6).

N-(1-phenylethyl)picolinamide (272)

![N-(1-phenylethyl)picolinamide](image)
Prepared according to general procedure III using **258** (212.3 mg, 1 mmol) and α-methyl benzylamine (129 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **272** as a white solid (183.0 mg, 81%).

Spectral data for this compound were consistent with those in the literature.²¹⁴

δ<sub>H</sub> (400 MHz, CDCl₃): 8.54 (1 H, d, J 4.4, H-1), 8.33 (1 H, br s, H-5), 8.20 (1 H, d, J 7.7, H-4), 7.84 (1 H, td, J 7.7, 1.7, H-3), 7.45-7.28 (6 H, m, H-2, H-8, H-9, H-10), 5.37-5.28 (1 H, m, H-6), 1.63 (3 H, d, J 6.9, H-7).

HRMS (m/z - APCI): Found: 227.1172 (M+H)<sup>+</sup> C<sub>14</sub>H<sub>15</sub>NO Requires: 227.1179.

**N-benzyl-N-methylpicolinamide (273)**

Prepared according to general procedure III using **258** (212.1 mg, 1 mmol) and methyl benzylamine (130 µL, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **273** as a colourless oil (150.2 mg, 66%).

Spectral data for this compound were consistent with those in the literature.²¹⁵

*An apparent degenerate mix of rotamers is observed in the <sup>1</sup>H spectrum of this compound.*

δ<sub>H</sub> (400 MHz, DMSO-d₆): Rotamer (a): 8.61-8.53 (1 H, m), 7.95-7.86 (1 H, m), 7.62-7.57 (1 H, m), 7.50-7.42 (1 H, m), 7.40-7.20 (5 H, m), 4.68 (2 H, s), 2.87 (3 H, s).

Rotamer (b): 8.61-8.53 (1 H, m), 7.95-7.86 (1 H, m), 7.62-7.57 (1 H, m), 7.50-7.42 (1 H, m), 7.40-7.20 (5 H, m), 4.54 (2 H, s), 2.83 (3 H, s).

HRMS (m/z - ESI): Found: 227.1168 (M+H)<sup>+</sup> C<sub>14</sub>H<sub>15</sub>N₂O Requires: 227.1179.
An oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was evacuated using high vacuum and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon-filled balloon. 2,2'-pyridil (258), 53 (180.2 mg, 1 mmol) and 25 (35.9 mg, 15 mol%, 0.15 mmol) were charged to the flask sequentially. The flask was again evacuated and put under an atmosphere of argon repeatedly. The flask was re-fitted with a septum seal and argon-filled balloon. THF (0.4 M) was charged to the flask followed sequentially by freshly distilled DBU (165 µL, 1.1 mmol) and the relevant freshly distilled amine (1 mmol) in rapid succession. The reaction was stirred at room temperature for 24 h. The residue obtained was purified by flash column chromatography to furnish the desired product.

\[N-(piperidin-2-ylmethyl)\text{picolinamide (287)}\]

Prepared according to general procedure IV using 258 (106.1 mg, 0.5 mmol) and 2-(aminomethyl)piperidine (146 µL, 1.2 mmol). Purified by flash chromatography, (eluting in 96:3:1 CH\(_2\)Cl\(_2\):MeOH:NEt\(_3\)) to isolate 287 as an orange oil (206.8 mg, 94%).

\[\delta_H (400 MHz, CDCl_3): \begin{align*}
8.53 & (1 \text{ H, d, J 4.4, H-1}), \ 8.45 & (1 \text{ H, br. s, H-5}), \ 8.16 & (1 \text{ H, d, J 7.7, H-4}), \ 7.83 & (1 \text{ H, app. t, J 7.7, H-3}), \ 7.44-7.38 & (1 \text{ H, m, H-2}), \ 4.08 & (1 \text{ H, br. s, H-12}), \ 3.67-3.57 & (1 \text{ H, m, H-6a}), \ 3.56-3.46 & (1 \text{ H, m, H-6b}), \ 3.24 & (1 \text{ H, d, J 12.1, H-11a}), \ 3.07-2.98 & (1 \text{ H, m, H-7}), \ 2.73 & (1 \text{ H, td, J 12.0, 2.0, H-11b}), \ 1.93-1.76 & (2 \text{ H, m, H-8a, H-9a}), \ 1.74-1.64 & (1 \text{ H, m, H-10a}), \ 1.63-1.32 & (3 \text{ H, m, H-8b, H-9b, H-10b}).
\end{align*}\]

\[\delta_C (100 MHz, CDCl_3): \begin{align*}
165.1 & (\text{C=O}), \ 149.7 & (q), \ 148.1, \ 137.4, \ 126.2, \ 122.3, \ 56.4, \ 46.3, \ 44.7, \ 29.6, \ 25.4, \ 23.8.
\end{align*}\]
\( \nu_{\text{max}} \text{(neat)/cm}^{-1} \): 3346, 2929, 2796, 1655 (C=O), 1589, 1568, 1528, 1434, 1022, 1087, 1054, 746, 670, 618, 579.

\text{HRMS (}\text{m/z - ESI})\text{: Found: 220.1444 (M+H)}^+\text{ C}_{12}H_{18}N_3O \text{ Requires: 220.1444.}

**N-(3-(methylamino)propyl)picolinamide (288)**

Prepared according to general procedure IV using 258 (212.2 mg, 1 mmol) and N-methyl-1,3-propanediamine (104 \( \mu \text{L} \), 1 mmol). Purified by flash chromatography (eluting in 96:3:1 \( \text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NET}_3 \)) to isolate 288 as an orange oil (190.2 mg, 98%).

\( \delta_H \) (400 MHz, CDCl\(_3\)): 8.55 (1 H, d, \( J \) 4.7, H-1), 8.39 (1 H, br s, H-5), 8.20 (1 H, d, \( J \) 7.8, H-4), 7.85 (1 H, td, \( J \) 7.8, 1.7, H-3), 7.42 (1 H, ddd, \( J \) 7.8, 4.7, 1.7, H-2), 3.58 (2 H, app. q, H-6), 3.29 (2 H, br s, H-9), 2.79 (2 H, t, \( J \) 6.8, H-8), 2.51 (3 H, s, H-10), 1.90 (2 H, quin., \( J \) 6.8, H-7).

\( \delta_C \) (100 MHz, CDCl\(_3\)): 164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.2, 49.1, 37.5, 35.9, 29.1.

\( \nu_{\text{max}} \text{(neat)/cm}^{-1} \): 3313, 3058, 2936, 1656 (C=O), 1589, 1568, 1568, 1524, 1378, 1288, 1167, 1147, 1088, 997, 821, 749, 692, 619.

\text{HRMS (}\text{m/z - ESI})\text{: Found: 194.1296 (M+H)}^+\text{ C}_{10}H_{16}N_3O \text{ Requires: 194.1288.}

**N-(2-aminopropyl)picolinamide (289)**

Prepared according to general procedure IV using 258 (106.1 mg, 1 mmol) and 1,2-diaminopropane (100 \( \mu \text{L} \), 1.2 mmol). Purified by flash chromatography (eluting in 96:3:1 \( \text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NET}_3 \)) to isolate 289 as an orange oil (190.2 mg, 98%).
\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

- 8.58 (1 H, d, J 4.6, H-1), 8.39 (1 H, br s, H-5), 8.23 (1 H, d, J 7.8, H-4), 7.88 (1 H, td, J 7.7, 1.7, H-3), 7.44 (1 H, ddd, J 7.7, 4.6, 1.7, H-2), 3.57-3.49 (1 H, m, H-7), 3.45-3.25 (1 H, m, H-6a), 3.25-3.15 (1 H, m, H-6b), 1.46 (2 H, br s, H-9), 1.19 (3 H, d, J 6.3, H-8).

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]

- 164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.3, 47.4, 46.9, 21.8.

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \]

- 3302, 3058, 2971, 2931, 1656 (C=O), 1589, 1569, 1522, 1464, 1434, 1381, 1289, 1145, 1089, 997, 821, 748, 691, 620.

\[ \text{HRMS (m/z - ESI)}: \]

- Found: 180.1136 (M+H)^+ C_9H_{14}N_3O Requires: 180.1131.

**N-(3-(isopropylamino)propyl)-N-methylpicolinamide (290)**

Prepared according to general procedure IV using 258 (212.2 mg, 1 mmol) and 164 (157.9 mg, 1.1 mmol). Purified by flash chromatography (eluting in 96:3:1 CH_2Cl_2:MeOH:NEt_3) to isolate 290 as an orange oil (215.5 mg, 92%).

*An apparent degenerate mix of rotamers is observed in the \(^1\)H and \(^{13}\)C NMR spectra of this compound.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

- Rotamer (a). 8.59 (1 H, dd, J 12.3, 4.8, H-1), 7.80 (1 H, td, J 7.7, 1.6, H-4), 7.66-7.59 (1 H, m, H-3), 7.36-7.32 (1 H, m, H-2), 3.65 (2 H, t, J 7.0, H-6), 3.13 (3 H, s, H-5), 2.83 (1 H, q, J 6.2, H-10), 2.76-2.69 (2 H, m, H-8), 1.90 (2 H, quin., J 6.9, H-7), 1.09 (6 H, d, J 6.2, H-11).

- Rotamer (b). 8.59 (1 H, dd, J 12.3, 4.8, H-1), 7.80 (1 H, td, J 7.7, 1.6, H-4), 7.66-7.59 (1 H, m, H-3), 7.36-7.32 (1 H, m, H-2), 3.51 (2 H, t, J 7.2, H-6), 3.06 (3 H, s, H-5), 2.76-2.69 (1 H, m, H-10), 2.51 (2 H, app. q, H-8), 1.82 (2 H, quin., J 7.2, H-7), 1.00 (6 H, d, J 6.2, H-11).
δH (400 MHz, CDCl₃):  
Rotamer (a). 8.53-8.47 (1 H, m, H-1), 7.75-7.68 (1 H, m, H-4), 7.57-7.49 (1 H, m, H-3), 7.29-7.23 (1 H, m, H-2), 3.57 (2 H, t, J 7.0, H-6), 3.04 (3 H, s, H-5), 2.69-2.56 (4 H, m, H-8, H-10), 1.87-1.78 (2 H, m, H-7), 1.51 (1 H, br s, H-9), 1.05 (3 H, t, J 7.1, H-11).

Rotamer (b). 8.53-8.47 (1 H, m, H-1), 7.75-7.68 (1 H, m, H-4), 7.57-7.49 (1 H, m, H-3), 7.29-7.23 (1 H, m, H-2), 3.41 (2 H, t, J 7.0, H-6), 2.97 (3 H, s, H-5), 2.54-2.40 (4 H, m, H-8, H-10), 1.78-1.70 (2 H, m, H-7), 1.51 (1 H, br s, H-9), 0.97 (3 H, t, J 7.1, H-11).

δC (100 MHz, CDCl₃):  
Rotamer (a). 169.0 (C=O), 154.7 (q), 148.2, 136.9, 124.2, 123.5, 48.9, 46.7, 44.1, 36.8, 28.6, 15.2.

*An apparent degenerate mix of rotamers is observed in the ¹H and ¹³C NMR spectra of this compound.
Rotamer (b). 168.8 (C=O), 154.6 (q), 148.1, 124.2, 123.3, 46.5, 45.7, 44.0, 33.3, 27.3, 15.2.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3432, 2935, 1622 (C=O), 1587, 1566, 1492, 1454, 1424, 1405, 1302, 1083, 1045, 994, 808, 750, 651, 618.

HRMS ($m/z$ - ESI): Found: 222.1601 (M+H)$^+$ C$_{12}$H$_{20}$N$_3$O Requires: 222.1601.

$N$-((1R,2R)-2-aminocyclohexyl)picolinamide (292)

Prepared according to general procedure IV using 258 (160.0 mg, 0.5 mmol) and (1R,2R)-cyclohexane-1,2-diamine (137.0 mg, 1.2 mmol). Purified by flash chromatography (eluting in gradient from 100:1:1 to 97:3:1 CH$_2$Cl$_2$:MeOH:NEt$_3$) to isolate 292 as an orange oil (169.1 mg, 77%).

$\delta_H$ (400 MHz, CDCl$_3$): 8.58 (1 H, d, $J$ 4.7, H-1), 8.23 (1 H, d, $J$ 7.7, H-4), 7.99 (1 H, d, $J$ 8.2, H-5), 7.88 (1 H, td, $J$ 7.7, 1.2, H-3), 7.45 (1 H, ddd, $J$ 7.7, 4.7, 1.2, H-2), 3.78-3.71 (1 H, m, H-6), 2.58 (1 H, td, $J$ 10.7, 4.1, H-11), 2.10-2.03 (2 H, m, H-7a, H-10a), 1.83-1.77 (2 H, m, H-8a, H-9a), 1.58 (3 H, br s, H-5, H-12), 1.47-1.24 (4 H, m, H-7b, H-8b, H-9b, H-10b).

$\delta_C$ (100 MHz, CDCl$_3$): 164.5 (C=O), 150.0 (q), 148.0, 137.4, 126.2, 122.4, 56.4, 55.7, 35.3, 32.5, 25.2, 25.1.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3266, 2923, 2851, 1650 (C=O), 1535, 1447, 956, 925, 851, 820, 755, 681, 618, 587.

HRMS ($m/z$ - ESI): Found: 220.1445 (M+H)$^+$ C$_{12}$H$_{18}$N$_3$O Requires: 220.1444.
Deprotection studies

General procedure V: Alkylation of secondary and tertiary amides

An oven dried 25 mL capacity sealed tube, equipped with a magnetic stirring bar, was charged with the appropriate amide (1.0 equiv.), 2-iodoethanol (334, 1.5 equiv.) and CH₃CN (1.0 M). The reaction mixture was heated to 120 °C and stirred for 18 h after which time the contents of the sealed tube were concentrated under reduced pressure and purified via flash column chromatography.

2-(Benzyl(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide (335)

Prepared according to general procedure V using N-benzyl-N-methylpicolinamide (273, 191.0 mg, 0.844 mmol) and 2-iodoethanol (334, 100 µL, 1.27 mmol). Purified by flash chromatography (eluting in gradient from 100% CH₂Cl₂ to 5% MeOH in CH₂Cl₂) to isolate 335 as a pale-yellow oil (332.1 mg, 98%).

*A non-degenerate mix of isomers is observed in the ¹H and ¹³C NMR spectra of this compound. The NMR spectra of this compound are recorded at 60°C for more defined resonance signals.

δH (600 MHz, DMSO-d₆): Major isomer. 9.12 (1 H, d, J 6.0, H-1), 8.74 (1 H, app. t, J 7.8, H-3), 8.33-8.19 (2 H, m, H-2, H-4), 7.47-7.30 (4 H, m, H-7, H-8), 7.30-7.25 (1 H, m, H-9), 5.28 (1 H, t, J 5.3, H-12), 4.77 (2 H, s, H-6), 4.70-4.58 (2 H, m, H-10), 3.95-3.83 (2 H, m, H-11), 2.88 (3 H, s, H-5).

Minor isomer. 9.07 (1 H, d, J 6.0, H-1), 8.69 (1 H, app. t, J 7.9, H-3), 8.33-8.19 (2 H, m, H-2, H-4), 7.47-7.30 (4 H, m, H-7, H-8), 7.30-7.25 (1 H, m, H-9), 5.28 (1 H, t, J 5.3, H-12), 4.70-4.58 (2 H, m, H-10), 4.50 (2 H, s, H-6), 3.95-3.83 (2 H, m, H-11), 3.05 (3 H, s, H-5).
\( \delta_C \) (100 MHz, DMSO-\( d_6 \)): Major isomer. 161.4 (C=O), 148.3 (q), 147.2, 136.2 (q), 129.3, 128.6, 128.5, 128.2, 127.1, 126.4, 61.5, 60.0, 50.7, 36.8.

Minor isomer. 161.5 (C=O), 148.5 (q), 147.2, 135.5 (q), 129.4, 128.4, 128.3, 127.9, 126.6, 61.4, 59.9, 54.2, 33.3.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1} \):

- 3300 (OH), 3028, 2928, 1646 (C=O), 1617, 1581, 1492, 1451, 1409, 1263, 1073, 926, 739, 697, 609.

HRMS (m/z - ESI):

- Found: 271.1448 (M)
- Requires: 271.1441.

1-(2-Hydroxyethyl)-2-(pyrrolidine-1-carbonyl)pyridin-1-ium iodide (336)

Prepared according to general procedure V using pyridin-2-yl(pyrrolidin-1-yl)methanone (262, 212.2 mg, 1 mmol) and 2-iodoethanol (334, 110 \( \mu \)L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% CH\(_2\)Cl\(_2\) to 5% MeOH in CH\(_2\)Cl\(_2\)) to isolate 336 as a pale-yellow oil (332.1 mg, 98%).

\( \delta_H \) (600 MHz, DMSO-\( d_6 \)): 9.13 (1 H, d, J 6.1, H-1), 8.75 (1 H, app. t, H-3), 8.35 (1 H, d, J 7.8, H-4), 8.25 (1 H, app. t, H-2), 5.36 (1 H, t, J 5.2, H-10), 4.73-4.65 (2 H, m, H-8), 3.87-3.82 (2 H, m, H-9), 3.57 (2 H, t, J 7.0, H-6), 3.38-3.31 (2 H, m, H-5), 1.96-1.90 (2 H, m, H-7), 1.89-1.82 (2 H, m, H-7).

\( \delta_C \) (100 MHz, DMSO-\( d_6 \)): 159.0 (C=O), 149.0 (q), 148.0, 147.3, 128.6, 126.9, 61.4, 60.3, 48.7, 46.5, 25.8, 24.2.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1} \):

- 3409 (OH), 3074, 3032, 2974, 2878, 1638 (C=O), 1582, 1443, 1343, 1297, 1163, 1064, 974, 871, 744, 667, 586.

HRMS (m/z - ESI):

- Found: 221.1283 (M)\(^+\) C\(_{12}\)H\(_{17}\)N\(_2\)O\(_2\) Requires: 221.1285.
An oven dried 25 mL capacity sealed tube equipped with a magnetic stirring bar was charged with \( N\)-(3-(isopropylamino)propyl)-N-methylpicolinamide (291, 40.9 mg, 0.185 mmol), di-\( \text{tert} \)-butyl dicarbonate (69.9 mg, 0.277 mmol) and CH\(_3\)CN (0.2 mL). The flask was sealed and heated to 120 °C until complete protection of 291 was detected (determined by \(^1\)H NMR spectroscopy using \( p \)-iodoanisole as an internal standard). Upon complete Boc-protection of 291, 2-iodoethanol (234, 22 \( \mu \)L, 0.277 mmol) was charged to the flask. The reaction mixture was heated to 120 °C and stirred for 12 h after which time the contents of the sealed tube were concentrated and purified \( \text{via} \) flash column chromatography (eluting in gradient from 100% CH\(_2\)Cl\(_2\) to 5% MeOH in CH\(_2\)Cl\(_2\)) to isolate 338 as an orange oil (81.7 mg, 90%).

*A non-degenerate mix of rotamers is observed in the \(^1\)H NMR and \(^{13}\)C spectra of this compound at 25 °C. However, when the \(^1\)H NMR spectrum of this compound was recorded at 80 °C, only the major rotamer was detected.

\[\delta_H(400\text{ MHz, DMSO-}d_6):\] 9.11 (1 H, app. d, H-1), 8.73 (1 H, app. t, H-3), 8.30-8.20 (2 H, m, H-2, H-4), 5.22 (1 H, br s, H-14), 4.74-4.56 (2 H, m, H-12), 3.98-3.83 (2 H, m, H-13), 3.54 (2 H, app. t, H-9), 3.31-3.18 (4 H, m, H-6, H-8), 2.94 (3 H, s, H-5), 1.94-1.77 (2 H, m, H-7), 1.44 (9 H, s, H-11), 1.13-1.04 (3 H, m, H-10).

\[\delta_C(100\text{ MHz, DMSO-}d_6):\] Major rotamer. 160.9 (C=O), 160.7 (C=O), 148.8 (q), 148.0, 147.1, 126.9, 126.3, 79.7 (q), 61.4, 60.1, 46.2, 43.8, 42.0, 37.1, 28.6, 25.7, 13.6.

Major rotamer. 160.8 (C=O), 160.6 (C=O), 148.7 (q), 148.1, 147.2, 128.4, 126.6, 78.9 (q), 61.5, 59.9, 46.2, 46.1, 41.8, 34.3, 28.5, 26.9, 12.6.
\[ \nu_{\text{max}} \text{(neat)/cm}^{-1}: \] 3334 (OH), 2974, 2932, 1648 (C=O), 1619, 1481, 1453, 1418, 1293, 1253, 1161, 1074, 963, 872, 775, 748.

HRMS (\(m/z\) - ESI): Found: 366.2399 (M)\(^+\) \(\text{C}_{19}\text{H}_{32}\text{N}_{3}\text{O}_{4}\) Requires: 366.2387.

1-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazin-5-ium iodide (331)

Prepared according to general procedure V. Upon complete conversion of 335 to 331, (determined by analysis of \(^1\)H NMR spectrum), CSA (2.0 equiv.) was charged to the reaction flask and the reaction was stirred for a further 2 h at 120 °C after which time the reaction mixture was cooled and filtered to obtain 331 as a pale-yellow solid (278.8 mg, 68%). M.p. 191-193 °C.

\[ \delta_H \text{ (600 MHz, DMSO-}d_6\text{):} \] 9.20 (1 H, d, \(J\ 5.8\), H-1), 8.82 (1 H, app. t, \(J\ 7.9\), H-3), 8.69 (1 H, d, \(J\ 7.9\), H-4), 8.42 (1 H, app. t, \(J\ 5.8\), H-2), 5.07-5.02 (2 H, m, H-5), 4.98-4.94 (2 H, m, H-6).

\[ \delta_C \text{ (100 MHz, DMSO-}d_6\text{):} \] 157.1 (C=O), 147.8, 145.7, 139.2 (q), 131.3, 129.7, 65.7, 52.6.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1}: \] 2987, 1744 (C=O), 1623 (C=O), 1399, 1282, 1137, 1040, 759, 669, 636.

HRMS (\(m/z\) - ESI): Found: 150.0554 (M-I)\(^+\) \(\text{C}_8\text{H}_8\text{NO}_2\) Requires: 150.0550.

Protection of secondary amides using di-tert-butyl dicarbonate

\textit{Tert}-butyl benzyl(picolinoyl)carbamate (341)

189
To a 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged N-benzylpicolinamide (271, 0.196 g, 0.922 mmol), DMAP (0.0563 g, 0.461 mmol), NEt₃ (0.2 mL, 1.38 mmol) and CH₃CN (0.92 mL). The flask was placed under an atmosphere of argon using an argon-filled balloon and septum. To the flask, di-tert-butyl dicarbonate (0.391 g, 1.83 mmol) was charged and the flask was equipped with a reflux condenser. The reaction mixture was heated under reflux and stirred until complete consumption of the starting material was detected (determined by TLC analysis of the crude reaction mixture). At the end of the reaction the solvent was removed in vacuo and the product was purified via flash column chromatography (eluting in gradient from 100% hexanes to 7:3 hexanes:EtOAc) to isolate 341 as a colourless oil (0.267 g, 93%).

δH (400 MHz, CDCl₃): 8.61 (1 H, d, J 4.8, H-1), 7.83 (1 H, td, J 7.8, 1.6, H-4), 7.72 (1 H, app. d, H-3), 7.48 (2 H, app. d, H-7), 7.44-7.39 (1 H, m, H-2), 7.35 (2 H, app. t, H-6), 7.31-7.25 (1 H, m, H-8), 5.05 (2H, s, H-5), 1.17 (9 H, s, H-9).

δC (100 MHz, CDCl₃): 171.4 (C=O), 154.5 (C=O) 153.2 (q), 148.1, 137.5 (q), 136.9, 128.4, 127.9, 127.3, 125.2, 122.9, 83.2 (q), 48.8, 27.3.

νmax (neat)/cm⁻¹: 2927, 2853, 2119, 1733 (C=O), 1684 (C=O), 1497, 1439, 1416 1380, 1343, 1256, 1233, 1173, 1146, 996, 985, 845, 747, 736, 624.

HRMS (m/z - ESI): Found: 335.1376 (M+Na)⁺ C₁₈H₂₀N₂NaO₃ Requires: 335.1366.

Tert-butyl (3-((tert-butoxycarbonyl)(methyl)amino)propyl)(picolinoyl)carbamate (346)

To a 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged N-(3-(methylamino)propyl)picolinamide (288, 0.033 g, 0.171 mmol), DMAP (0.042 g, 0.342 mmol), NEt₃ (0.24 mL, 1.71 mmol) and THF (0.7 mL). The flask was placed under an atmosphere of argon using an argon-filled balloon and septum. To the flask, di-tert-butyl dicarbonate (0.448 g, 2.05 mmol) was charged and the flask was equipped with a reflux.
condenser. The reaction mixture was heated under reflux and stirred until complete consumption of the starting material was detected (determined by TLC analysis of the crude reaction mixture). At the end of the reaction, the solvent was removed in vacuo and the product was purified via flash column chromatography (eluting in 1:1 hexanes:EtOAc) to isolate 346 as a colourless oil (0.061 g, 93%).

$$\delta_H (400 \text{ MHz, CDCl}_3):$$

8.58 (1 H, d, $J = 4.7$, H-1), 7.82 (1 H, td, $J = 7.7$, 1.6, H-4), 7.67 (1 H, d, $J = 7.8$, H-3), 7.43-7.37 (1 H, m, H-2), 3.85 (2 H, t, $J = 7.5$, H-5), 3.41-3.29 (2 H, m, H-7), 2.89 (3 H, s, H-8), 1.95 (2 H, quint., $J = 7.4$, H-6), 1.47 (9 H, s, H-10), 1.20 (9 H, s, H-9).

$$\delta_C (100 \text{ MHz, CDCl}_3):$$

171.5 (C=O), 155.7 (C=O), 154.8 (C=O), 153.1 (q), 148.1, 136.9, 125.2, 122.7, 83.0 (q), 79.3 (q), 46.8, 43.4, 34.0, 28.5, 27.4, 27.1.

$$\nu_{\text{max}} (\text{neat})/\text{cm}^{-1}:$$

2977, 2932, 1736 (C=O), 1687 (C=O), 1671 (C=O), 1479, 1392, 1365, 1289, 1141, 1059, 995, 871, 858, 772, 748, 669, 619.

HRMS ($m/z$ - ESI):

Found: 416.2156 (M+Na)$^+$ C$_{20}$H$_{31}$N$_3$NaO$_5$ Requires: 416.2156.

**Reductive cleavage of N-substituted pyridoyl amides**

**General procedure VI:** Reductive cleavage of N-substituted pyridoyl amides using NaBH$_4$

To an oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was charged the appropriate N-substituted pyridoyl amide (1 equiv.) and EtOH (0.12 M). NaBH$_4$ (2 equiv.) was charged to the flask in one portion and the reaction mixture was stirred at room temperature for 2 h after, which time the reaction mixture was diluted with acetone (1 mL) and stirred for a further 1 h. The crude mixture was concentrated in vacuo and the resulting residue dissolved in Et$_2$O (10 mL). The organic layer was washed sequentially with KHSO$_4$ (1 M, 3 x 5 mL), a saturated sodium hydrogen carbonate solution (3 x 5 mL) and brine (3 x 5 mL). The organic layer was dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to provide the Boc-protected amine, which requires no further purification.
**tert-butyl benzyl(methyl)carbamate (344)**

Prepared according to general procedure VI using *tert*-butyl benzyl(picolinoyl)carbamate (341, 110.0 mg, 0.352 mmol), NaBH₄ (28.5 mg, 0.704 mmol) and EtOH (2.8 mL) to isolate 344 as a colourless oil (65.5 mg, 90%).

Spectral data for this compound were consistent with those in the literature.²¹⁶

δ_H (400 MHz, CDCl₃): 7.63-7.23 (5 H, m, H-4, H-5, H-6), 4.82 (1 H, br s, H-2), 4.32 (2 H, d, J 5.0, H-3), 1.46 (9 H, s, H-1).

HRMS (m/z - ESI): Found: 230.1152 (M+Na)⁺ C_{12}H_{17}N_{3}NaO_{2} Requires: 230.1151.

**tert-butyl (3-((tert-butoxycarbonyl)amino)propyl)(methyl)carbamate (347)**

Prepared according to general procedure VI using *tert*-butyl (3-((tert-butoxycarbonyl)(methyl)amino)propyl)(picolinoyl)carbamate (346, 83.8 mg, 0.221 mmol), NaBH₄ (17.0 mg, 0.442 mmol) and EtOH (1.8 mL) to isolate 347 as a colourless oil (51.7 mg, 81%).

δ_H (400 MHz, CDCl₃): 3.27 (2 H, t, J 6.5, H-3), 3.13-3.05 (2 H, m, H-5), 2.82 (3 H, s, H-6), 1.71-1.59 (3 H, m, H-2, H-4), 1.46 (9 H, s, H-1), 1.44 (9 H, s, H-7).

δ_C (100 MHz, CDCl₃): 156.1 (C=O), 155.7 (C=O), 79.5 (q), 79.0 (q), 45.9, 45.3, 37.2, 34.0, 28.4.

ν_max (neat)/cm⁻¹: 3357 (NH), 2976, 2931, 1679 (C=O), 1509, 1454, 1365, 1307, 1248, 1152, 1084, 872, 772, 640, 592.

HRMS (m/z - ESI): Found: 311.1953 (M+Na)⁺ C_{14}H_{28}N_{2}NaO_{4} Requires: 311.1941.
4.3 Experimental data for Chapter 3
Azlactone synthesis

Benzoylphenylalanine (360)

To a 50 mL round-bottomed flask equipped with a magnetic stirring bar DL-phenylalanine (359, 1.61 g, 9.7 mmol) was charged and dissolved in distilled H₂O (21 mL). NaOH (2 M, 19.4 mmol) was charged to the flask and the reaction mixture was cooled to 0 °C in a H₂O/ice bath. Benzoyl chloride (1.2 mL, 9.7 mmol) was added to the stirring reaction mixture dropwise at 0 °C and the mixture was warmed to room temperature slowly overnight. At the end of the reaction, the resulting suspension was filtered, and the precipitate washed with distilled water (10 mL). Upon drying of the product under high vacuum, the title product 360 was furnished as a white solid (1.82 g, 69%). M.p. 188-190 °C (lit., 217 M.p. 188-189 °C).

Spectral data for this compound were consistent with those in the literature.²¹⁸

\[ \delta_H (400\text{ MHz, CDCl}_3): \]

7.68 (2 H, d, \( J 8.5, H-8 \)), 7.55-7.49 (1 H, m, H-10), 7.45-7.39 (2 H, m, H-9), 7.35-7.27 (2 H, m, H-4), 7.24-7.19 (3 H, m, H-5, H-6), 6.52 (1 H, d, \( J 7.0, H-7 \)), 5.06 (1 H, dd, \( J 6.1, 5.7, H-2 \)), 3.39 (1 H, dd, \( J 14.2, 5.7, H-3a \)), 3.29 (1 H, dd, \( J 14.2, 6.1, H-3b \)).

* The protic signal (H-1) is not visible in CDCl₃.

4-Benzyl-2-phenyloxazol-5-(4H)-one (354)
To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar, was charged benzoylphenylalanine (360, 1.81 g, 6.74 mmol) followed by CH$_2$Cl$_2$ (52 mL). DCC (1.42 g, 6.74 mmol) was added to the flask in one portion and the resulting suspension was stirred at room temperature overnight. At the end of the reaction the suspension was filtered, the filtrate was concentrated in vacuo and the resulting residue was purified via flash column chromatography (eluting in gradient from 100% petroleum ether to 40% CH$_2$Cl$_2$ in petroleum ether) to isolate 354 as a white solid (0.711 g, 42%). M.p. 96-98 °C (lit., 218 M.p. 97-98 °C).

Spectral data for this compound were consistent with those in the literature. $^{218}$

$\delta_H$ (400 MHz, CDCl$_3$):

- 7.90 (2 H, d, $J$ 7.4, H-6), 7.56-7.50 (1 H, m, H-8), 7.43 (2 H, app. t, H-7), 7.27-7.16 (5 H, m, H-3, H-4, H-5), 4.67 (1 H, dd, $J$ 6.8, 4.9, H-1), 3.38 (1 H, dd, $J$ 14.2, 4.9, H-2a), 3.19 (1 H, dd, $J$ 14.2, 6.8, H-2b).

2-Benzamido-2-methylpropanoic acid (366)

To a 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged, 2-methylalanine (365, 2.0 g, 19.4 mmol) and it was dissolved in distilled H$_2$O (40 mL). NaOH (2 M, 38.3 mmol) was charged to the flask and the reaction mixture was cooled to 0 °C in a H$_2$O/ice bath. Benzoyl chloride (2.3 mL, 19.4 mmol) was added to the stirring reaction mixture dropwise at 0 °C and the mixture was warmed to room temperature gradually overnight. At the end of the reaction the resulting suspension was filtered, and the precipitate washed with distilled water (25 mL). Upon drying of the product under high vacuum, the title product 366 was furnished as a white solid (1.35 g, 34%). M.p. 200-202 °C (lit., 158 M.p. 201-202 °C).

Spectral data for this compound were consistent with those in the literature. $^{158}$

$\delta_H$ (400 MHz, MeOD):

- 8.40 (1 H, br s, H-4), 7.80 (2 H, d, $J$ 7.2, H-3), 7.50 (1 H, t, $J$ 7.5, H-1), 7.44 (2 H app. t, H-2), 1.59 (6 H, s, H-5).
* The protic signal (H-6) is not visible in MeOD.

4,4-Dimethyl-2-phenyloxazol-5(4H)-one (367)

![Chemical structure of 4,4-Dimethyl-2-phenyloxazol-5(4H)-one (367)]

To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar, was charged 2-benzamido-2-methylpropanoic acid (366, 1.35 g, 6.51 mmol) followed by CH₂Cl₂ (80 mL). DCC (1.48 g, 7.16 mmol) was added to the flask in one-portion and the resulting suspension was stirred at room temperature overnight. At the end of the reaction the suspension was filtered, the filtrate was concentrated in vacuo and the resulting residue was purified via flash column chromatography (eluting in 15:1 CH₂Cl₂: petroleum ether) to isolate 367 as a white solid (0.665 g, 54%).

Spectral data for this compound were consistent with those in the literature.¹⁵⁸

δ_H (400 MHz, CDCl₃): 8.40 (1 H, app. s, H-4), 7.80 (2 H, app. d, H-2), 7.50 (1 H, app. t, H-3), 1.59 (6 H, s, H-1).

HRMS (m/z - ESI): Found: 190.0868 (M+H)+ C₁₁H₁₂NO₂ Requires: 190.0863.

2,3,4,5-Tetrachloro-6-(isopropoxycarbonyl)benzoic acid (383)

![Chemical structure of 2,3,4,5-Tetrachloro-6-(isopropoxycarbonyl)benzoic acid (383)]

To a 100 mL round-bottomed flask containing a magnetic stirring bar, 3,4,5,6-tetrachlorophthalic anhydride (382, 5.07 g, 17.5 mmol) was charged following which the flask was flushed with argon and maintained under a protective argon atmosphere (using a septum and argon-filled balloon). IPA (35 mL) and NEt₃ (2.5 mL, 17.5 mmol) were added to the flask and the reaction mixture was stirred at room temperature overnight. After 16 h,
aqueous HCl (2 N, 35 mL) was charged to the flask and the reaction mixture was extracted into Et₂O (3 x 35 mL). The combined organic extracts were dried over MgSO₄ and the solvent concentrated under reduced pressure to yield 383 as a white solid (5.72 g, 94%). M.p. 143-145 °C (lit.,¹⁵⁶ M.p. 143-145 °C).

Spectral data for this compound were consistent with those in the literature.¹⁵⁶

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

5.27 (1 H, sept., \( J 6.3 \), H-2), 1.35 (6 H, d, \( J 6.3 \), H-3).

* The protic signal (H-1) is not visible in CDCl₃.

**Tert-butyl phenylalaninate (384)**

To a 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with DL-phenylalanine (359, 5.03 g, 30 mmol), the flask was flushed with argon and maintained under a protective argon atmosphere (septum and argon-filled balloon). Tert-butyl acetate (69 mL) was charged and the flask was cooled to 0 °C in a \( \text{H}_2\text{O}/\text{ice bath}. \) Concentrated HClO₄ (70%, aq., 3.7 mL) was added dropwise to the reaction mixture via syringe. The reaction was warmed to room temperature with stirring. After 16 h, aqueous HCl (1 N, 70 mL) was added and the reaction mixture was adjusted to pH 9.0 using aqueous K₂CO₃ (10%). The reaction mixture was extracted with CH₂Cl₂ (3 x 50 mL) and the combined extracts were dried over MgSO₄ and the solvent concentrated under reduced pressure to yield 384 as a colourless oil (6.46 g, 97%).

Spectral data for this compound were consistent with those in the literature.¹⁵⁶

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

7.35-7.14 (5 H, m, H-1, H-2, H-3), 3.63-3.56 (1 H, m, H-5), 3.06 (1 H, dd, \( J 13.5, \) 5.7, H-4a), 2.82 (1 H, dd, \( J 13.5, \) 7.8, H-4b), 1.41 (9 H, s, H-7).

* The protic signal (H-6) is not visible in CDCl₃.

HRMS (m/z - ESI): Found: 222.1445 (M+H)⁺ \( \text{C}_{13}\text{H}_{20}\text{NO}_2 \) Requires: 222.1416.
Isopropyl 2-((1-\textit{tert}-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (387)

![Chemical Structure]

To a 250 mL oven-dried round-bottomed flask containing a magnetic stirring bar, 2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzoic acid (383, 10.7 g, 30.8 mmol) and \textit{tert}-butyl phenylalaninate (384, 6.46 g, 29.2 mmol) were charged and the reaction vessel was flushed with argon and maintained under a protective argon atmosphere (using a septum and balloon). CH$_2$Cl$_2$ (103 mL) was charged to the flask \textit{via} syringe followed by the addition of DCC (6.64 g, 32.1 mmol) in one portion. After 16 h, the suspension was allowed to stand at 0 °C in a H$_2$O/ice bath for 30 minutes and the resulting precipitate was filtered. The filtrate was concentrated under reduced pressure, the residue was dry loaded onto silica and purified \textit{via} flash column chromatography (eluting in gradient from 100% petroleum ether to 60% EtOAc in petroleum ether) to isolate 387 as a white solid (9.94 g, 62%). M.p. 126-129 °C (lit.,$^{156}$ M.p. 126-128 °C).

Spectral data for this compound were consistent with those in the literature.$^{156}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.32-7.16 (5 H, m, H-6, H-7, H-8), 6.43 (2 H, d, $J$ 7.5, H-3), 5.20 (1 H, app. sept., H-2), 4.88 (1 H, app. q, H-4), 3.24 (1 H, dd, $J$ 14.0, 5.2, H-5a), 3.12 (1 H, dd, $J$ 14.0, 6.6, H-5b), 1.36 (9 H, s, H-9), 1.34-1.30 (6 H, m, H-1).
(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzoyl)phenylalanine (388)

To a 25 mL oven-dried round-bottomed flask containing a magnetic stirrer, isopropyl 2-((1-(tert-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (387, 1.00 g, 1.83 mmol) was charged. The flask was flushed with argon and maintained under a protective argon atmosphere (using a septum and argon-filled balloon). CH$_2$Cl$_2$ (4.5 mL) and TFA (4.5 mL) were charged to the flask and the reaction mixture was stirred at room temperature overnight. After 16 h the solvent was concentrated under reduced pressure. TFA was removed from carboxylic acid 388 by continuous azeotroping with cyclohexane to yield the product as a white solid (0.875 g, 97%). M.p. 178-181 °C (lit.,$^{156}$ M.p. 178-182 °C).

Spectral data for this compound were consistent with those in the literature.$^{156}$

δ$_H$ (400 MHz, DMSO-d$_6$): 12.85 (1 H, br s, H-9), 9.14 (1 H, d, J 8.1, H-3), 7.31-7.11 (5 H, m, H-6, H-7, H-8), 4.99 (1 H, app. sept., H-2), 4.61 (1 H, app. q, H-4), 3.08 (1 H, dd, J 13.7, 5.6, H-5a), 2.90 (1 H, dd, J 13.7, 8.5, H-5b), 1.19 (6 H, app. t, H-1).

Isopropyl 2-(4-benzyl-5-oxo-4,5-dihydrooxazol-2-yl)-3,4,5,6-tetrachlorobenzoate (381)

To a 25 mL oven-dried round-bottomed flask containing a magnetic stirrer, (2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzoyl)phenylalanine (388, 1.03 g, 2.10 mmol) was charged. The flask was flushed with argon and maintained under a protective argon atmosphere (using a septum and argon-filled balloon). CH$_2$Cl$_2$ (8.5 mL) was charged to the flask followed by dropwise addition TFAA (0.44 mL, 3.15 mmol). The reaction mixture was
stirred at room temperature for 1 h after which time the solvent was removed in vacuo. The resulting residue purified by passage through a plug of silica using CH$_2$Cl$_2$ as the eluent to yield the azlactone 381 as a colourless oil which upon trituration in hexanes became a white solid (0.738 g, 74%).

Note: It is important that neither the reaction mixture nor the product is not heated above 40 °C during the course of the purification as decomposition will occur.

Spectral data for this compound were consistent with those in the literature.$^{156}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.32-7.19 (5 H, m, H-5, H-6, H-7), 5.19 (1 H, app. sept, H-2), 4.60 (1 H, dd, $J$ 6.6, 5.1 H-3), 3.23 (1 H, dd, $J$ 14.1, 5.1, H-4a), 3.26 (1 H, dd, $J$ 14.1, 6.6, H-4b), 1.30 (6 H, d, $J$ 6.2, H-1).

HRMS ($m/z$ - APCI): Found: 473.9830 (M+H)$^+$ C$_{20}$H$_{16}$Cl$_4$NO$_4$ Requires: 473.9828.

**Fluorinolysis of azlactone 354**

**General procedure VII: Aminolysis of azlactone 354 via fluoride ring-opening**

To an oven-dried argon flushed 5 mL round-bottomed flask equipped with activated 3 Å molecular sieves and an argon balloon and septum, azlactone (354, 25.1 mg, 0.10 mmol), $p$-iodoanisole (12.1 mg, 0.05 mmol), and CH$_2$Cl$_2$ (2.5 mL) were added to the flask. Benzoyl fluoride (11 µL, 0.1 mmol) and TBAF (10 µL, 0.01 mmol) were charged to the flask and the solution was monitored by $^1$H NMR spectroscopy using $p$-iodoanisole as the internal standard. The reaction mixture was quenched at room temperature with benzylamine (11 µL, 0.1 mmol) and the now quenched mixture stirred stood for an hour. After this time the resulting suspension was filtered, and the filter cake was washed with CH$_2$Cl$_2$. The precipitate obtained was collected and the filtrate was concentrated under reduced pressure and the residue purified via flash column chromatography.
N-(1-benzylamino)-1-oxo-3-phenylpropan-2-yl)benzamide (361)

Prepared according to general procedure VII. This product was obtained as a white solid collected after quenching the reaction and filtering the suspension. The title compound 361 required no further purification. (16.8 mg, 47%). M.p. 196-199 °C

$\delta_H$ (600 MHz, DMSO-d$_6$): 8.64-8.58 (2 H, m, H-6, H-11), 7.82 (2 H, d, J 7.4, H-12), 7.51 (1 H, t, J 7.5, H-14), 7.44 (2 H, app. t, H-13), 7.35 (2 H, d, J 7.5, H-8), 7.31 (2 H, app. t, H-9), 7.28-7.21 (5 H, m, H-1, H-2, H-3), 7.17 (1 H, t, J 7.5, H-10), 4.78-4.72 (1 H, ddd, J 10.8, 6.5, 4.5, H-5), 4.32 (2 H, d, J 5.9, H-7), 3.16 (1 H, dd, J 13.5, 4.5, H-4a), 3.04 (1 H, dd, J 13.5, 10.8, H-4b).

$\delta_C$ (100 MHz, DMSO-d$_6$): 171.8 (C=O), 166.8 (C=O), 139.8 (q), 138.9 (q), 134.5 (q), 131.7, 129.6, 128.7, 128.6, 128.5, 127.9, 127.5, 127.2, 126.7, 55.6, 42.6, 37.7.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3230 (NH), 3029 (NH), 1660 (C=O), 1630 (C=O), 1535, 1455, 1327, 1289, 1185, 1026, 905, 873, 797, 616, 607, 588.

HRMS (m/z - ESI): Found: 381.1576 (M+Na)$^+$ C$_{23}$H$_{22}$N$_2$NaO$_2$ Requires: 381.1573

N-(1-Oxo-3-phenyl-115-prop-1-en-2-yl)benzamide (364)
Prepared according to general procedure VII. However, ketene 364 was isolated when the reaction was not quenched with benzylamine (285). After 100% consumption of 354 (determined by $^1$H NMR spectroscopy using $p$-iodoanisole as the internal standard) 364 was isolated by flash column chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate the ketene as a colourless oil. Due to the multiple products produced from this reaction and the instability of 364 an isolated yield was not determined.


*Protic signal (H-8) is not visible in CDCl$_3$.

$\delta_C$ (100 MHz, CDCl$_3$): 176.4 (C=O), 161.9 (C=O), 133.1 (q), 132.9, 132.8 (q), 130.6, 130.4 (q) 128.6, 128.2, 128.2, 127.5, 37.5, 29.7(q).

$\nu_{\text{max}}$(neat)/cm$^{-1}$: 2922 (NH), 1825 (C=O), 1732 (C=O), 1655, 1451, 1319, 1653, 975, 879, 788, 698.

HRMS (m/z - ESI): Found: 251.0937 (M)$^+$ C$_{16}$H$_{13}$NO$_2$ Requires: 251.0941

**General procedure VIII: Aminolysis of azlactones via ring-opening by carboxylate salts**

To an oven-dried argon-flushed 5 mL round-bottomed flask containing a magnetic stirring bar equipped with an argon-filled balloon and septum, azlactone (381, 118.9 mg, 0.25 mmol), $p$-iodoanisole (29.2 mg, 0.125 mmol), benzoic acid (30.7 mg, 0.25 mmol) and TBAOBz (18.3 mg, 0.05 mmol) were added to the flask sequentially followed by the addition of CH$_2$Cl$_2$ (2.5 mL). The reaction mixture was stirred under an atmosphere of argon for 120 hours after which time 72% consumption of azlactone was observed (determined by $^1$H NMR spectroscopy using $p$-iodoanisole as the internal standard). The reaction mixture was quenched with benzylamine (285, 41 µL, 0.375 mmol) and the mixture stirred for a further 1 h after which time the solvent was concentrated under reduced pressure and the residue purified via flash column chromatography.
Isopropyl 2-((1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (392)

Prepared according to general procedure VIII. Purified via flash column chromatography eluting in gradient from 100% CH₂Cl₂ to 100:1 CH₂Cl₂:EtOAc to 100:2.5 CH₂Cl₂:EtOAc to 100:10 CH₂Cl₂:EtOAc to isolate 392 as a white solid (29.8 mg, 20%). M.p. 195-197 °C.

δH (600 MHz, CDCl₃): 7.33-7.23 (8 H, m, H-6, H-8, H-11, H-12, H-13), 7.21 (2 H, app. d, H-7), 6.70 (1 H, br s, H-3), 6.24 (1 H, d, J 7.9, H-9), 4.99 (1 H, sept., J 6.3, H-2), 4.93 (1 H, dd, J 6.2, 6.8, H-4), 4.44 (2 H, d, J 5.8, H-10), 3.39 (1 H, dd, J 14.0, 6.2, H-5a), 3.21 (1 H, dd, J 14.0, 6.8, H-5b), 1.31 (3 H, d, J 6.3, H-1a), 1.27 (3 H, d, J 6.3, H-1b).

δC (100 MHz, CDCl₃): 169.4 (C=O), 164.5 (C=O), 163.3 (C=O), 137.9 (q), 136.0 (q), 135.4 (q), 135.3 (q), 134.6 (q), 132.6 (q), 130.6 (q), 130.3 (q), 129.5, 129.0, 128.5, 127.9, 127.4, 127.3, 71.8, 54.9, 43.7, 37.6, 21.5, 21.4.

υmax (neat)/cm⁻¹: 3302 (NH), 3212 (NH), 3064, 2931, 1733 (C=O), 1680 (C=O), 1635 (C=O), 1564, 1455, 1389, 1260, 1098, 931, 842, 741, 697.

HRMS (m/z - ESI): Found: 603.0394 (M+Na)⁺ C₂⁷H₂₄Cl₄N₂NaO₄ Requires: 603.0382.
**N-benzyl-3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propenamide (393)**

Prepared according to general procedure VIII. Purified via flash column chromatography eluting in gradient from 100% CH$_2$Cl$_2$ to 100:1 CH$_2$Cl$_2$:EtOAc to 100:2.5 CH$_2$Cl$_2$:EtOAc to 100:10 CH$_2$Cl$_2$:EtOAc to isolate 393 as a white solid (19.8 mg, 15%). M.p. 225-228 °C.

δ$_H$ (600 MHz, CDCl$_3$): 7.35 (2 H, app. t, H-9), 7.30 (1 H, app. d, H-10), 7.26-7.22 (4 H, m, H-4, H-8), 7.19 (3 H, app. t, H-3, H-5), 6.13 (1 H, br s, H-6), 5.18 (1 H, dd, J 9.9, 6.9, H-1), 4.48 (2 H, d, J 5.6, H-7), 3.63-3.54 (2 H, m, H-2a, H-2b).

δ$_C$ (100 MHz, CDCl$_3$): 167.3 (C=O), 163.3 (C=O), 140.5 (q), 137.4 (q), 136.0 (q), 129.9 (q), 129.0, 128.8, 128.6, 127.8, 127.7, 127.4, 127.1 (q), 56.1, 44.1, 34.8.

ν$_{max}$ (neat)/cm$^{-1}$: 3298 (NH), 2919, 1775, 1721 (C=O), 1651 (C=O), 1562, 1386, 1374, 1355, 1203, 1127, 1016, 936, 790, 739, 700, 633, 594.

HRMS ($m$/z - ESI): Found: 520.9974 (M+H)$^+$ C$_{24}$H$_{17}$Cl$_4$N$_2$O$_3$ Requires: 520.9988

**N-benzylbenzamide (394)**

Prepared according to general procedure VIII. Purified via flash column chromatography eluting in gradient from 100% CH$_2$Cl$_2$ to 100:1 CH$_2$Cl$_2$:EtOAc to 100:2.5 CH$_2$Cl$_2$:EtOAc to 100:10 CH$_2$Cl$_2$:EtOAc to isolate 394 as a white solid (25.8 mg, 49%). M.p. 104-106 °C (lit.,$^{19}$ M.p. 104-106 °C).

Spectral data for this compound were consistent with those in the literature.$^{220}$

δ$_H$ (400 MHz, CDCl$_3$): 7.82-7.74 (2 H, m, H-3), 7.52-7.19 (8 H, m, H-1, H-2, H-6, H-7, H-8), 6.37 (1 H, br s, H-4), 4.64 (2 H, d, J, 5.7, H-5).
3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioisoindolin-2-yl)propanoic acid (396)

Prepared according to general procedure VIII. The product was collected via filtration and the precipitate washed with CH₂Cl₂ (3 x 5 mL) to isolate 396 as a white solid (2.16 mg, 2%). M.p. 264-266 °C (lit.¹⁵⁶ M.p. 263-265 °C).

δ_{H} (400 MHz, CH₃OD): 7.26-7.08 (5 H, m, H-3, H-4, H-5), 5.07 (1 H, dd J 10.8, 3.6, H-1), 3.60 (1 H, dd, J, 13.7, 4.6, H-2a), 3.53 (1 H, app. t, H-2b).

* Protic signal (H-6) is not visible in CH₃OD.

General procedure IX: Thiolysis of azlactones via ring-opening by thiophenolate salts

To an oven-dried argon flushed 5 mL round-bottomed flask containing a magnetic stirring bar equipped with an argon-filled balloon and septum, 381 (47.5 mg, 0.10 mmol), p-iodoanisole (11.7 mg, 0.05 mmol), the appropriate thiophenol (0.10 mmol), the appropriate sodium thiophenolate (0.005 mmol) and TBAB (1.6 mg, 0.005 mmol) were added to the flask sequentially followed by the addition of THF (1.0 mL). The reaction mixture was stirred under an atmosphere of argon and monitored by ¹H NMR spectroscopy (using p-iodoanisole as the internal standard) until 100% consumption of azlactone was detected. The reaction mixture was concentrated under reduced pressure and the residue purified via flash column chromatography.
Isopropyl 2,3,4,5-tetrachloro-6-((1-oxo-3-phenyl-1-(phenylthio)propan-2-yl)carbamoyl)benzoate (406)

Prepared according to general procedure IX using 404 (0.7 mg, 0.005 mmol) and 405 (47.5 mg, 0.1 mmol). Purified via flash column chromatography (150:10 hexanes:EtOAc) to isolate 406 as a white solid (20.6 mg, 69%). M.p. 128-131 °C.

δ_H (400 MHz, CDCl_3): 7.46-7.38 (2 H, m, H-9), 7.38-7.31 (5 H, m, H-6, H-10, H-11), 7.30-7.24 (3 H, m, H-7, H-8), 6.38 (1 H, d, J 8.4, H-3), 5.30-5.16 (2 H, m, H-2, H-4), 3.29 (1 H, dd, J 13.7, 5.6, H-5a), 3.23 (1 H, dd, J 13.7, 6.8, H-5b), 1.34 (6 H, app. t, H-1).

δ_C (100 MHz, CDCl_3): 196.6 (C=O), 163.4 (C=O), 162.9 (C=O), 135.4 (q), 135.1 (q), 134.8 (q), 134.5, 133.6 (q), 133.1 (q), 130.2 (q), 129.9 (q), 129.8, 129.7, 129.4 (q), 128.8, 127.5, 126.4, 71.4, 59.9, 38.7, 21.5.

ν_max (neat)/cm⁻¹: 3289 (NH), 2977, 1737 (C=O), 1697 (C=O), 1644 (C=O), 1539, 1520, 1478, 1455, 1258, 1101, 887, 778, 699, 570.

HRMS (m/z - ESI): Found: 605.9836 (M+Na)^+ C_{26}H_{21}Cl_4NNaO_4S Requires: 605.9838.
**Isopropyl 2,3,4,5-tetrachloro-6-(1-((4-nitrophenyl)thio)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (410)**

Prepared according to general procedure IX using **404** (0.7 mg, 0.005 mmol) and p-nitrothiophenol (**407**, 15.7 mg, 0.1 mmol). Purified via flash column chromatography (eluting in gradient from 100% hexanes to 7:3 hexanes:EtOAc) to isolate **410** as a white solid (42.8 mg, 68%). M.p. 139-142 °C.

δ_H (600 MHz, CDCl3): 8.29 (2 H, d, J 8.6, H-10), 7.57 (2 H, d, J 8.6, H-9), 7.38 (2 H, app. t, H-6), 7.33 (1 H, app. t, H-8), 7.31-7.27 (2 H, m, H-7), 6.40 (1 H, d, J 7.8, H-3), 5.32-5.20 (2 H, m, H-2, H-4), 3.36 (1 H, dd, J 14.2, 6.3, H-5a), 3.26 (1 H, dd, J 14.2, 6.9, H-5b), 1.38 (6 H, dd, J 8.8, 6.4, H-1).

δ_C (100 MHz, CDCl3): 195.1 (C=O), 163.5 (C=O), 163.2 (C=O), 148.5 (q), 135.6 (q), 135.3 (q), 135.0 (q), 134.9, 134.4 (q), 133.3 (q), 133.2 (q), 130.3 (q), 129.8 (q), 129.5, 129.0, 127.8, 124.4, 71.5, 60.3, 38.3, 21.6, 21.5.

ν_max (neat)/cm⁻¹: 3272 (NH), 2892, 1730 (C=O), 1659 (C=O), 1522 (NO₂), 1343 (NO₂), 1262, 1201, 1099, 1013, 934, 897, 849, 701, 657, 557.

HRMS (m/z - ESI): Found: 650.9683 (M+Na)^+ C_{26}H_{20}Cl_{4}N_{2}NaO_{6}S Requires: 650.9688.
Synthesis of sodium salts for azlactone ring opening

**General procedure X: Synthesis of carboxylate sodium salts and phenolate-derived sodium salts**

To an oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar was charged NaH (1 equiv.). The NaH was washed with hexanes to remove any mineral oil, care was taken when carrying this out. After washing, the flask containing the NaH was fitted a septum and an argon-filled balloon. THF (0.2 M) was charged to the flask and the flask was cooled to 0 °C in a H2O/ice bath, after which the appropriate phenol (1 equiv.) was charged to the flask. The reaction mixture was stirred at room temperature for 1 h after which time MeOH (5 mL) was added to the flask at 0 °C. The reaction mixture was concentrated in vacuo and the resulting precipitate was triturated with hexanes (10 mL), CH₂Cl₂ (10 mL) and dried under high vacuum.

**Note:** These salts were stored under an atmosphere of argon in the freezer and compared to the parent carboxylic acid/phenol by ¹H NMR spectroscopy to ensure hydrolysis has not occurred prior to use.

**Sodium pivalate (398)**

\[
\text{CH}_3\text{COO}^- \quad \text{Na}^+ \\
\text{NaH} + \text{pivalic acid} \rightarrow \text{Sodium pivalate} \]

Prepared according to general procedure X using pivalic acid (400, 0.52 g, 5.1 mmol), NaH (0.21 g, 5.1 mmol) and THF (25.5 mL). Purified by trituration to isolate 398 as a white solid (0.47 g, 74%).

Spectral data for this compound were consistent with those in the literature.

\[\delta_H (400 \text{ MHz, DMSO-d}_6): \ 0.92 (9 \text{ H, s, H-1}).\]

HRMS (m/z - ESI): Found: 101.0606 (M-Na)^+ \text{C}_5\text{H}_9\text{O}_2 \text{Requires: 101.0608.}

**Sodium phenolate (412)**
Prepared according to general procedure X using phenol (411, 0.10 g, 1.1 mmol), NaH (0.04 g, 1.1 mmol) and THF (5 mL). Purified by trituration to isolate 412 as a white solid (0.11 g, 89%). M.p. 58-60 °C (lit., \textsuperscript{222} M.p. 57-60 °C).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{223}

\[ \delta_H (400 \text{ MHz, DMSO-d}_6): \quad 6.71-6.60 \ (2 \ H, \ m, \ H-1), \ 6.09-5.95 \ (2 \ H, \ m, \ H-2), \ 5.88-5.76 \ (1 \ H, \ m, \ H-3). \]

\textbf{Sodium p-nitrophenolate (414)}

Prepared according to general procedure X using p-nitrophenol (415, 0.14 g, 1.0 mmol), NaH (0.04 g, 1.0 mmol) and THF (5 mL). Purified by trituration to isolate 414 as a red solid (0.13 g, 83%).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{224}

\[ \delta_H (400 \text{ MHz, DMSO-d}_6): \quad 7.69 \ (2 \ H, \ d, \ J 9.5, \ H-2), \ 5.87 \ (2 \ H, \ d, \ J 9.5, \ H-1). \]

HRMS (m/z - ESI): Found: 138.0197 (M-Na)\(^+\) \text{C}_6\text{H}_4\text{NO}_3 \text{ Requires: } 138.0197.

\textbf{Sodium o-nitrophenolate (443)}

Prepared according to general procedure X using o-nitrophenol (445, 0.50 g, 3.6 mmol), NaH (0.14 g, 3.6 mmol) and THF (18 mL). Purified by trituration to isolate 443 as an orange solid (0.46 g, 79%). M.p. >250 °C.

\[ \delta_H (400 \text{ MHz, DMSO-d}_6): \quad 7.61 \ (1 \ H, \ d, \ J 8.6, \ H-1), \ 6.93-6.86 \ (1 \ H, \ m, \ H-3), \ 6.31 \ (1 \ H, \ d, \ J 8.8, \ H-4), \ 5.85 \ (1 \ H, \ app. \ t, \ H-2). \]

\[ \delta_C (100 \text{ MHz, DMSO-d}_6): \quad 169.3 \ (q), \ 135.6 \ (q), \ 133.9, \ 128.3, \ 126.6, \ 107.6. \]
\[ \nu_{\text{max}} \text{(neat)/cm}^{-1}: \quad 3091, 1615, 1543 \text{ (NO}_2\text{)}, 1513, 1421, 1378, 1332 \text{ (NO}_2\text{)}, 1236, 1215, 1074, 966, 742, 560. \]

HRMS (\(m/z\) - ESI): Found: 138.0195 (M-Na\(^+\)) \(\text{C}_6\text{H}_4\text{NO}_3\) Requires: 138.0197.

Sodium \(m\)-nitrophenolate (444)

\[
\begin{array}{c}
\text{O}^- \\
\text{Na}^+ \\
\end{array}
\]

Prepared according to general procedure X using \(m\)-nitrophenol (446, 0.25 g, 1.8 mmol), NaH (76.5 mg, 1.8 mmol) and THF (9 mL). Purified by trituration to isolate 443 as an orange solid (0.32 g, 75%). M.p. >250 °C.

\[ \delta_{\text{H}} \text{(400 MHz, DMSO-d}_6\text{)}: \quad 6.82 \text{ (1 H, app t, H-1)}, 6.64 \text{ (1 H, app. s, H-2)}, 6.60 \text{ (1 H, app. d, } J \text{ 7.6, H-3)}, 6.35 \text{ (1 H, app. d, H-4)}. \]

\[ \delta_{\text{C}} \text{(100 MHz, DMSO-d}_6\text{)}: \quad 149.5 \text{ (q)}, 128.6 \text{ (q), 126.6, 111.5, 102.0}. \]

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1}: \quad 3247, 1600, 1555, 1512 \text{ (NO}_2\text{)}, 1466, 1437, 1358 \text{ (NO}_2\text{)}, 1308, 1279, 1250, 1078, 991, 865, 736, 667. \]

HRMS (\(m/z\) - ESI): Found: 138.0193 (M-Na\(^+\)) \(\text{C}_6\text{H}_4\text{NO}_3\) Requires: 138.0197.

General procedure XI: Alcoholysis of azlactones \textit{via} ring-opening by sodium phenolate salts

To an oven-dried argon-flushed carousel tube containing a magnetic stirring bar was charged 381 (47.5 mg, 0.1 mmol), \(p\)-iodoanisole (11.7 mg, 0.05 mmol), the appropriate sodium phenolate salt (0.005 mmol), the appropriate phenol (0.1 mmol) and toluene (1 mL). For racemic reactions, TBAB (0.005 mmol) was charged to the flask prior to the addition of toluene. For asymmetric reactions, the appropriate catalyst (0.005 mmol) was charged to the flask prior to the addition of toluene. The reaction mixture was stirred under an atmosphere of argon, at room temperature. The reaction was monitored by \(^1\text{H} \text{NMR spectroscopy (using } p\text{-iodoanisole as the internal standard) until 100% consumption of 381 was observed in the }^1\text{H NMR spectrum of the reaction mixture. The reaction mixture was concentrated under reduced pressure and the residue purified \textit{via} flash column chromatography.}
Isopropyl 2,3,4,5-tetrachloro-6-((1-(4-nitrophenoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (417)

Prepared according to general procedure XI using 414 (0.8 mg, 0.005 mmol), TBAB (1.7 mg, 0.005 mmol) and 415 (14.0 mg, 0.1 mmol). Purified via flash column chromatography (eluting in 100:1 CH$_2$Cl$_2$:EtOAc) to isolate 417 as a white solid (8.3 mg, 14%). M.p. 122-125 °C.

$\delta_H$ (600 MHz, CDCl$_3$): 8.28 (2 H, d, $J$ 8.9, H-10), 7.38 (2 H, app. t, H-6), 7.36-7.31 (3 H, m, H-7, H-8), 7.18 (2 H, d, $J$ 8.9, H-9), 6.47 (1 H, d, $J$ 7.4, H-3), 5.30-5.21 (2 H, m, H-2, H-4), 3.43 (1 H, dd, $J$ 14.1, 5.9, H-5a), 3.34 (1 H, dd, $J$ 14.1, 6.9, H-5b), 1.36 (6 H, d, $J$ 6.2, H-1).

$\delta_C$ (100 MHz, CDCl$_3$): 168.5 (C=O), 163.6 (C=O), 163.1 (C=O), 154.7 (q), 154.6 (q), 135.7 (q), 135.3 (q), 134.7 (q), 133.4 (q), 133.2 (q), 130.3 (q), 129.8 (q), 129.4, 129.1, 127.8, 125.3, 122.2, 71.4, 54.1, 37.9, 21.5.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3302 (NH), 2988, 1776 (C=O), 1733 (C=O), 1655 (C=O), 1525 (NO$_2$), 1491, 1349 (NO$_2$), 1290, 1202, 1165, 1127, 991, 887, 776, 704, 650.

HRMS ($m/z$ - ESI): Found: 634.9911 (M+Na)$^+$ C$_{26}$H$_{26}$Cl$_4$N$_2$NaO$_7$ Requires: 634.9917.
4-nitrophenyl 3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (416)

Prepared according to general procedure XI using 414 (0.8 mg, 0.005 mmol), TBAB (1.7 mg, 0.005 mmol) and 415 (14.0 mg, 0.1 mmol). Purified via flash column chromatography eluting in 100:1 CH₂Cl₂:EtOAc to isolate 416 as a white solid (33.4 mg, 60%). M.p. 211-214 °C.

δ_H (600 MHz, CDCl₃): 8.31 (2 H, d, J 9.0, H-7), 7.32 (2 H, d, J 9.0, H-6), 7.30-7.27 (2 H, m, H-3), 7.23 (3 H, app. t, H-4, H-5), 5.45 (1 H, dd, J 11.1, 5.4, H-1), 3.74 (1 H, dd, J, 14.4, 5.4, H-2a), 3.59 (1 H, dd, J 14.4, 11.1, H-2b).

δ_C (100 MHz, CDCl₃): 166.3 (C=O), 162.6 (C=O), 154.8 (q), 145.9 (q), 140.8 (q), 135.4 (q), 130.1 (q), 128.9, 128.8, 127.5, 127.0 (q), 125.4, 122.4, 53.7, 34.7.

ν_max (neat)/cm⁻¹: 1765 (C=O), 1721 (C=O), 1594, 1521 (NO₂), 1455, 1392, 1355(NO₂), 1202, 1169, 1118, 941, 860, 741, 698, 552.


Isopropyl 2,3,4,5-tetrachloro-6-((1-(2-nitrophenoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (447)
Prepared according to general procedure XI using 443 (0.8 mg, 0.005 mmol), TBAB (1.7 mg, 0.005 mmol) and 445 (13.8 mg, 0.1 mmol). Purified via flash column chromatography (eluting in gradient from 100% hexanes to 7:3 hexanes:EtOAc) to isolate 447 as a colourless oil (39.9 mg, 65%).

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 8.11 (1 H, dd, J 8.2, 1.5, H-9), 7.66 (1 H, td, J 8.2, 1.5, H-10), 7.45 (1 H, app. t, H-11), 7.38-7.27 (5 H, m, H-6, H-7, H-8), 7.19 (1 H, dd, J 8.2, 1.5, H-12), 6.39 (1 H, d, J 7.4, H-3), 5.27 (1 H, td, J 7.4, 5.4, H-4), 5.15 (1 H, app. sept., H-2), 3.53 (1 H, dd, J 14.6, 5.4, H-5a), 3.34 (1 H, dd, J 14.6, 7.4, H-5b), 1.30 (6 H, app. t, H-1).

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 168.4 (C=O), 163.4 (C=O), 163.1 (C=O), 143.5 (q), 141.6 (q), 135.4 (q), 135.3 (q), 135.2 (q), 134.9, 133.4 (q), 133.2 (q), 130.1 (q), 130.0 (q), 129.4, 128.9, 127.5, 127.1, 126.0, 125.1, 71.9, 54.1, 37.2, 21.5.

ν\textsubscript{max} (neat)/cm\textsuperscript{-1}: 3295 (NH), 2926, 1774 (C=O), 1732 (C=O), 1655 (C=O), 1530 (NO\textsubscript{2}), 1348 (NO\textsubscript{2}), 1262, 1135, 1093, 931, 897, 734, 699, 590, 557.

HRMS (m/z - ESI): Found: 634.9923 (M+Na)\textsuperscript{+} C\textsubscript{26}H\textsubscript{20}Cl\textsubscript{4}N\textsubscript{2}O\textsubscript{7} Requires: 643.9917.

**Isopropyl 2,3,4,5-tetrachloro-6-((1-(3-nitrophenoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (448)**

![Chemical structure](image)

Prepared according to general procedure XI using 444 (0.8 mg, 0.005 mmol), TBAB (1.7 mg, 0.005 mmol) and 446 (14.0 mg, 0.1 mmol). Purified via flash column chromatography
(eluting in gradient from 9:1 hexanes:EtOAc to 8:2 hexanes:EtOAc) to isolate 448 as a pale yellow oil (36.5 mg, 59%).

$$\delta_H (400 \text{ MHz}, \text{CDCl}_3):$$
8.15 (1 H, ddd, J 8.1, 2.1, 0.9, H-10), 7.86 (1 H, app. t, H-9), 7.58 (1 H, app. t, H-11), 7.44-7.32 (6 H, m, H-6, H-7, H-8, H-12), 6.47 (1 H, d, J 7.6, H-3), 5.33-5.22 (2 H, m, H-2, H-4), 3.45 (1 H, dd, J 14.0, 6.7, H-5a), 3.32 (1 H, dd, J 14.0, 7.6, H-5b), 1.38 (6 H, d, J 6.3, H-1).

$$\delta_C (100 \text{ MHz}, \text{CDCl}_3):$$
168.8 (C=O), 163.6 (C=O), 163.1 (C=O), 150.3 (q), 148.8 (q), 135.6 (q), 135.3 (q), 134.7 (q), 133.5 (q), 133.2 (q), 130.2, 129.8 (q), 129.7 (q), 129.4, 129.1, 127.9, 127.7, 121.3, 117.2, 71.5, 54.0, 38.0, 21.5.

$$\nu_{\text{max}} \text{(neat)/cm}^{-1}:$$
3286 (NH), 2926, 1772 (C=O), 1726 (C=O), 1654 (C=O), 1529 (NO$_2$), 1498, 1350 (NO$_2$), 1261, 1203, 1145, 1095, 898, 733, 665, 565.

HRMS ($m/z$ - ESI):
Found: 613.0105 (M+H)$^+$  C$_{26}$H$_{21}$Cl$_4$N$_2$O$_7$  Requires: 613.0097.

3-nitrophenyl 3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (462)

Prepared according to general procedure XI using 444 (0.8 mg, 0.005 mmol). TBAB (1.7 mg, 0.005 mmol) and 446 (14.0 mg, 0.1 mmol). Purified via flash column chromatography (eluting in gradient from 9:1 hexanes:EtOAc to 8:2 hexanes:EtOAc) to isolate 462 as a white solid (4.4 mg, 8%). M.p. 210-213 °C.

$$\delta_H (400 \text{ MHz}, \text{CDCl}_3):$$
8.18 (1 H, ddd, J 8.3, 2.1, 1.1, H-7), 8.03 (1 H, app. t, H-6), 7.62 (1 H, app. t, H-8), 7.52 (1 H, ddd, J 8.3, 2.1, 1.1, H-9), 7.32-7.27 (2 H, m, H-3), 7.26-7.21 (3 H, m, H-4, H-5), 5.46 (1

$\delta_c$ (100 MHz, CDCl$_3$): 166.6 (C=O), 162.6 (C=O), 150.5 (q), 148.9 (q), 140.8 (q), 135.4 (q), 130.3, 130.1 (q), 128.9, 128.8, 127.9, 127.5, 127.0 (q), 121.4, 117.2, 53.7, 34.7.

$\nu_{max}$ (neat)/cm$^{-1}$: 3081, 2923, 2853, 1790 (C=O), 1772 (C=O), 1722 (C=O), 1533 (NO$_2$), 1457, 1351 (NO$_2$), 1278, 1197, 1003, 946, 801, 738, 628, 553.


**General procedure XII: Aminolysis of azlactones via ring-opening by phenolate sodium salts**

To an oven-dried carousel tube containing a magnetic stirring bar was charged with 381 (47.5 mg, 0.1 mmol), $p$-iodoanisole (11.7 mg, 0.05 mmol), the appropriate phenolate sodium salt (0.005 mmol), the appropriate phenol (0.1 mmol) and toluene (1 mL). For racemic reactions, TBAB (0.005 mmol) was charged to the flask prior to the addition of toluene. For asymmetric reactions, the appropriate catalyst (0.005 mmol) was charged to the flask prior to the addition of toluene. The reaction mixture was stirred under an atmosphere of argon at room temperature. The reaction was monitored by $^1$H NMR spectroscopy (using $p$-iodoanisole as the internal standard) until 100% conversion of azlactone 381 to the corresponding phenolic ester was observed in the $^1$H NMR spectrum of the crude reaction mixture. At 100% conversion, THF (1 mL) was charged to the reaction vessel and the solution stirred at room temperature for 15 minutes. After this time the appropriate amine (1 mmol) was charged to the reaction flask and the amine quench was monitored by $^1$H NMR spectroscopy. The reaction mixture was concentrated under reduced pressure and the residue obtained was purified via flash column chromatography.
N-benzyl-3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxiisoindolin-2-yl)propenamide (393)

Prepared according to general procedure XII using 414 (0.8 mg, 0.005 mmol), catalyst 429 (3.1 mg, 0.005 mmol), 415 (13.8 mg, 0.1 mmol) and quenched with 285 (11 µL, 0.1 mmol). Purified via flash column chromatography eluting in gradient from 10:1 hexanes:EtOAc to 6:4 hexanes:EtOAc isolate 393 as a white solid (44.8 mg, 89%, 20% ee). M.p. 225-228 °C.

CSP-HPLC analysis. Acquity UPC2 step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 4.868 min (major enantiomer) and 5.494 min (minor enantiomer).

δH (600 MHz, CDCl₃): 7.35 (2 H, app. t, H-9), 7.30 (1 H, app. d, H-10), 7.26-7.22 (4 H, m, H-4, H-8), 7.19 (3 H, app. t, H-3, H-5), 6.13 (1 H, br s, H-6), 5.18 (1 H, dd, J 9.9, 6.9, H-1), 4.48 (2 H, d, J 5.6, H-7), 3.63-3.54 (2 H, m, H-2a, H-2b).

δC (100 MHz, CDCl₃): 167.3 (C=O), 163.3 (C=O), 140.5 (q), 137.4 (q), 136.0 (q), 129.9 (q), 129.0, 128.8, 128.6, 127.8, 127.7, 127.4, 127.1 (q), 56.1, 44.1, 34.8.

νmax (neat)/cm⁻¹: 3298 (NH), 2919, 1775, 1721 (C=O), 1651 (C=O), 1562, 1386, 1374, 1355, 1203, 1127, 1016, 936, 790, 739, 700, 633, 594.

HRMS (m/z - ESI): Found: 520.9974 (M+H)+ C₂₄H₁₇Cl₄N₂O₃ Requires: 520.9988

Methyl-(3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxiisoindolin-2-yl)propanoyl)alaninate (451)
Prepared according to general procedure XII using 414 (0.9 mg, 0.005 mmol), catalyst 429 (3.0 mg, 0.005 mmol), 415 (13.8 mg, 0.1 mmol) and quenched with L-alanine methyl ester (450, 11.5 µL, 0.1 mmol) at -10 °C. Purified via flash column chromatography (eluting in gradient from 100:2 CH₂Cl₂:EtOAc to 100:10 CH₂Cl₂:EtOAc) to isolate 451 as a white solid (0.338 g, 65%). M.p. 165-168 °C.

δH (600 MHz, CDCl3): 7.27 (2 H, app. t, H-3), 7.22 (3 H, app. d, H-4, H-5), 6.59 (1 H, d, J 6.6, H-6), 5.18 (1 H, app. t, H-1), 4.61 (1 H, q, J 6.8, H-7), 3.78 (3 H, s, H-9), 5.81 (2 H, app. d, H-2), 1.43 (3 H, app. t, H-8).

δC (100 MHz, CDCl3): 173.0 (C=O), 167.1 (C=O), 163.2 (C=O), 140.4 (q), 135.9 (q), 129.9 (q), 129.0, 128.8, 127.4, 127.0 (q), 55.8, 52.7, 48.7, 34.7, 18.2.

νmax (neat)/cm⁻¹: 3322 (NH), 2953, 1779 (C=O), 1754 (C=O), 1722 (C=O), 1670, 1647 (C=O), 1515, 1492, 1384, 1195, 1001, 953, 853, 795, 652.

HRMS (m/z - APCI): Found: 516.9887 (M+H)⁺ C₂₁H₁₇Cl₄N₂O₅ Requires: 516.9886.

Methyl-L-phenylalanyl-L-alaninate (452)

To an oven-dried 5 mL round-bottomed flask equipped with a magnetic stirring bar, was charged methyl-(3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoyl)alaninate (451, 45.9 mg, 0.0886 mmol) followed by THF (0.9 mL). The reaction flask was cooled to 0 °C in a H₂O/ice bath and ethylenediamine (12 µL, 0.177 mmol) was charged to the flask dropwise. The reaction was warmed to room temperature over 1 hour after which the reaction mixture was concentrated and the resulting residue purified via flash column chromatography (eluting in 95:5 CH₂Cl₂:MeOH) isolate 452 as a white solid (12.8 mg, 58%, 60:40 d.r.). M.p. >250 °C (lit.,198 M.p. >250 °C).

Spectral data for this compound were consistent with those in the literature.198
\[ \delta_H (400 \text{ MHz}, \text{CD}_3\text{OH}): \quad 7.30-7.24 \text{ (2 H, m, H-1), 7.24-7.16 (3 H, m, H-2, H-3), 4.40 (1} \\
\text{H, q, J 7.3, H-8), 3.67 (3 H, s, H-10), 3.61-3.53 (1 H, m, H-5),} \\
\text{3.04 (1 H, dd, J 13.6, 5.6, H-4a), 2.89-2.73 (1 H, m, H-4b), 0.96} \\
\text{(3 H, d, J 7.3, H-9).} \\
\]

* The protic signals H-6 and H-7 are not visible in \text{CD}_3\text{OH}.
5. References


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A new strategy for the protection of amines has been developed involving reaction with pyridil under the influence of N-heterocyclic carbene catalysis. The methodology is capable of distinguishing between two amines characterised by small differences in steric bulk and the resulting pyridoyl amides can be cleaved without requiring either strongly acidic or basic hydrolysis.

The wide utility of amide bonds continues to inspire chemists to develop new and unconventional methods for their synthesis. We recently developed an N-heterocyclic carbene (NHC)-catalysed oxidative amidation of aldehydes, which allows the coupling of benzaldehydes with a range of primary and secondary amines in the presence of precatalyst, stoichiometric DBU and phenazine to produce amides in good to excellent yields at ambient temperature. We could show that the reaction proceeded through symmetrical 1,2-diketones of general type (Fig. 1A). In addition, in the absence of the 1,2,4-triazole nucleophilic co-catalyst, it was postulated that amidation occurred via the sterically hindered pre-transition state assembly.

The steric congestion associated with (see the ESI for a mechanistic rationale) led us to speculate that the system could potentially be adapted to bring about highly chemoselective amine acylation with a view to developing a new, sterically sensitive strategy for the protection of the least hindered amino functionality in a molecule. Despite impressive advances in protection–free synthesis, the temporary masking of amine (Lewis)-basicity and nucleophilicity via a variety of methods usually remains a sine qua non in the synthesis of complex molecules.

While the selective acylation of primary over secondary amines in polynamines is often possible, and the exploitation of biomolecules to achieve high selectivity has been reported, the use of a small molecule to discriminate between two amines when the steric discrepancy between amino groups is exceedingly small has been considerably less successful.

The state-of-the-art in this domain is the recent comprehensive study of the use of as an acylating agent by Doyle et al. (Fig. 1B). The heterocycle could transfer a single benzoyl group with consistently (and uniformly) outstanding selectivity to a range of polynamines: for instance – diamine could be transformed into the monobenzoyl-protected in excellent yield; driven by the formation of an aromatic conjugate base of the leaving group. While the selectivity possible is akin to that which one would expect from biocatalysis – the harsh acidic/basic conditions required to cleave N-benzoyl amides and the non-trivial synthesis of from simple starting materials are two obstacles to the adoption of this technology as a protection group strategy in complex molecule synthesis.

Herein we report the development of an NHC-catalysed highly chemoselective acylation of amines and challenging diamines...
(e.g. 13) using pyridil (12) as a commercially available unconventional acylating agent to give products such as 14 in excellent yield (Fig. 1C). Significantly, we show that the pyridoyl-unit is demonstrably cleavable without resorting to either strongly acidic or basic aqueous conditions.

We began by examining the ability of pyridil (12) to acylate a range of amines of general type 2 under the influence of carbene catalysis (in the absence of catalyst, no reaction occurs) in the presence of phenazine (4) to generate product amides 15–26 (Table 1). Simple primary benzyl-, allyl- and propargyl amines could be acylated in good-excellent yields to yield pyridine derivatives 15–18 respectively. Substitution at the β-carbon of a primary amine is well tolerated (i.e. amide 19), however, while acylation of primary amines substituted at the α-carbon atom is possible in good yield (i.e. products 20 and 21), these are clearly more difficult substrates for the system – pointing to the possibility of being able to discriminate between these groups in acylation events.

The cyclic secondary amine pyrrolidine and piperidine could be smoothly transformed to 22 and 23, however, the installation of an electron-withdrawing group on the piperidine-ring led to significantly decreased efficacy (i.e. amide 24). More sterically encumbered secondary amines such as dipropylamine and N-methylbenzylamine gave rise to 25 and 26 respectively in moderate yield.

Next, a small library of diamines was selected to further probe the acylation proclivities of the system and its ability to discriminate between amino groups in different steric environments (Table 2).

The acylation of diamine 29 – which incorporates both a primary amine and a cyclic secondary amino unit – with 12 proceeded chemoselectively to afford 30 in excellent yield (entry 1). Since the piperidine amine is sterically encumbered by the chain at the 2-position, the acylation of 31 was next examined. Here the competition is between a primary and a secondary amine differing only by one N-methyl substituent. Gratifyingly, acylation occurred exclusively at the less hindered site to furnish 32 in near quantitative yield (entry 2). In a similar vein, the system is capable of selecting between two primary amines distinguished only by an α-methyl group at carbon (i.e. 8) to product 33 in 98% yield (entry 3).

None of the reactions outlined above produced bis-acylated products. To provide a significant challenge in this context; we examined the monoacylation of diamine 34 (an important molecule in asymmetric catalysis); which is notoriously difficult to monoacylate chemoselectively without using excess amine. Under NHC catalysis the reaction formed the monoacetyl product 35 in reduced yet appreciable yield; with the remainder bis-acetylated material (entry 4).

The methodology can also act upon steric variations between two different secondary amines. For instance, the preference for efficient reaction at the N-Me group associated with diamine 36 over its N-iPr counterpart is clear (entry 5). More strikingly, complete N-Me vs. N-Et selectivity is possible under these conditions – affording amide 38 from amine 13 in 98% yield (entry 6). We are not aware of another small molecule-based system capable of such discriminatory ability in the acylation of secondary amines in the literature.

To put these results in context: in our hands the acylation of either 29, 31 or 33 by either one equivalent of benzoyl chloride (1.0 eq.) or (Boc)₂O (1.0 eq.) in either THF or CH₂Cl₂ (0.1 M) in the presence of NEt₃ at temperatures from ambient to −78 °C provided only bis-acylated products and starting materials. No monoacetyl compounds were formed.

We considered that intramolecular hydrogen bonding may be an actor in the experiments summarised in Table 2. Accordingly, we carried out the competition experiments outlined in Scheme 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₂H₂N₂</td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>N₂H₂N₂</td>
<td>31</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>N₂H₂N₂</td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>N₂H₂N₂</td>
<td>35</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>N₂H₂N₂</td>
<td>33</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>N₂H₂N₂</td>
<td>36</td>
<td>98</td>
</tr>
</tbody>
</table>

* Isolated yield. a 0.5 eq. of 12 utilised.

Table 1 Influence of amine structure on NHC-catalysed acylation by pyridil

Table 2 Chemoselective acylation of diamines
When pyridil was offered a choice between benzylamine (39) and equimolar loadings of its N-methyl analogue 40, 15 was the sole amide detected and isolated (Scheme 1A). Similarly, competition for acylation between 39 and its α-methyl variant 41 resulted in the smooth and exclusive formation of 15 and the complete absence of the more hindered product 21 (Scheme 1B). Thus it would appear that the ability of the system to acylate the least hindered N-atom in a diamine is related to steric sensitivity and not the formation of intramolecular hydrogen bonds between the termini of either the substrates or products.

While dramatic levels of chemoselectivity are possible, for the system to be considered of potential utility relative to (for example) benzoylation, the amide must be cleavable under milder conditions. After considerable experimentation, a suite of conditions were developed under which any amide generated for the system to be considered of potential utility relative to the substrates or products.

For a small molecule-based system: an amine, the reaction is unprecedentedly sterically discerning group are sufficient for total control. In the case of secondary amines in a diamine – always reacting at the least hindered N-atom. Thus, in general, primary amines can be acylated in preference to secondary analogues (even when the steric difference derives from a methyl group), while two primary amines can be distinguished based on substituents at the adjacent C-atom (again, discrepancies as small as a methyl group are sufficient for total control). In the case of secondary amines, the reaction is unprecedentedly sterically discerning for a small molecule-based system: an N-Me group can be exclusively acylated in the presence of an N-Et unit.

Competition experiments demonstrated that the origin of this selectivity is not ascribable to intramolecular hydrogen bonding between the amines. Novel methods were developed which allow the resulting monoacylated pyridoyl amides to be cleaved without requiring the harsh acidic and basic hydrolytic conditions associated with benzoyl protection of aliphatic amines; thereby allowing the methodology to potentially serve as a highly chemoselective protection group strategy for amino groups.

We are grateful to Science Foundation Ireland and the Solid State Pharmaceutical Centre (12/RC/2275) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references


Scheme 1 Influence of N- and C-substitution on competition experiments.

Scheme 2 Pyridoyl-amide cleavage.


17 The process is mechanistically complex (see ref. 3, 6 and 7). Phenazine aids in the *in situ* conversion of pyridoin (a by-product of the acylation event) back to pyridil. The phenazine is reoxidized by air upon workup and be recovered and reused if desired.

18 The lower yield of 16 and 18 may be related to the volatility of allyl amine (b.p. 54 °C) and propargyl amine (b.p. 83 °C) at STP; since the solid cinnamylamine produced 17 in near quantitative yield.


21 Doyle et al. (ref. 14) were able to benzoylate this substrate with an impressive 98% isolated yield.