

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
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January 2020

Declaration

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A. C. Maguire, V. Kumar, S.J. Connon, *Chem Commun.*, 2019, **55**, 13526.

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Acknowledgements

First and foremost, I would like to thank my supervisor Prof. Stephen Connon. His enthusiasm and encouragement made it easy to keep persevering, even when the challenges of completing a PhD seemed so daunting. And his fervour for caramel squares never failed to make me laugh!

A massive thank you to my parents that have stood by me with endless support over the past eight years that I have spent in college. To my mum Suzanne: all those early morning chats on the way to the lab were invaluable, especially in getting me through this final stretch. To my dad Dermot for always coming to the rescue when money was scarce. To my (favourite) aunt Mairead for always looking out for me. To my brother Stephen for continuously being there to make jokes at my expense! And a very special mention to my grandad Johnny who sadly passed away before he got a chance to see me finish my PhD, he meant the world to me and I know how proud he was of me.

To all my friends that have been there throughout my PhD, particularly Tommy and Kevin, the best pals a girl could have. Your endless enthusiasm for pints and chats has kept me going throughout this PhD. And a very special thank you to my boyfriend Graeme for his unwavering support and patience with me.

I would like to thank all the members of the Connon group, past and present, for making the lab an enjoyable place to work. A huge thank you to my OG and desk buddy Ryan for the endless cups of tea and hummus breaks. To the unofficial Connon group member, Ruairi for keeping me busy searching for raisin boxes throughout every inch of the lab and office! The biggest thank you goes to Ciara who started this whole process out with me and who has been such a good friend for the past four years (and never judged how much chocolate I consumed daily).

An enormous thank you goes to my expert correctors Michelle and Simon. I'm so grateful for all the pages you two trawled through, with little or no bribery and for also being great friends to have.

Lastly a massive thank you to the TCD School of Chemistry staff, in particular Dr John O'Brien and Dr Manuel Ruether for their expert NMR analysis. And to Dr Gary Hessman for running all those pesky mass specs.

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

Ac	Acetyl
AcOH	Acetic acid
APCI	Atmospheric-pressure chemical ionization
app. d	Apparent doublet
app. s	Apparent singlet
app. t	Apparent triplet
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
b.p.	Boiling point
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
bs	Broad singlet
CAN	Ceric(IV) ammonium nitrate
cat.	Catalyst
CI	Chemical ionisation
conc.	Concentrated
conv.	Conversion
CSA	Camphorsulfonic acid
CSP	Chiral stationary phase
d	Days
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -Diisopropylethylamine
DKR	Dynamic kinetic resolution
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide

DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
EDC	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
EDG	Electron donating group
<i>ee</i>	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-Hexafluoroisopropyl 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>i</i> -	<i>iso</i> -
IPA	<i>iso</i> -propyl alcohol
<i>i</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

<i>m</i> -	<i>meta</i> -
MAO	Monoamine oxidases
m.p.	Melting point
<i>m/z</i>	Mass/Charge
Me	Methyl
MeOH	Methanol
min	Minutes
mol. sieves	Molecular sieves
MTBE	Methyl- <i>tert</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
NCL	Native chemical ligation
NCS	<i>N</i> -chlorosuccinimide
NDMBA	<i>N,N'</i> -dimethylbarbituric acid
NEt ₃	Triethylamine
NHC	<i>N</i> -heterocyclic carbene
NMA	<i>N</i> -methylacetamide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
<i>o</i> -	<i>ortho</i> -
OAc	Acetate
<i>p</i> -	<i>para</i> -
Ph	Phenyl
PMP	<i>p</i> -methoxyphenyl
PTC	Phase-transfer catalyst
Pr	Propyl
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid
q	Quartet
rt	Room temperature
s	Singlet
s.t.p.	Standard temperature and pressure
t	Triplet
<i>t</i> -	<i>tert</i> -

TBAF	Tetra- <i>n</i> -butyl ammonium fluoride
TBAB	Tetra- <i>n</i> -butyl ammonium bromide
TBACl	Tetra- <i>n</i> -butyl ammonium chloride
TBAOAc	Tetra- <i>n</i> -butyl ammonium acetate
TBAOBz	Tetra- <i>n</i> -butyl ammonium benzoate
<i>t</i> -Bu	<i>tert</i> -Butyl
<i>t</i> -BuOH	<i>tert</i> -Butyl alcohol
TBS	<i>tert</i> -Butyldimethylsilyl
TCIC	Tetrachloroisopropoxycarbonyl
TCP	<i>N</i> -tetrachlorophthaloyl
temp.	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
<i>tert</i> -	<i>tertiary</i> -
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet

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 $R_2C:$. 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 ($H_2C:$) from its then believed hydrated complex, methanol ($CH_2 \cdot H_2O$) 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 ($Cl_2C:$) through the base-catalysed α -elimination of HCl from chloroform (or as Guether viewed it at the time, $CCl_2 \cdot HCl$).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 sp^2 -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 sp^2 -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.

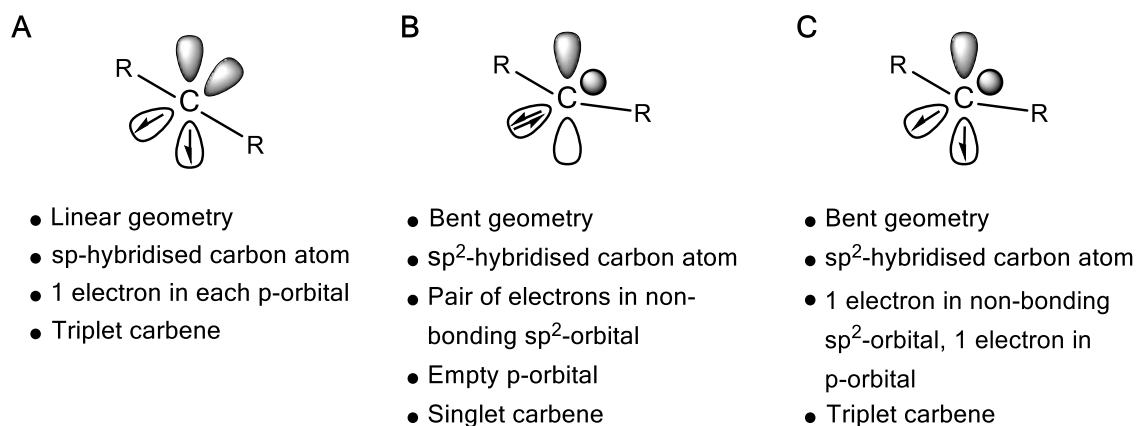


Figure 1 Orbital depiction of carbenes with linear and bent geometries

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 ($130\text{--}150^\circ$) 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 ($100\text{--}110^\circ$).³

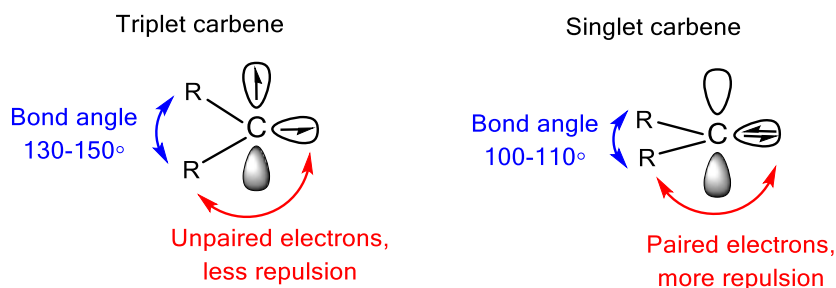


Figure 2 Effect of electronic repulsions on bond angles of carbene substituents

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.^{12–14} 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.⁹ 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).

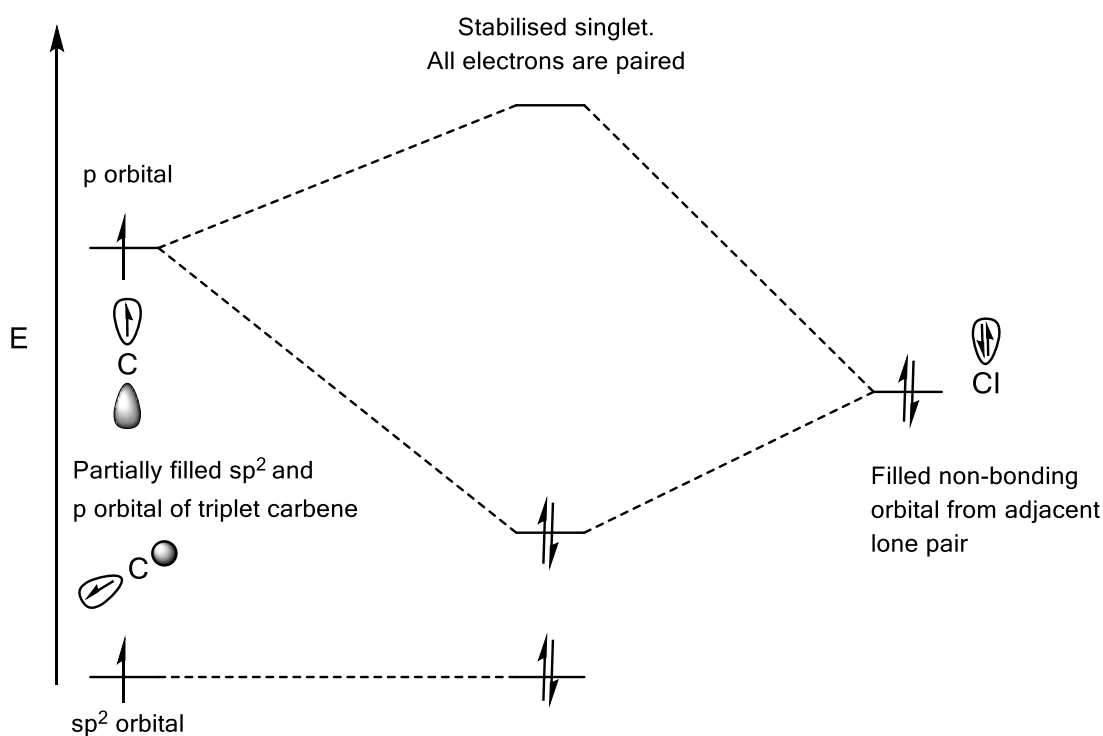


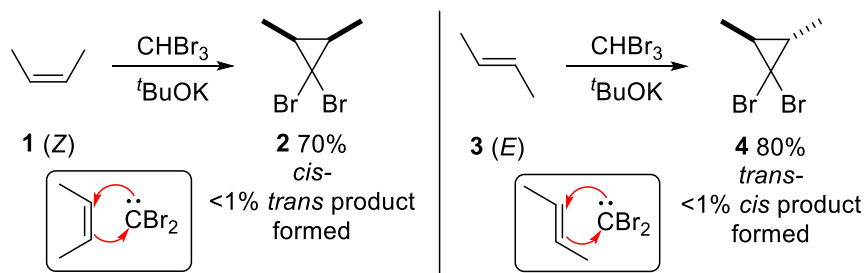
Figure 3 Stabilisation of a singlet carbene by lone pairs on adjacent substituents

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.

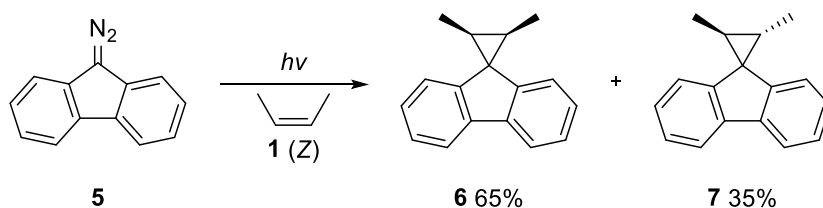
Perhaps one of the most common uses of carbenes, and also one of the most common methods of synthesising cyclopropanes, is the reaction between a carbene and an alkene.³

The spin-state of the carbene used in the cyclopropanation reaction determines the stereochemical outcome of the product.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**.¹⁵



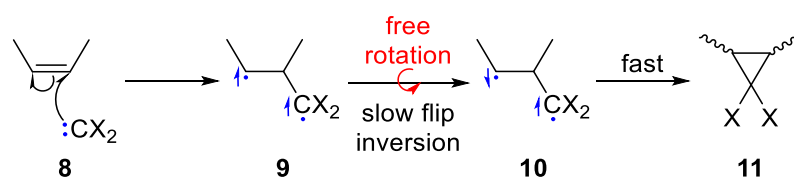
Scheme 1 Stereochemical outcome of cyclopropanations involving singlet carbenes

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).¹⁶



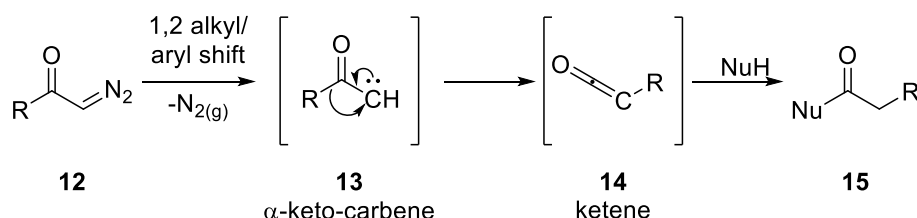
Scheme 2 Stereochemical outcome of cyclopropanations using triplet carbenes

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).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.



Scheme 3 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.¹⁷ This methodology has been used in the synthesis of natural products such as the work by Lee *et al.* to make the antibiotic platensimycin¹⁸ and by Cane and co-workers to produce pentalenolactone.¹⁹ Another frequent use of carbenes are in rearrangement reactions, perhaps the most notable of these being the Wolff rearrangement.²⁰ In this carbene rearrangement, an α -diazocarbonyl **12** undergoes decomposition by elimination of nitrogen gas to form an α -keto-carbene intermediate **13** (Scheme 4). This intermediate undergoes a rapid [1,2]-alkyl/aryl shift to produce ketene **14**, which can be hydrolysed to form carboxylic acids or intercepted with nucleophiles such as amines and alcohols to give amide or ester products **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 1835.²¹ Work by Wanzlick^{22–26} in the 1960s, Bertrand^{27,28} in the 1980s and Arduengo²⁹ in the 1990s have resulted in the synthesis of an array of persistent carbenes (Figure 4).

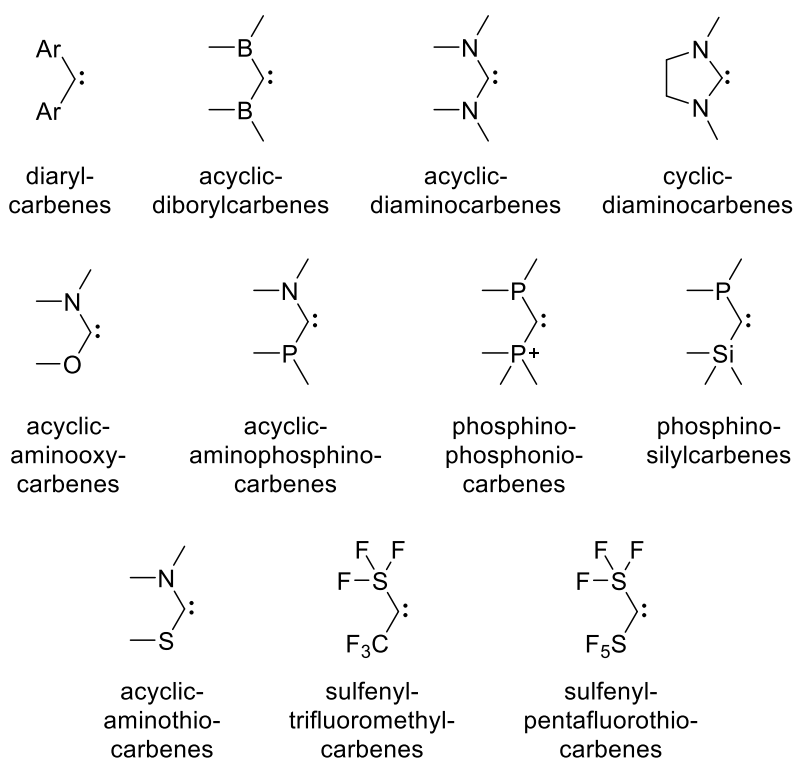


Figure 4 A selection of common B, N, O, Si, P and S-containing carbenes

While Bertrand *et al.* reported the first isolatable carbene stabilised by favourable interactions with adjacent phosphorus and silicon substituents in 1988,²⁷ Arduengo and co-workers were the first to isolate a stable crystalline carbene: 1,3-di-1-adamantyl-imidazol-2-ylidene (**16**, IAd). This discovery was spearheaded by earlier insightful studies by Öfele³⁰ and Wanzlick²⁶ into metal-carbene complexes.

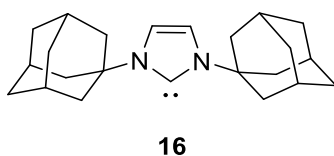


Figure 5 IAd, the first stable crystalline carbene isolated by Arduengo *et al.*

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.⁹ In contrast to most ‘classical’ carbenes, NHCs have a singlet ground state electronic configuration.³¹ The inherent cyclic

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

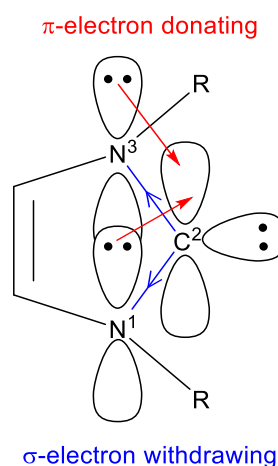
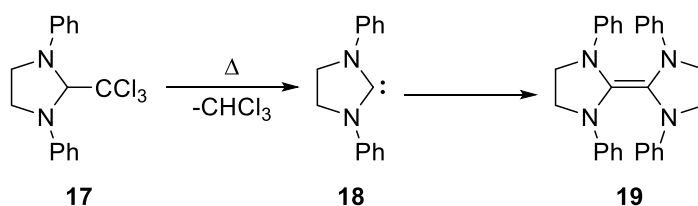


Figure 6 Schematic depiction of the ‘push-pull’ effect observed in NHCs

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.

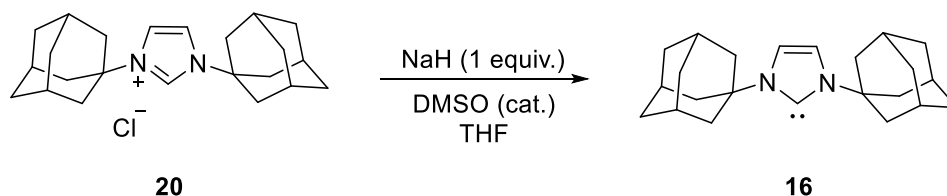
1.2.1 Historical perspective

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.^{22–26} In 1960, Wanzlick and Schikora attempted to isolate a carbene from imidazolidine **17** via thermal elimination of chloroform to form 1,3-diphenylimidazolidin-2-ylidene (**18**, Scheme 5).²³ Carbene **18** was not isolated as it was found to dimerise to form **19** due to its inherent reactive nature.



Scheme 5 Attempts by Wanzlick to isolate carbene **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, **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).

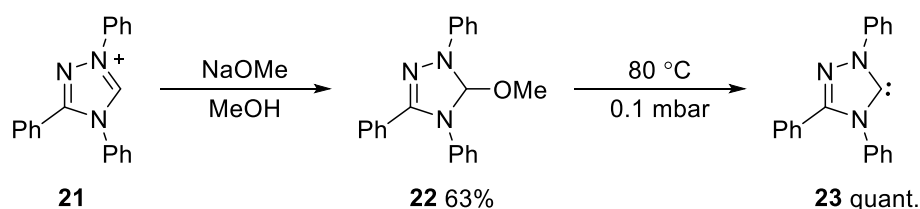


Scheme 6 Preparation of the first stabilised carbene by Arduengo *et al.*

Prepared via deprotonation of salt **20** by sodium hydride to carbene **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 **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 (**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-1*H*-1,2,4-triazol-5-ium perchlorate (**21**, Scheme 7) underwent reaction with sodium methoxide to produce adduct **22** which when heated to 80 °C undergoes thermal decomposition to produce triazolylidene carbene **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.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^{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.

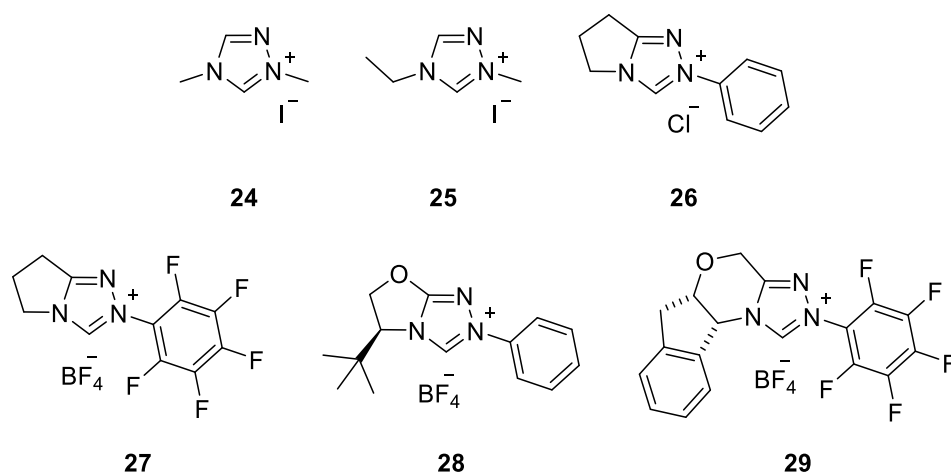


Figure 7 A selection of triazolium precatalysts currently used in the field

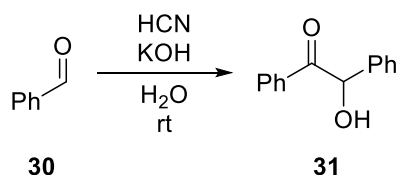
1.3 N-Heterocyclic carbenes and the Benzoin condensation

The use of NHCs as ligands for metal-based catalysis is well studied,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 1943,³⁶ following reports by Arduengo and Enders in the 1990s, there has been much research conducted in this area.^{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 ‘*umpolung* reaction’.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 1832.⁴⁷ 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).

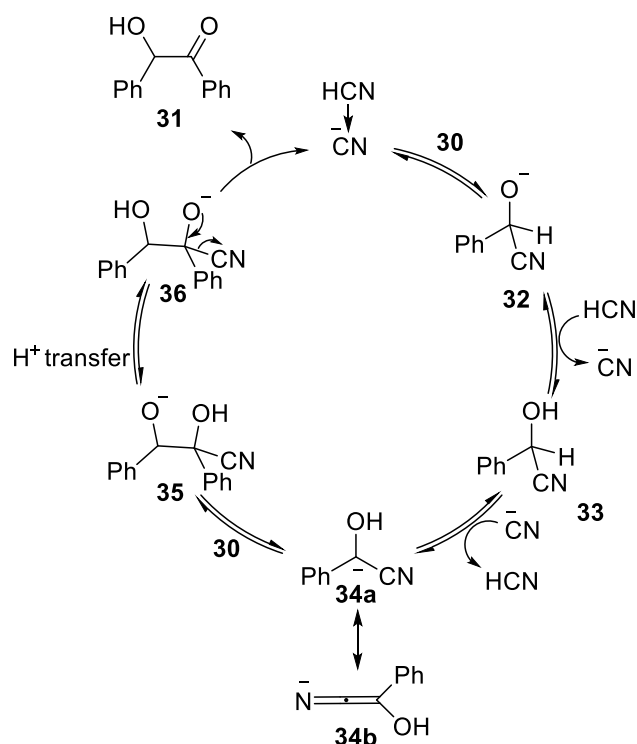


Scheme 8 The first benzoin condensation carried out by Liebig and Wöhler

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

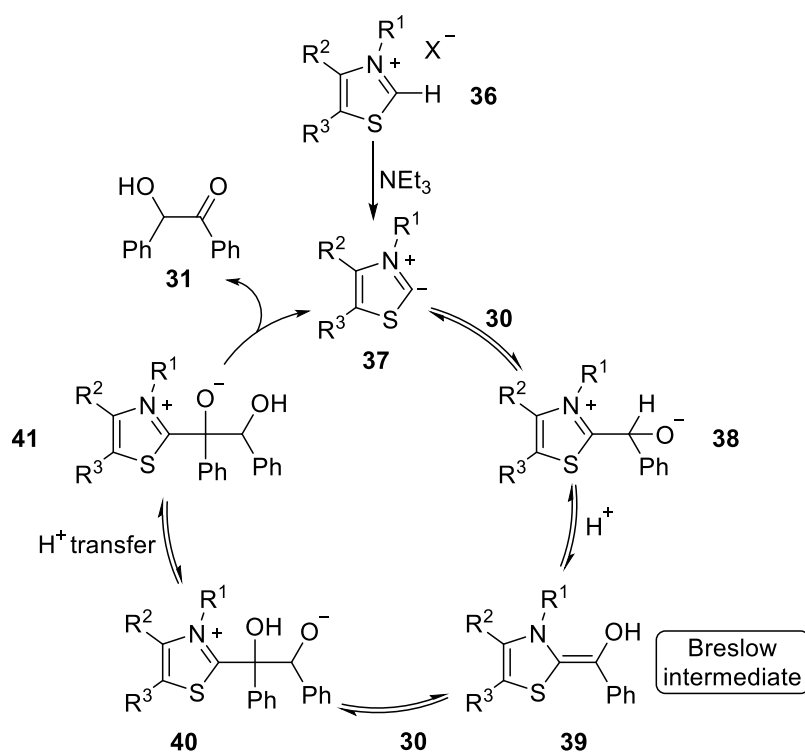
In 1839, Zinin^{49,50} introduced the first cyanide-mediated catalytic benzoin condensation, however it was in 1904 that Lapworth proposed a possible reaction mechanism (Scheme 9).⁴⁸ In Lapworth's proposed mechanism, the first step in the reaction is a nucleophilic attack of a cyanide ion on **30** to form oxyanion **32**.⁴⁸ 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.



Scheme 9 Lapworth's proposed reaction mechanism for the cyanide-mediated benzoin condensation

In 1943, Ugai discovered that thiazolium salts can replace the cyanide ion in the self-condensation of **30** to **31**.³⁶ However, Breslow was the first to investigate this process and establish a mechanism in 1958 (Scheme 10).⁵¹ Similar to the role of the cyanide anion in Lapworth's proposed mechanism (Scheme 9),⁴⁸ 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.⁵¹



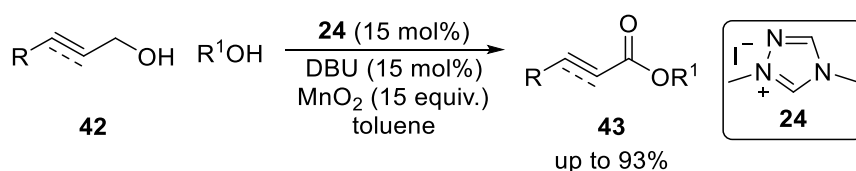
Scheme 10 Thiazolylidene-catalysed benzoin reaction mechanism proposed by Breslow

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 understated.^{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.

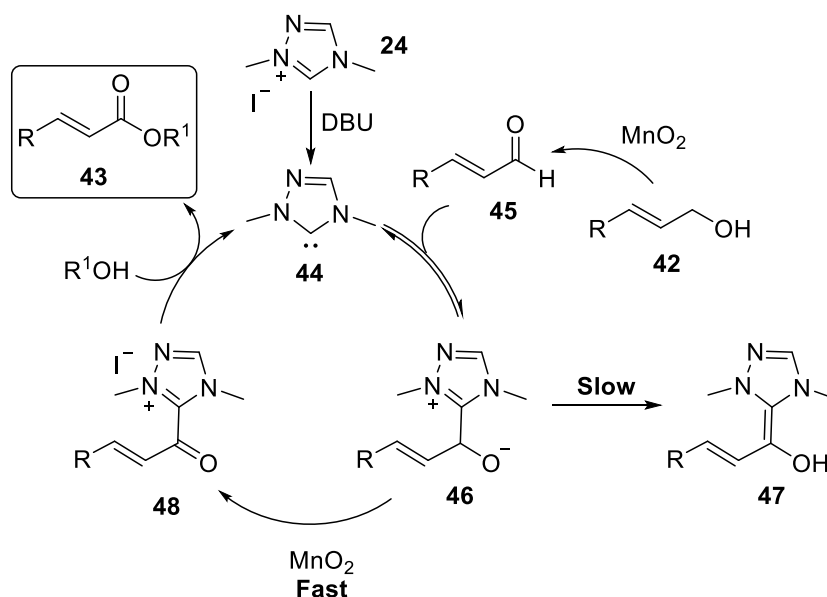
1.4.1 Studies with external oxidants

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_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 MnO_2 . 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 intermediate⁵¹ **47** or, fast oxidation by excess MnO_2 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**.

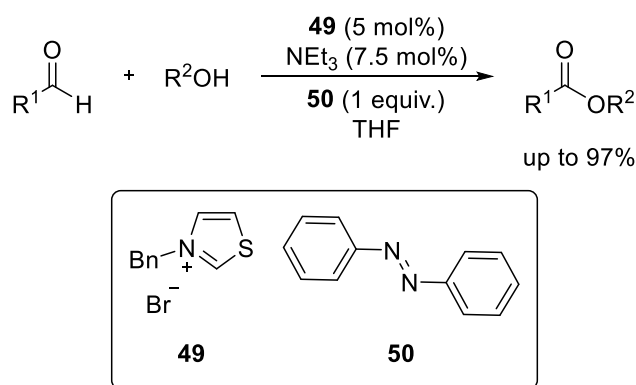


Scheme 12 Scheidt's proposed pathway for the tandem oxidation process

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.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.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.

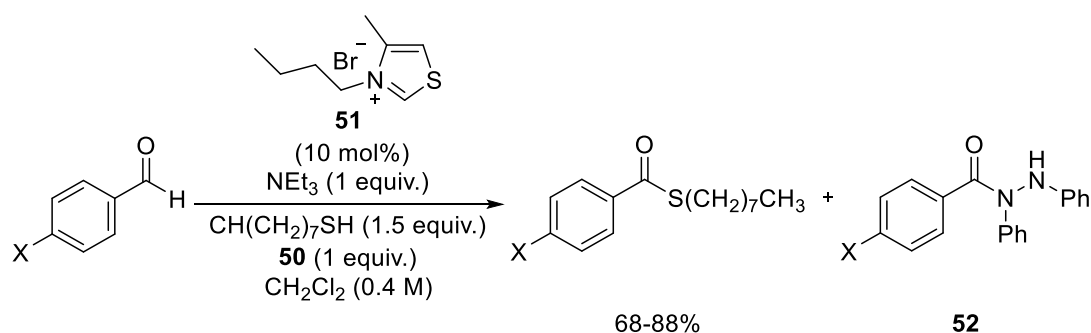


Scheme 13 Connon co-worker's NHC-catalysed aldehyde esterification

Interest in other oxidants have since been explored, such oxidants include; nitrobenzene,⁵⁸ TEMPO,⁵⁹ diphenoquinone⁶⁰ and phenazine.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.

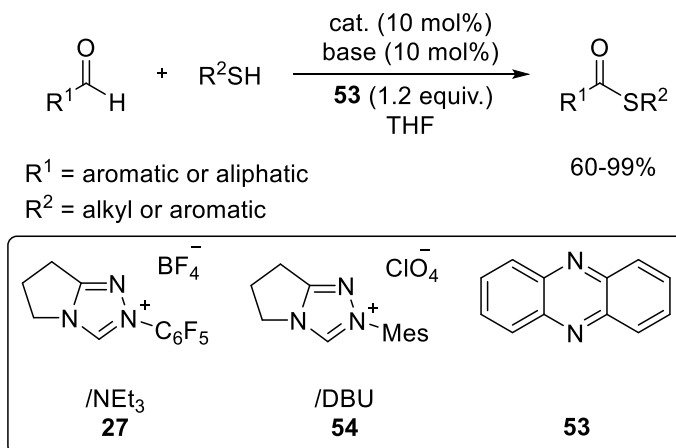
Murata was the first to produce thioesters *via* an NHC-catalysed oxidative thioesterification of an aldehyde using thiazolium precatalyst **51** (Scheme 14).⁶² Although this was the first example of such, the reaction was limited in scope, only a modest selection of *p*-substituted aromatic aldehydes 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 *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.⁶³ A range of enantioenriched 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 (**53**) as the external oxidant (Scheme 15).⁶¹ 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

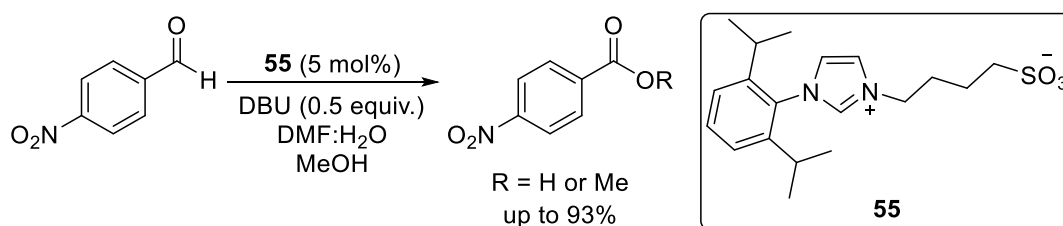
Following Takemoto's report, further investigation into these types of thioesterifications have been carried out. Yadav detailed the NHC-catalysed thioesterification of aromatic aldehydes and enals using disulfides as the thiol source and DEAD as the oxidant, to furnish the corresponding thioesters and α,β -unsaturated thioesters in good to excellent yields.⁶⁴ 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.⁶⁵ 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.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.^{67,68} While Yashima demonstrated NHC-catalysed aerobic esterifications using a flavin-derived co-catalyst⁶⁹ there are limited studies on such esterifications using strictly aerobic, oxidative conditions.

Yoshida *et al.* were the first to report the NHC-catalysed aerobic oxidation of aromatic aldehydes to the corresponding esters.⁷⁰ Their work focused on transformations of aromatic aldehydes to carboxylic acids in the presence of a sulfoxyalkyl substituted precatalyst **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.



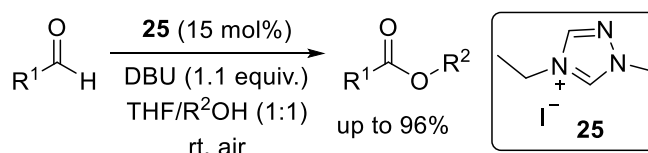
Scheme 16 Aerobic aldehyde carboxylation using an imidiazolium precatalyst

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

Liu *et al.* detailed the NHC-catalysed oxidative esterification of α,β -unsaturated aldehydes with cinnamyl bromides using either air or MnO₂ as the oxidant in 2011.⁷¹ 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 *N*-acylureas under aerobic conditions.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 *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-workers⁴² 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).



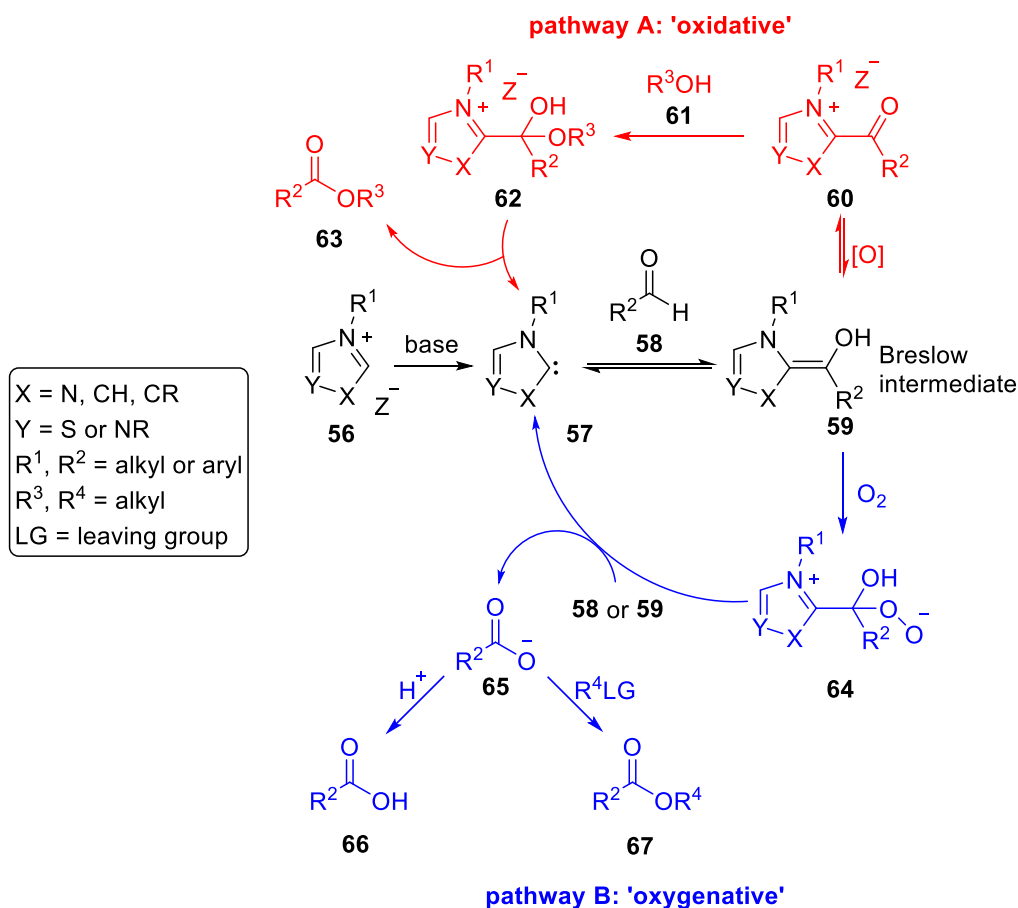
Scheme 17 Connon co-worker’s NHC-catalysed esterification without the use of a co-catalyst or stoichiometric oxidant

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%). *Ortho*-substituted aldehydes did not perform well in this reaction with lower yields being observed (e.g. *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.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 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).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**.

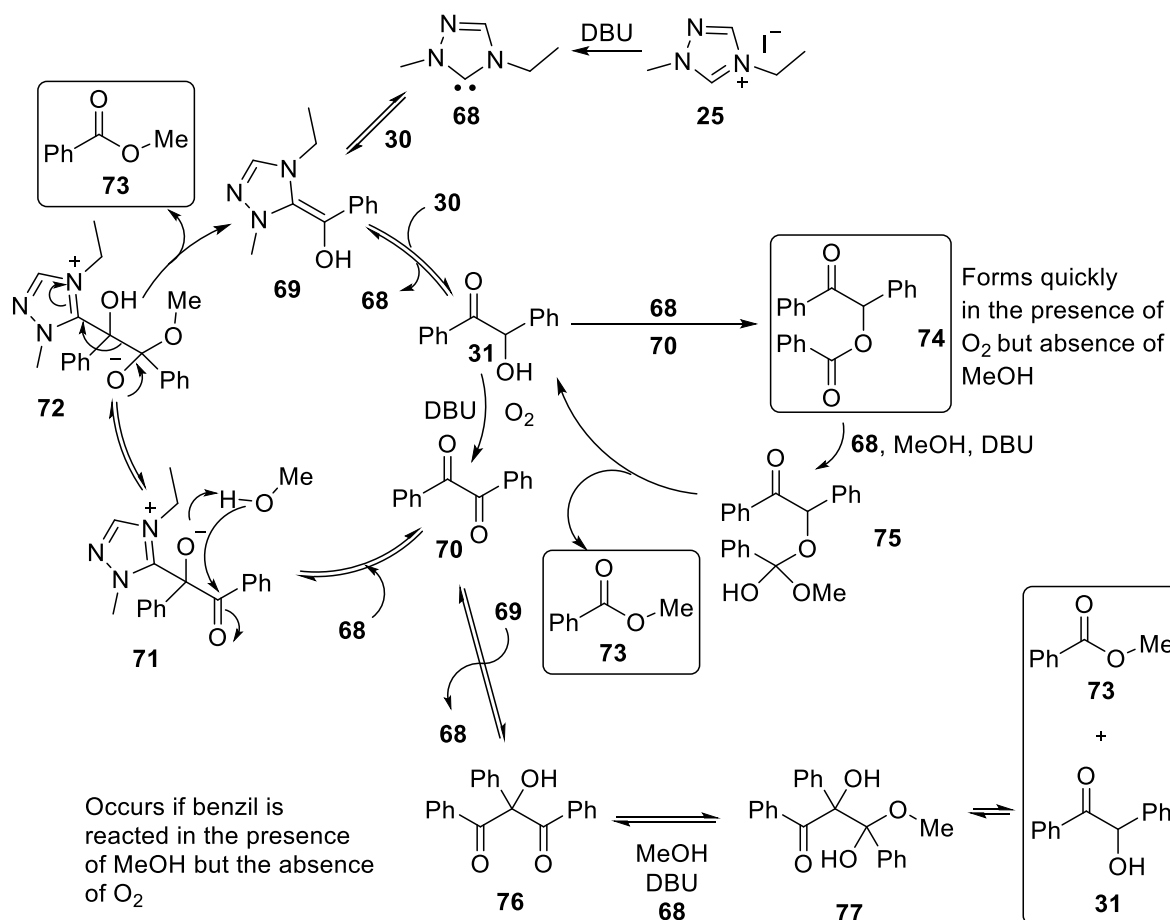
In pathway B, the ‘oxygenative’ pathway, the fate of the Breslow intermediate **59** differs in that it is oxidised by molecular oxygen rather than a stoichiometric oxidant. Transfer of an oxygen molecule to **59** establishes the internal peroxy Zwitterion⁷⁵ **64**, which subsequently reacts with another molecule of aldehyde **58** (via peroxyacid intermediates) or enaminol **59** to form carboxylate ion **65**.⁷¹ 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 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 rationale 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.⁷⁶

Precatalyst **25** is deprotonated to give the active carbene species **68**, which attacks **30** to form the Breslow intermediate⁵¹ **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**.

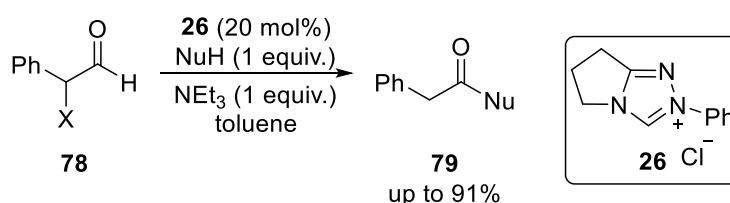
This mechanistic rationale is plausible as all the compounds highlighted in Scheme 19 along with benzil and benzoin, have either been isolated or detected *in situ* using ^1H NMR spectroscopic methods.

1.5 N-Heterocyclic carbene mediated oxidative amidations

The amide functional group is ubiquitous throughout natural products, the pharmaceutical industry and synthetic chemistry,⁷⁷ 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.⁷⁸ 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.

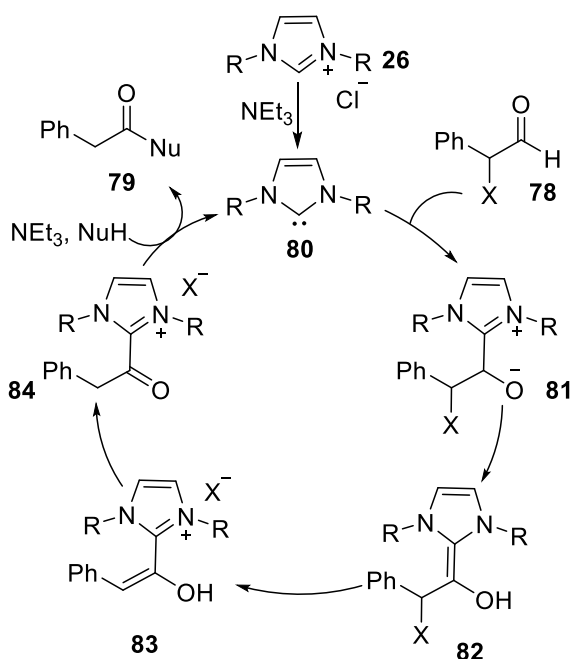
1.5.1 Amidation of aldehydes *via* internal redox

Rovis demonstrated an example of an NHC-catalysed oxidative amidation in 2004.⁷⁹ 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).



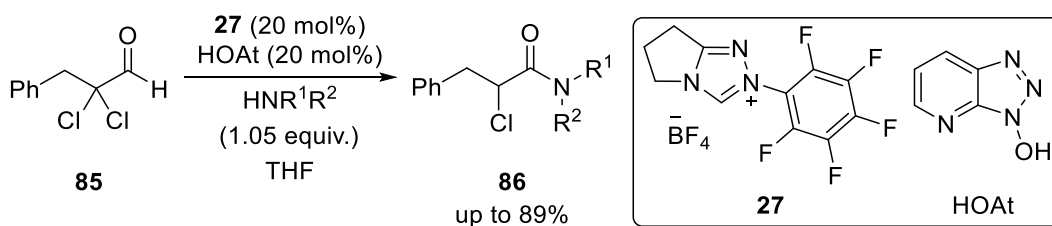
Scheme 20 Rovis *et al.*'s NHC-catalysed oxidative amidation of α -haloaldehydes

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).⁷⁹



Scheme 21 Internal redox mechanism proposed by Rovis

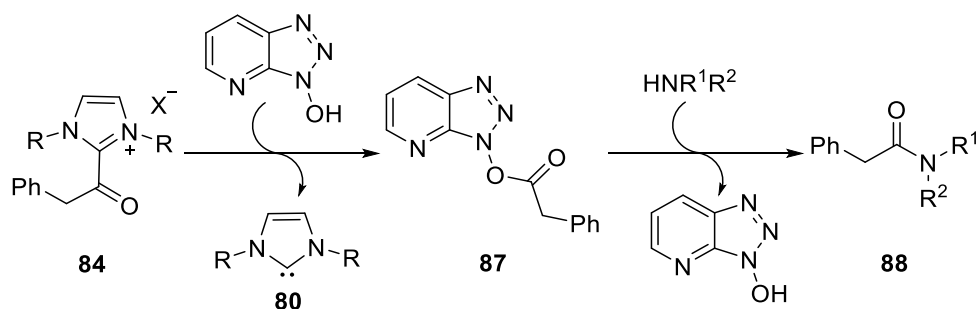
In Rovis' proposed mechanism, addition of active carbene species **80**, to α -haloaldehyde **78** initiates formation of the Breslow intermediate **82** via oxanion intermediate **81**. The presence of a leaving group (i.e. the α -halogen atom) in **82** allows for production of enol **83** which, upon 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.⁸⁰ 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).



Scheme 22 Rovis' NHC-catalysed oxidative amidation of α -haloaldehydes assisted by HOAt

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

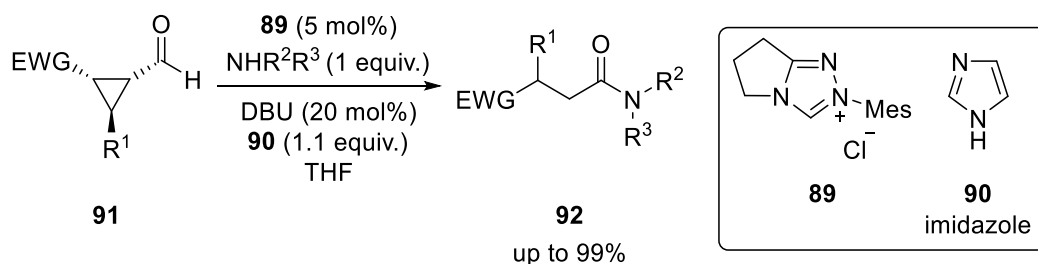
of **87** by an amine affords amide **88**, and regenerates HOAt, which can now enter another catalytic cycle.



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.⁸¹ 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).



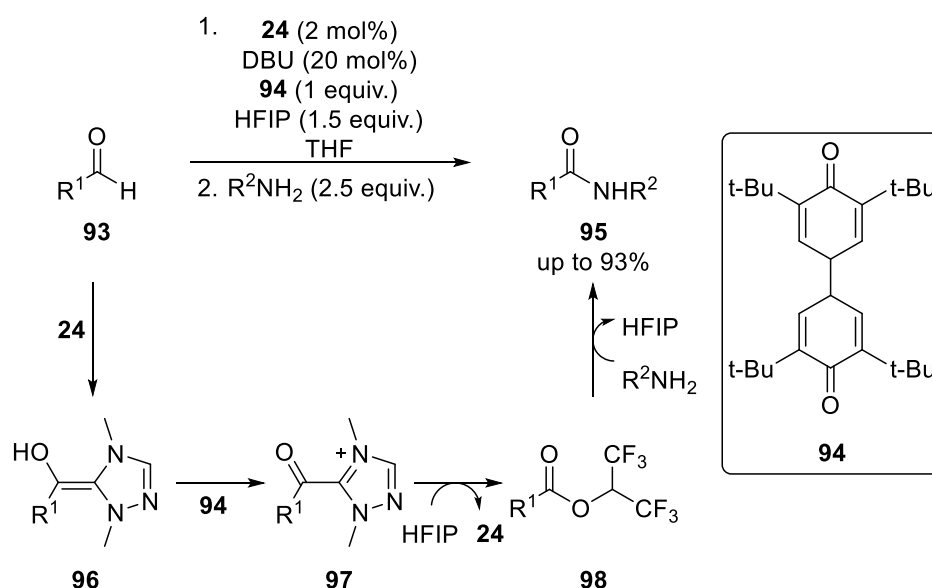
Scheme 24 Bode's NHC-catalysed oxidative amidation of α -functionalised aldehydes assisted by imidazole

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).⁷⁹

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

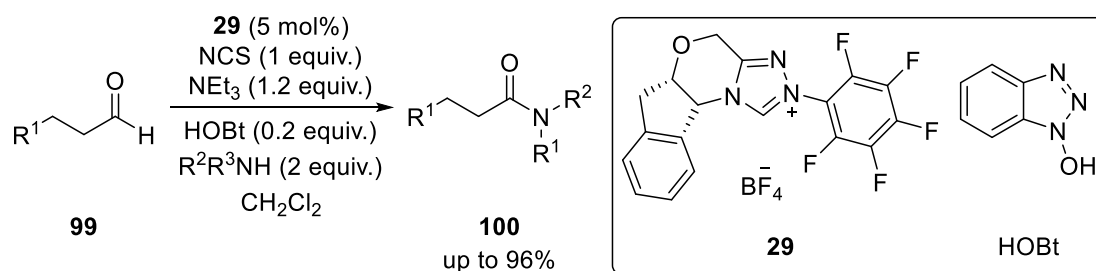
Another example of NHC-mediated amide bond formation is the oxidative amidation of aldehydes *via* an active ester intermediate. In 2010, Studer reported NHC-catalysed amidations of aldehydes in the presence of an organic oxidant and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP, Scheme 25).⁸² In Studer's 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*-butyldiphenylquinone (**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

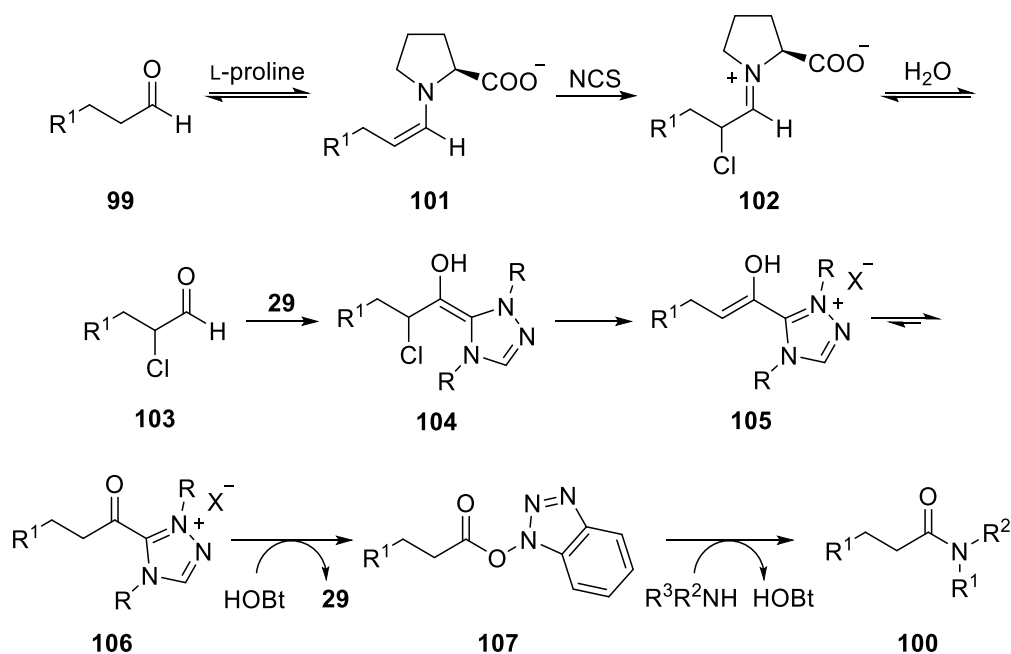
The scope of Studer's report was limited to aryl and alkenyl aldehydes. Jiao *et al.* went on to further exploit the intermediacy of hexafluoroisopropyl esters, to form amides from NHC-catalysed oxidative esterifications of bromoenals and α,β -dibromoenals.⁸³ Again this process was very limited in scope 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 α -unbranched aldehydes *via* an active ester intermediate (Scheme 26).⁸⁴



Scheme 26 Amidations of α -unbranched aldehydes carried out by Yamada *et al.*

In Yamada's report, aldehyde **99** is first functionalised at the α -position *via* formation of enamine **101** followed by electrophilic chlorination by *N*-chlorosuccinimide (NCS, Scheme 27). Imine **102** obtained by α -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 α -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 (HOBT) forms the active ester intermediate **107** which can be intercepted by an amine to form the desired amide **100**.

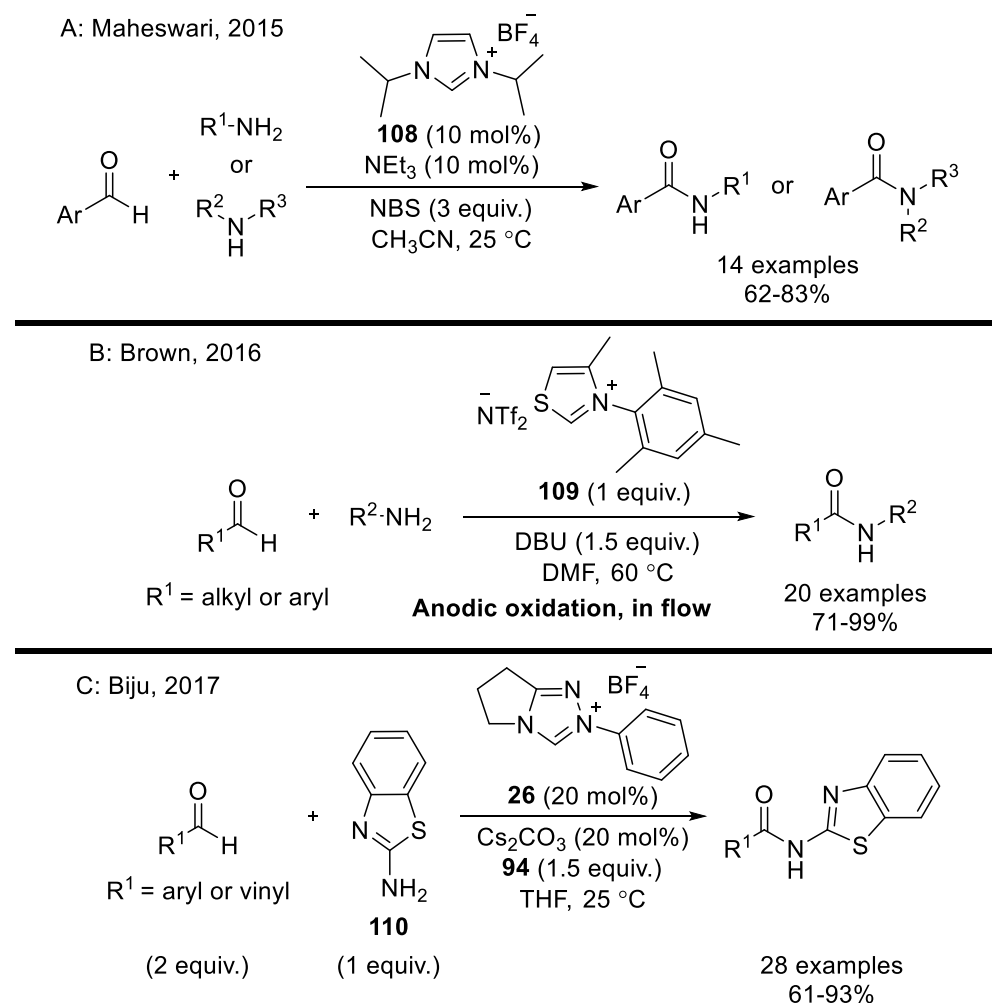


Scheme 27 Mechanism of Yamada's amidations of α -unbranched aldehydes

1.5.3 One-step oxidative amidations of aldehydes and benzils

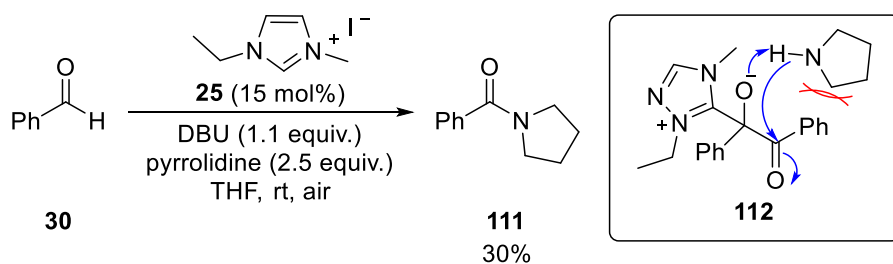
While there is a plethora of methodologies available pertaining to the NHC-catalysed oxidative esterification of aldehydes (see Section 1.4). The analogous reaction for the synthesis of amides in one-step (without the need to have specific functionalities in the aldehyde partner or employ the use of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



Scheme 28 One-step oxidative amidations by Maheswari, Brown and Biju

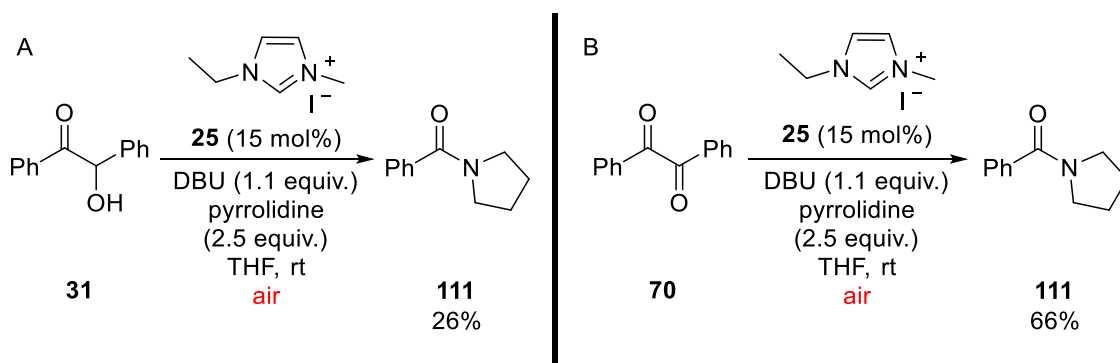
While carrying out mechanistic studies into the NHC-catalysed oxidative esterification of aldehydes, Connon and co-workers showed that benzaldehyde (**30**) could be converted to the corresponding pyrrolidine amide, albeit in low yield, under aerobic conditions (Scheme 29).⁷⁶ The catalytic cycle for 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

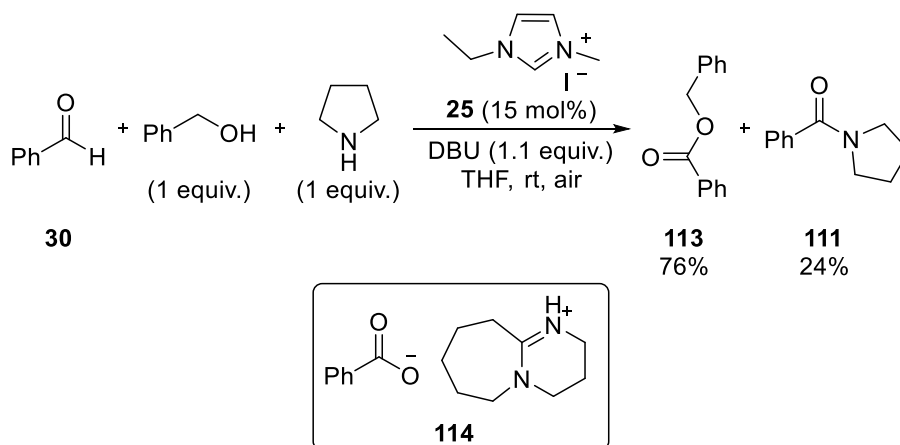
Following this initial finding, Connon went on to develop an efficient NHC-catalysed oxidative amidation methodology which uses phenazine (**53**) as the stoichiometric oxidant.⁸⁸ Initially Connon and co-workers used the reaction conditions as outlined in their earlier work into NHC-catalysed oxidative esterifications under aerobic conditions.⁴² 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.⁸⁸ 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).⁷⁶ 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 Cannon and co-workers, to highlight the inferiority of the amine nucleophile in comparison to its alcohol counterpart.⁸⁸ 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 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, Cannon 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.

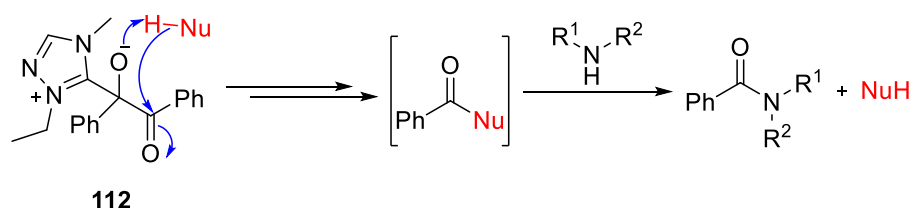
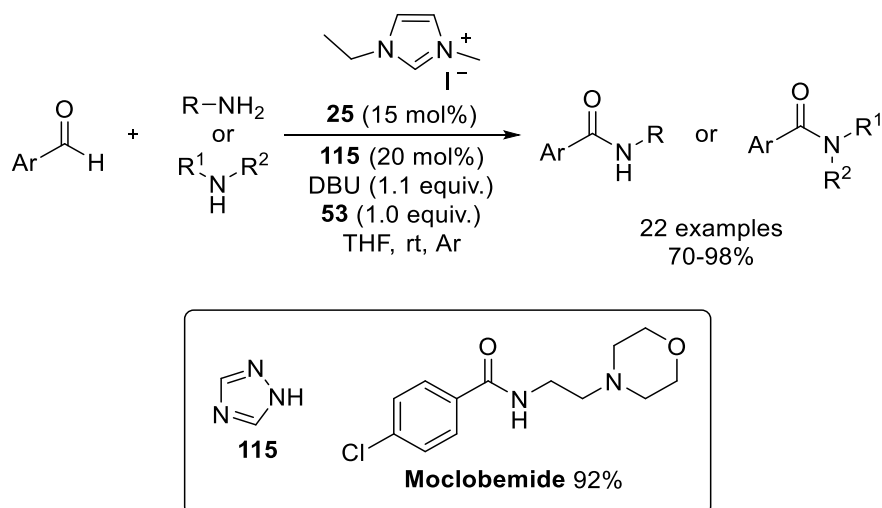


Figure 8 Role of a nucleophilic co-catalyst in the NHC-catalysed oxidative amidation

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 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*-protections 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.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 *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.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.^{92,93} The use of Boc as a protecting group for amino acids and in peptide synthesis has been widely studied.^{94,95} It is installed by reaction of the amine with di-*tert*-butyl dicarbonate and is most often removed by treatment with 25-50% TFA in CH₂Cl₂. 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 α -proton of a trityl-protected amino acid from base abstraction and subsequent racemisation.⁹⁶ One of the most common methods to deprotect a trityl group is with 1% TFA in CH₂Cl₂. Orthogonal deprotection strategies, *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. α,α -Dimethyl-3,5-dimethoxybenzyloxycarbonyl (Ddz,⁹⁷ Figure 9) can be deprotected using 1-5% TFA in CH₂Cl₂ while 2-(4-biphenyl)isopropoxycarbonyl (Bpoc)⁹⁸ can be removed with as little as 0.2-0.5% TFA in CH₂Cl₂. 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.

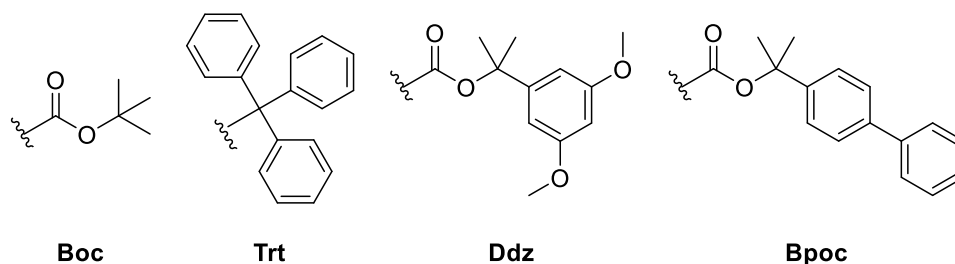


Figure 9 A selection of commonly used acid-labile *N*-protecting groups

1.6.1.2 Base-labile amine protecting groups

Some commonly used base-labile *N*-protecting groups include 9-fluorenylmethoxycarbonyl (Fmoc),^{99,100} 2-(4-nitrophenylsulfonyl)ethoxycarbonyl (Nsc)¹⁰¹ and *N*-tetrachlorophthaloyl (TCP, Figure 10).¹⁰² Fmoc is widely used in peptide synthesis as a base-labile amino protecting group.⁹¹ Its deprotection is generally carried out by secondary amine bases (piperidine is most often used as the base of choice)^{99,100,103} and while Fmoc is stable to acid, under certain circumstances (in cases where Pd/C or PtO₂ 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.^{104–106} 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.¹⁰¹ 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.¹⁰² It has been employed in recent times as a protecting group for amino acids^{102,107,108} and, previous to this, it was used as a protecting group in carbohydrate synthesis.¹⁰⁹ 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.¹¹⁰ *p*-Methoxyphenyl (PMP) is another protecting group that can readily protect both amines and alcohols^{111,112} and is cleavable at low pHs in aqueous media using ceric(IV) ammonium nitrate (CAN).¹¹²

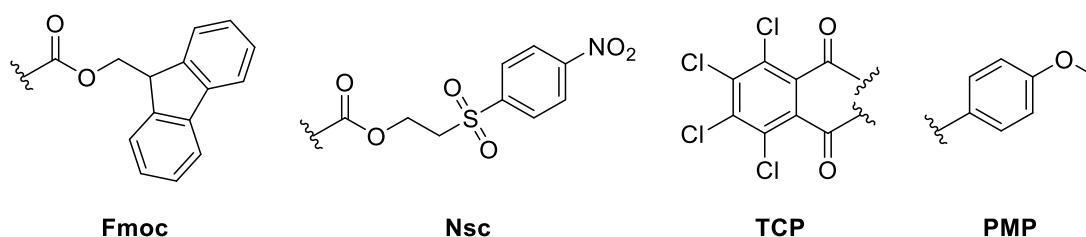


Figure 10 A selection of commonly used base-labile *N*-protecting groups

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. Benzyloxycarbonyl (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.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.¹¹⁴ 2,2,2-Trichloroethyloxycarbonyl (Troc,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 *via* a reduction reaction using zinc in acetic acid or other reducing agents.^{115,116} *p*-Nitrobenzyloxycarbonyl (*p*NZ)¹¹⁷ is a commonly utilised *N*-protecting group which is useful in the synthesis of complex peptides and can be used to lessen the instances of un-wanted side reactions.¹¹⁸ *p*NZ 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_(dioxane)) in solid-phase synthesis¹¹⁸ and in solution synthesis it can be removed by catalytic hydrogenolysis or Na₂S₂O₄.¹¹⁹ Photolabile protecting groups are also available for use in organic synthesis. *o*-Nitrobenzyloxycarbonyl (*o*NZ) is cleavable using additives such as N₂H₄, NH₂OH·HCl at wavelengths greater than 320 nm.¹²⁰ while 2-(2-Nitrophenyl)propyloxycarbonyl (NPPOC) cleaved at $\lambda = 365$ nm and is cleaved faster than other photolabile groups.¹²¹

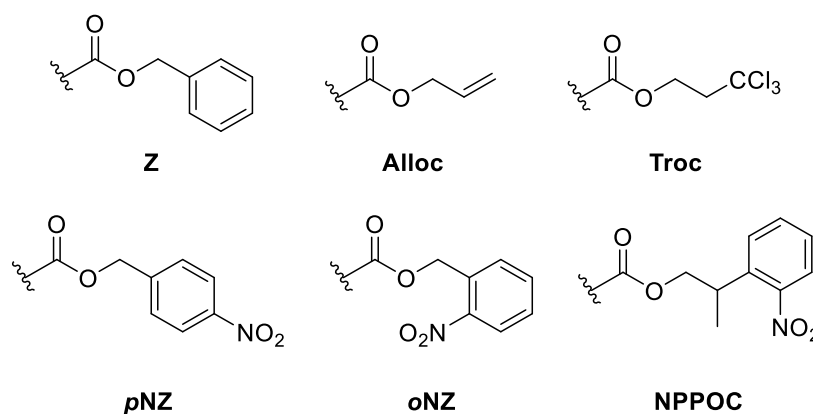
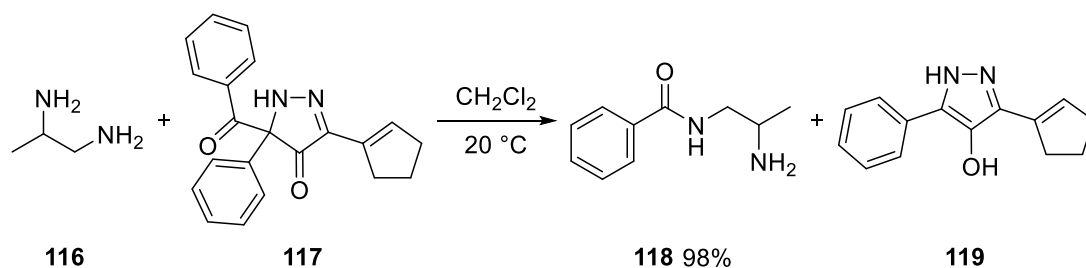


Figure 11 A selection of *N*-protecting groups which are removed under alternative conditions

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^{122–126} as have the use of biomolecules to selectively acylate amines.^{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 dicarbonate¹²⁹ or require the use of highly corrosive HCl gas in the reaction.¹³⁰

An interesting study into the selective acylation of diamines was recently carried out by Doyle *et al.*¹³¹ Using 5-benzoyl-3-(cyclopent-1-en-1-yl)-5-phenyl-1,5-dihydro-4*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 selectivity (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,¹³² means that other alternatives to selectively protect di- and polyamines require further investigation.



Scheme 33 Selective benzoylation of diamine **116** carried out by Doyle *et al.*¹³¹

1.6.3 Limitations of current amine protecting groups

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.

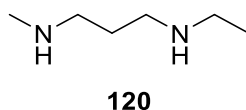


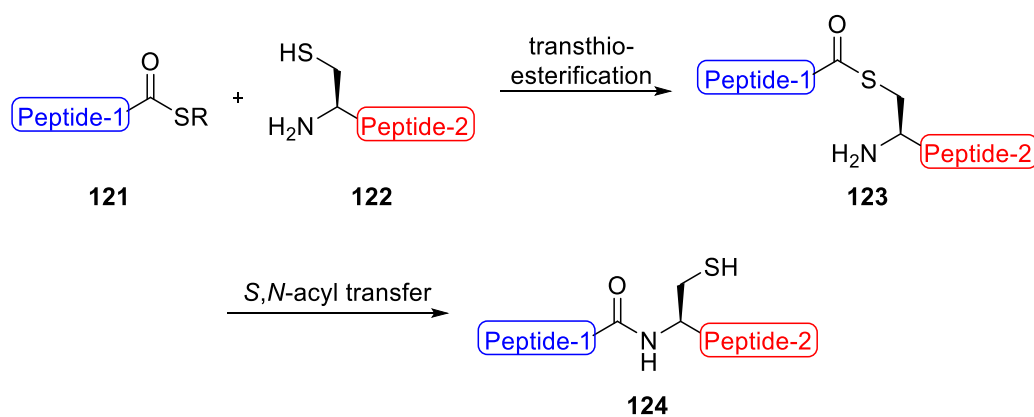
Figure 12 Diamine **120**

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.¹³³ The general principle of native chemical ligation is shown below in Scheme 34.



Scheme 34 General mechanism of native chemical ligation

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.¹³³ 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.^{134–137} 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, α -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.^{138,139} Azlactones are α -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%.¹⁴⁰ As a kinetic resolution process can never obtain a 100% yield of product, it is not considered atom economical.⁷³ DKR was introduced as a means to overcome this problem of wasted starting material.

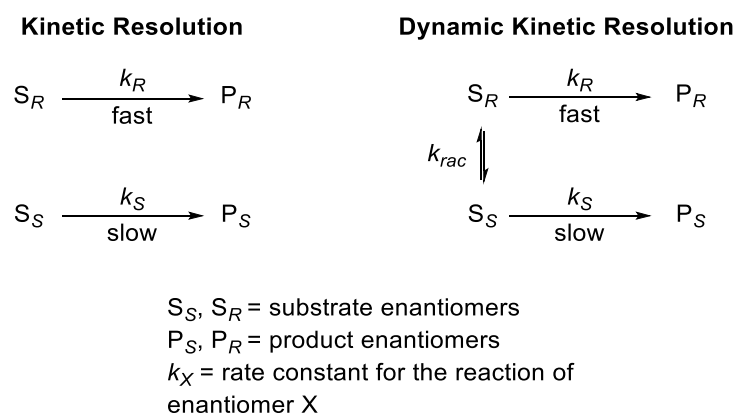
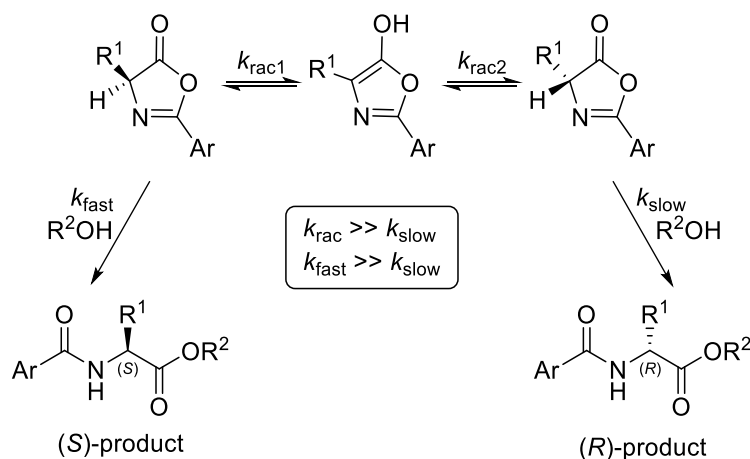


Figure 13 Basic principles of kinetic resolution and dynamic kinetic resolution

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.¹⁴¹ 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.* $k_{rac} > k_R > k_S$).¹⁴² The *in situ* racemisation of the substrate can be carried out chemically, biocatalytically or can even occur spontaneously,¹⁴³ however, the conditions required to do so must be sometimes carefully chosen to avoid racemising the product.¹⁴¹

1.8.2 DKR of azlactones *via* alcoholysis and thiolysis

Alcoholysis is one method by which racemic azlactones can be resolved to produce enantioenriched α -amino acids by DKR. As outlined in Section 1.8, the α -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.

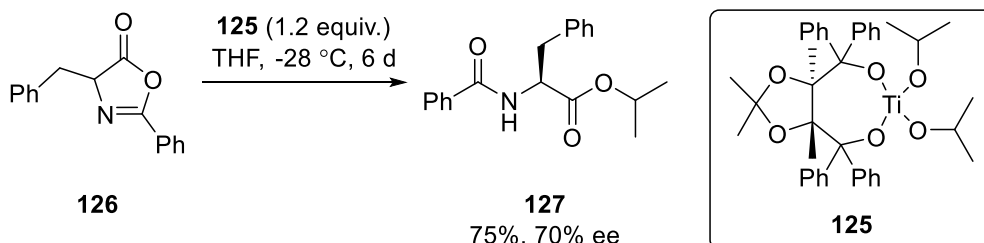


Scheme 35 DKR of azlactones by alcoholysis: a general overview of the process

In 1993, Sih *et al.* reported a successful, enzymatic variant for azlactone DKR to produce enantioenriched α -amino acids.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).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).

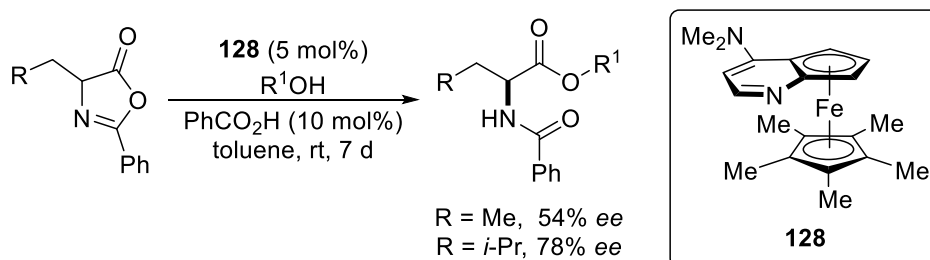


Scheme 36 Ti-TADDOLate-promoted DKR of azlactones carried out by Seebach *et al.*

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.¹⁴⁶ 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

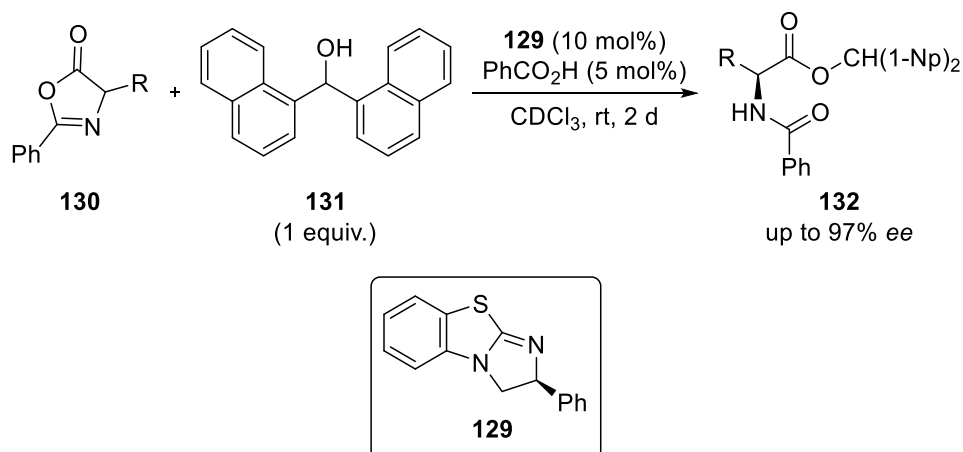
In 1998, Fu *et al.* published their findings into a non-enzymatic DKR of azlactones *via* alcoholysis.¹⁴⁷ This methodology employed the use of **128**, a chiral, DMAP-derived catalyst to promote the reaction, and furnish the ring-opened products in high yields and *ees* of up to 78% (Scheme 37). While 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 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).¹⁴⁸ 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

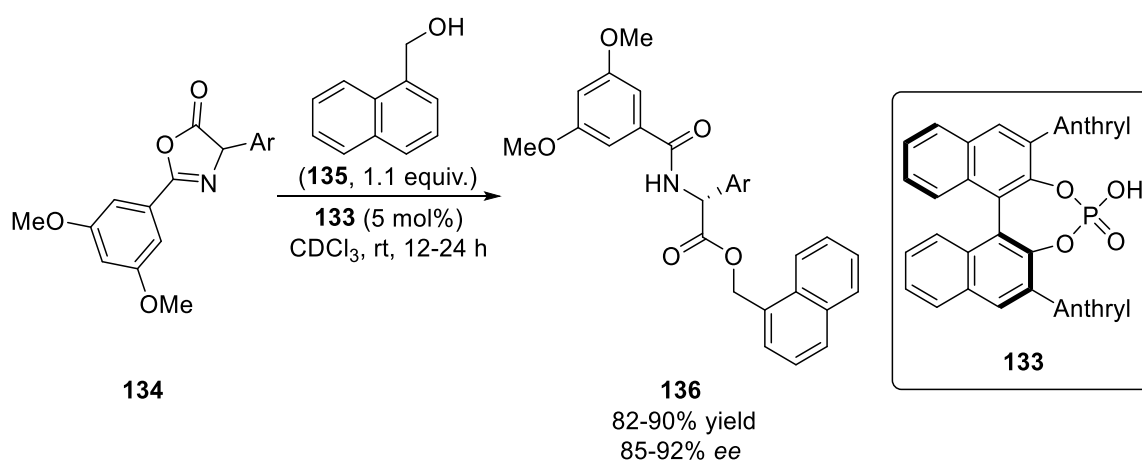
went on to publish the stereochemical rationale for the observed enantioselectivity, which was explained by π - π interactions between the substrate and catalyst.¹⁴⁹



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

1.8.2.3 DKR of azlactones via Brønsted acid catalysis

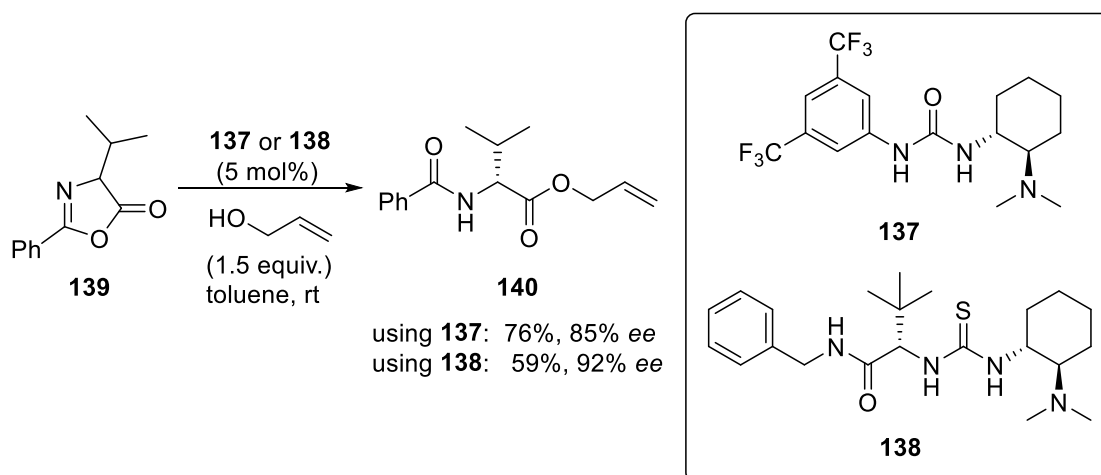
Further to his studies into the DKR of azlactones by alcoholysis catalysed by acyl transfer catalysts (Section 1.8.2.2, Scheme 38), Birman also utilised a chiral Brønsted acid catalyst to promote this transformation (Scheme 39).¹⁵⁰ Using a disubstituted BINOL phosphoric acid derivative **133**, this DKR process was tolerant of a range of different alcohols, however, sterically encumbered alcohol 1-naphthyl-CH₂OH (**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 *ees*; 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 2005.¹³⁹ 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.¹⁵¹ 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** is 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).¹⁵² 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.

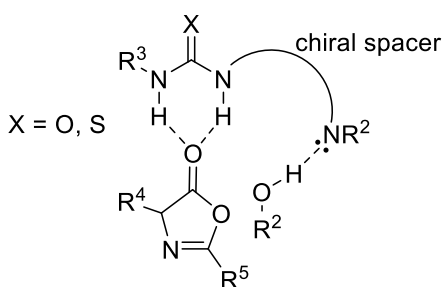
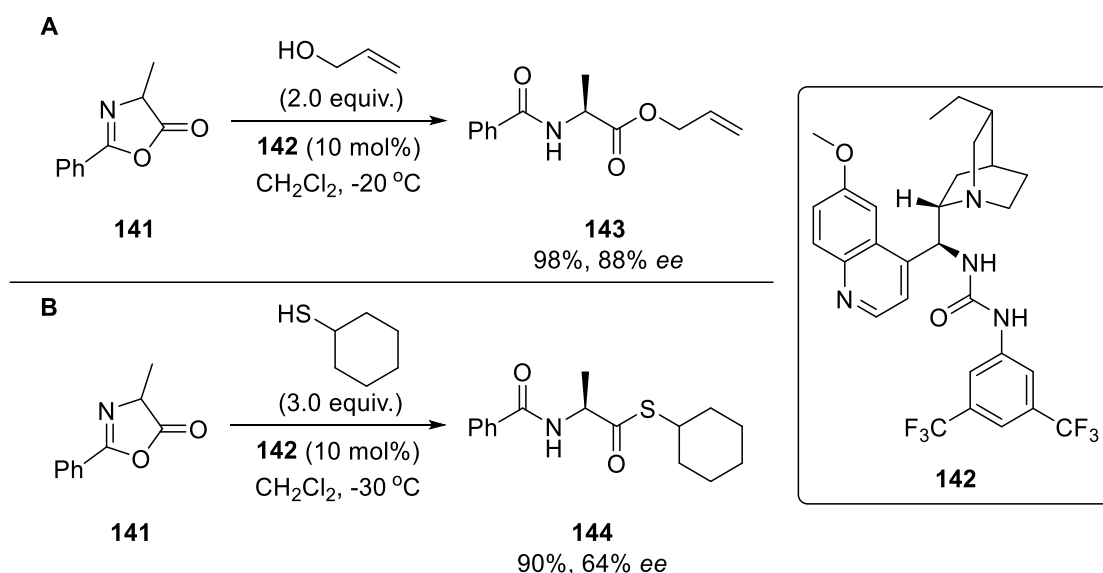


Figure 14 Proposed activation of an azlactone and an alcohol by a bifunctional (thio)urea catalyst

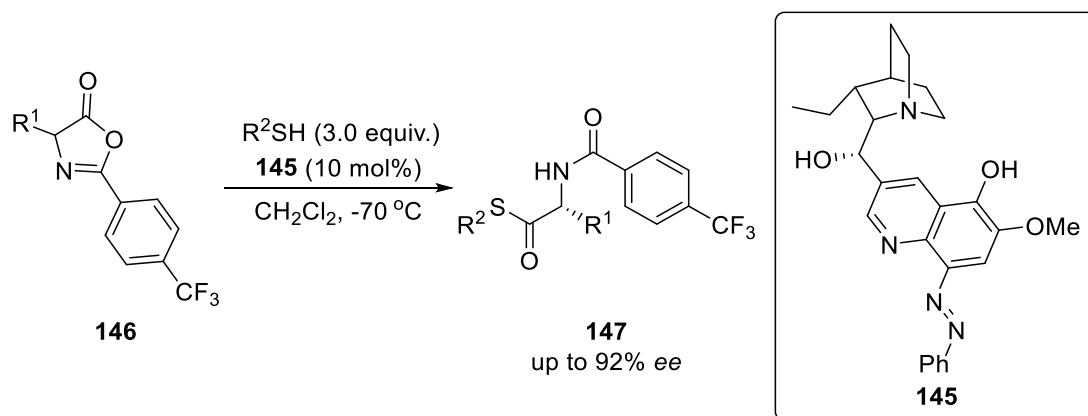
In 2008, Connon and co-workers published their findings into the DKR of azlactones by alcoholysis and thiolysis using *cinchona* alkaloid-derived catalysts.¹⁵³ Yields and enantiomeric excesses in this study were comparable to those reported by Berkessel¹³⁹ in the alcoholysis of azlactones (Scheme 41 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 **141** was carried out *via* thiolysis using cyclohexyl thiol in the presence of *cinchona* alkaloid-derived catalyst **142**, to form the corresponding thioester **143** in an excellent yield (90%) and with moderate enantioselectivity (64% *ee*, Scheme 41 B).



Scheme 41 Alcoholysis and thiolysis of azlactones using bifunctional catalyst **142**

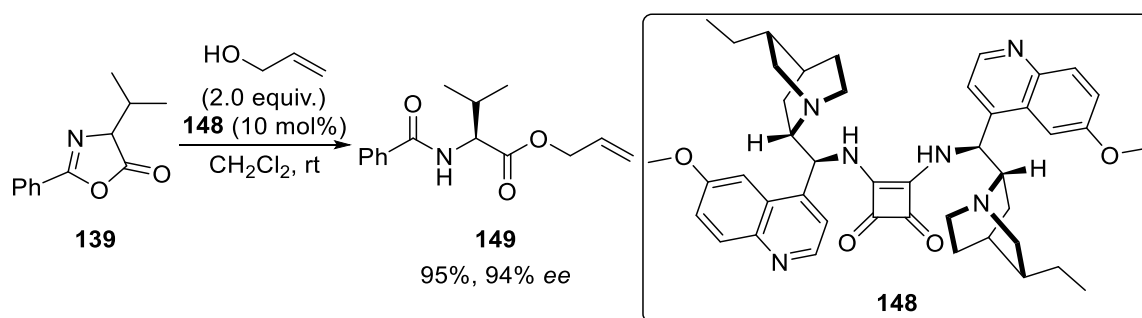
Following on from their 2008 report, in 2013 Connon and co-workers went on to resolve the previous problems observed with the enantiodiscrimination in the thiolysis of azlactones.¹⁵⁴

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).



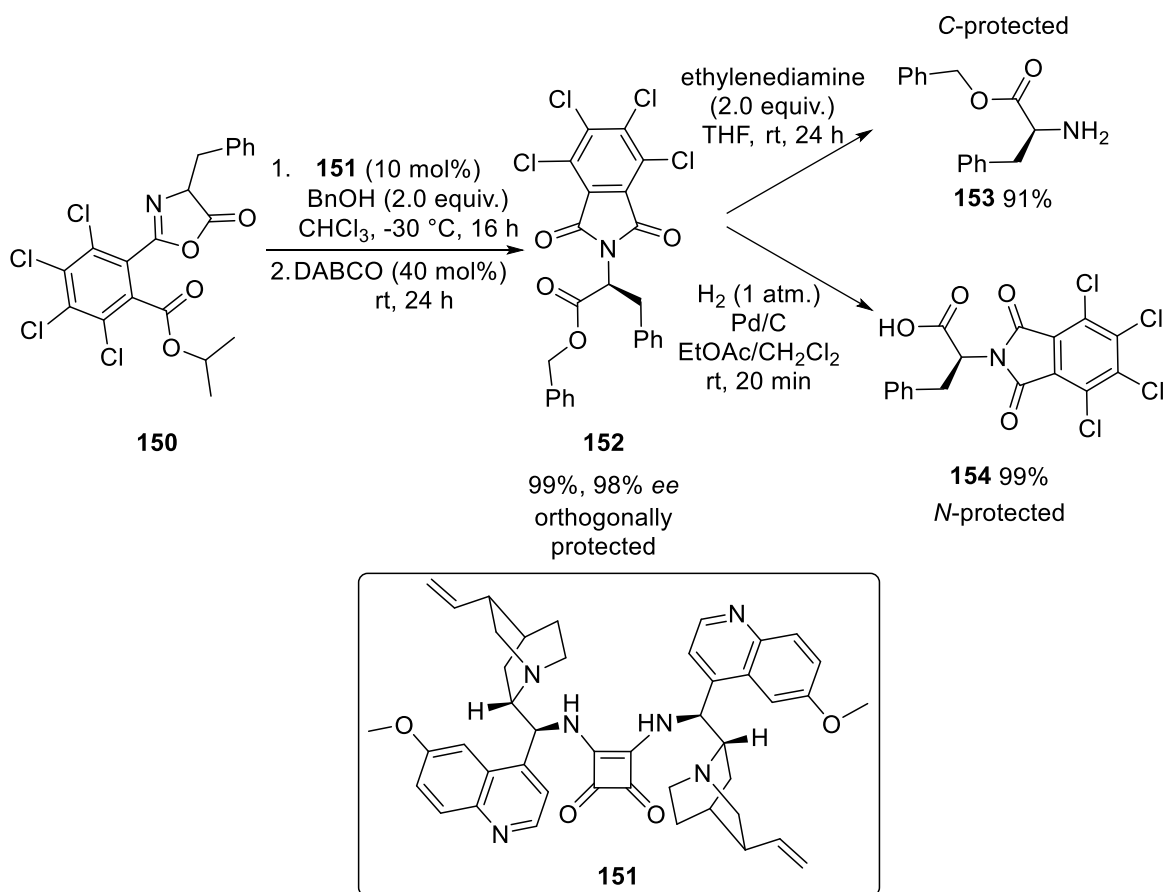
Scheme 42 Optimised DKR of azlactones *via* thiolysis reported by Cannon and co-workers

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.¹⁵⁵ 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 C_2 -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).¹³² 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 $-20\text{ }^\circ C$.



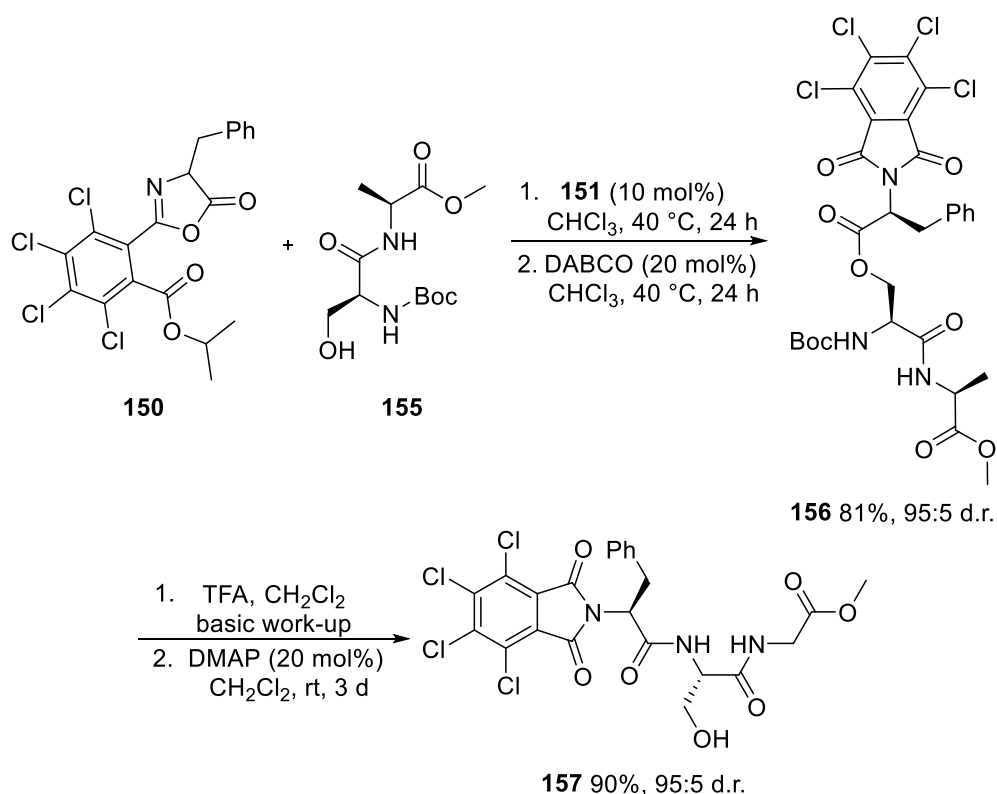
Scheme 43 Song's DKR of azlactones promoted by catalyst **148**

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 C_2 -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*-phthalimido-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.).



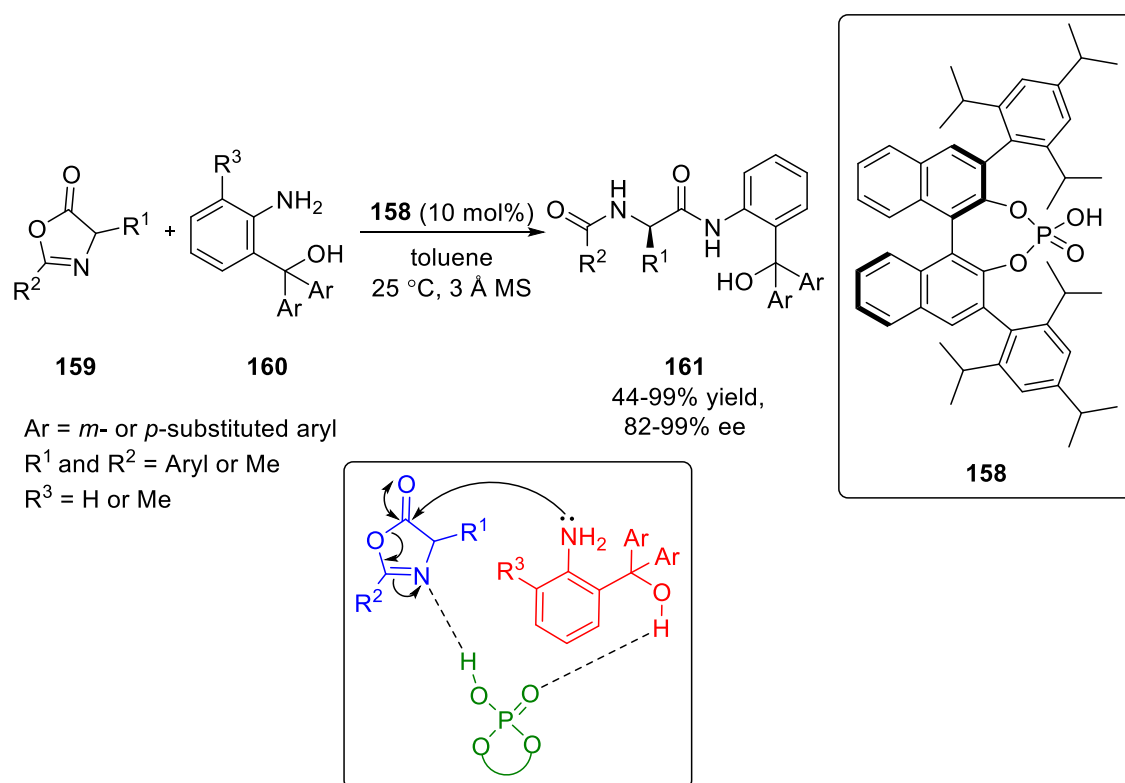
Scheme 45 The DKR-peptide coupling methodology designed by Connon and co-workers

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 ($\pm$)-CSA as a Brønsted acid catalyst to perform the aminolysis of azlactones racemically using a small pool of amines¹⁵⁷ while Dujardin ring-opened 2-methylalanine-derived azlactones with amines, uncatalysed, to prepare vinyl ether linkers used in the preparation of ($\pm$)-2-deoxy-glycoside.¹⁵⁸ Other examples of azlactone aminolysis have been carried out using chiral starting materials (chiral azlactones and amines).^{159,160} 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.¹⁶¹ Other methodologies require harsh reaction conditions such as: high temperatures,^{162,163} the use of a strong Lewis acid¹⁶² and long reaction times,¹⁶⁴ to achieve aminolysis.

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.¹⁶⁵ 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 un substituted aniline) to a significant loss in enantiomeric excess (only 37 % *ee*).



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

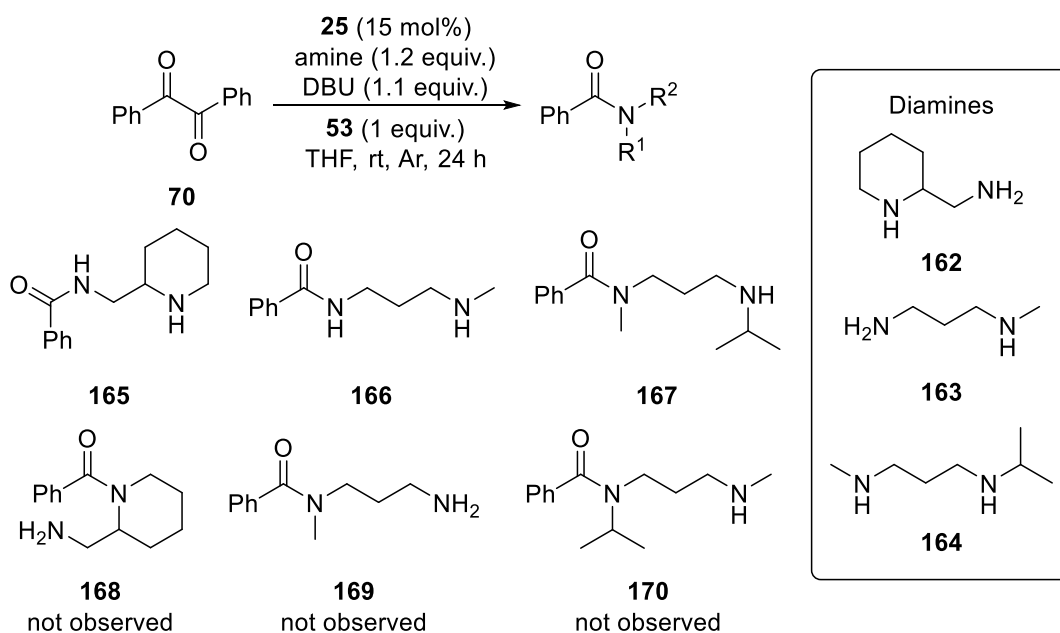
Although the aminolysis of azlactones by a DKR process has been carried out using Brønsted acid catalysis, the limited scope of the amine nucleophile means that more investigation into this protocol is necessary. Presented with this challenge, one of the aims of this thesis was

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

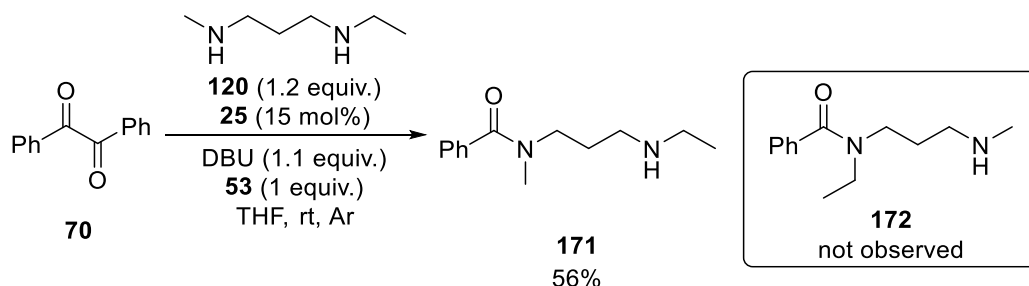
2.1. Selective acylation of diamines *via* NHC catalysis using benzil

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).⁸⁸ 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,⁸⁸ 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).⁸⁸ 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 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 benzoylation 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 Selective amidation of diamine **120** via NHC catalysis

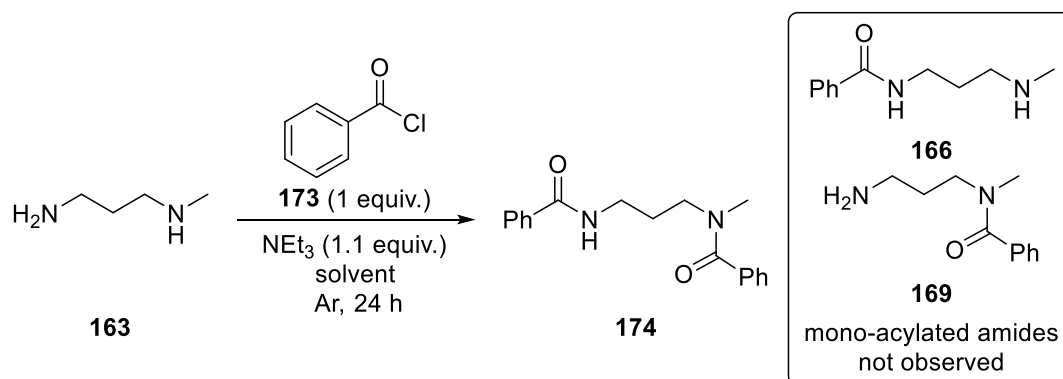
As a result of the unprecedented selectivity observed in amine acylation using **70**, it was decided that a benzil derivative would be the structural basis for protecting group design. As an addition to being a highly electrophilic species, benzil is also the oxidised form of an aromatic aldehyde and 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*-benzoylation 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



entry	solvent	concentration (M)	temperature (°C)	yield (%) ^a	selectivity ^b 174:166:169
1	THF	0.4	rt	49	100:0:0
2	THF	0.1	rt	50	100:0:0
3	THF	0.1	-30	46	100:0:0
4	THF	0.1	-78	50	100:0:0
5	CH_2Cl_2	0.1	rt	48	100:0:0
6	CH_2Cl_2	0.1	-30	50	100:0:0
7	CH_2Cl_2	0.1	-78	45	100:0:0

^aIsolated yield. ^bRefers 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 °C (Table 1, entry 3) and -78 °C (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, CH₂Cl₂, the solvent more typically associated with such reactions was used. At room temperature at a concentration of 0.1 M, the use of CH₂Cl₂ 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.

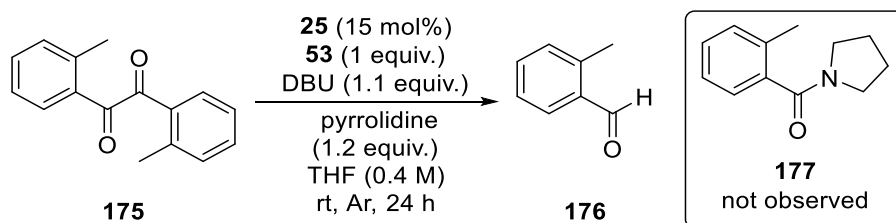
In each case discussed above, the mono-acylated amides **166** and **169** were not observed. It was postulated that, as the more nucleophilic secondary amine of **163** is likely acylated first to form **169**, the newly acylated nitrogen atom may then accelerate acylation of the free primary amine (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)^{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 (*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.

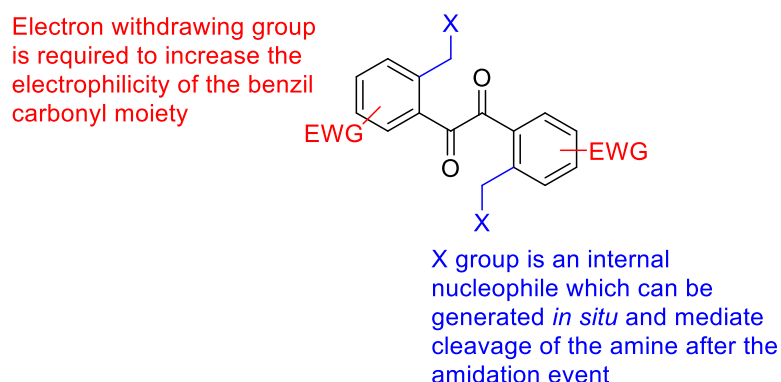


Figure 15 Model compound for first-generation protecting group design

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 Cannon and co-workers, pyridine-derived aldehydes are competent coupling partners in

NHC-catalysed oxidative amidation reactions (*e.g.* 2-pyridinecarboxaldehyde: 81% yield).⁸⁸
 The first-generation substrate **178** is shown in Figure 16.

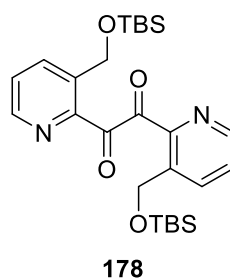
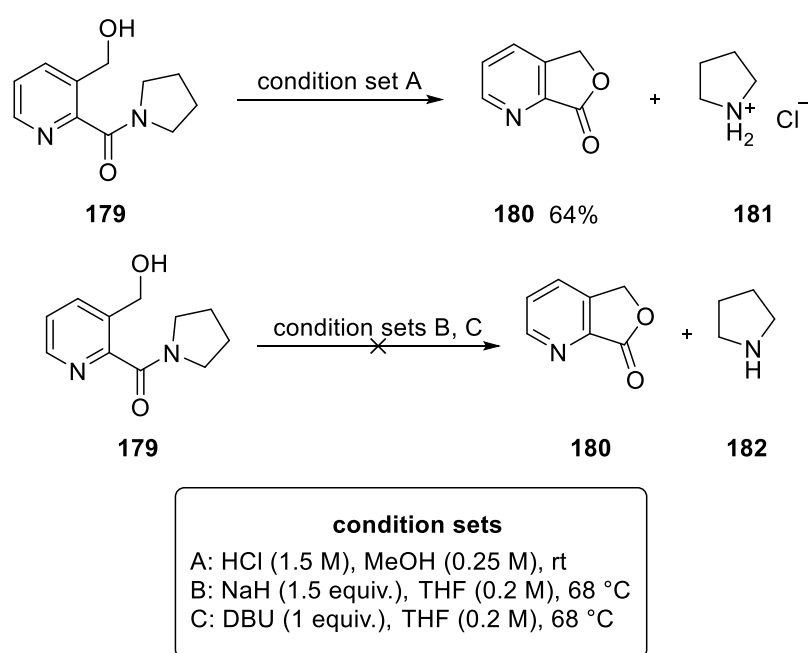


Figure 16 First generation acylating agent

2.3.1 First-generation substrate: deprotection studies

In order to determine suitable deprotection conditions, the final amide product (after de-silylation) **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

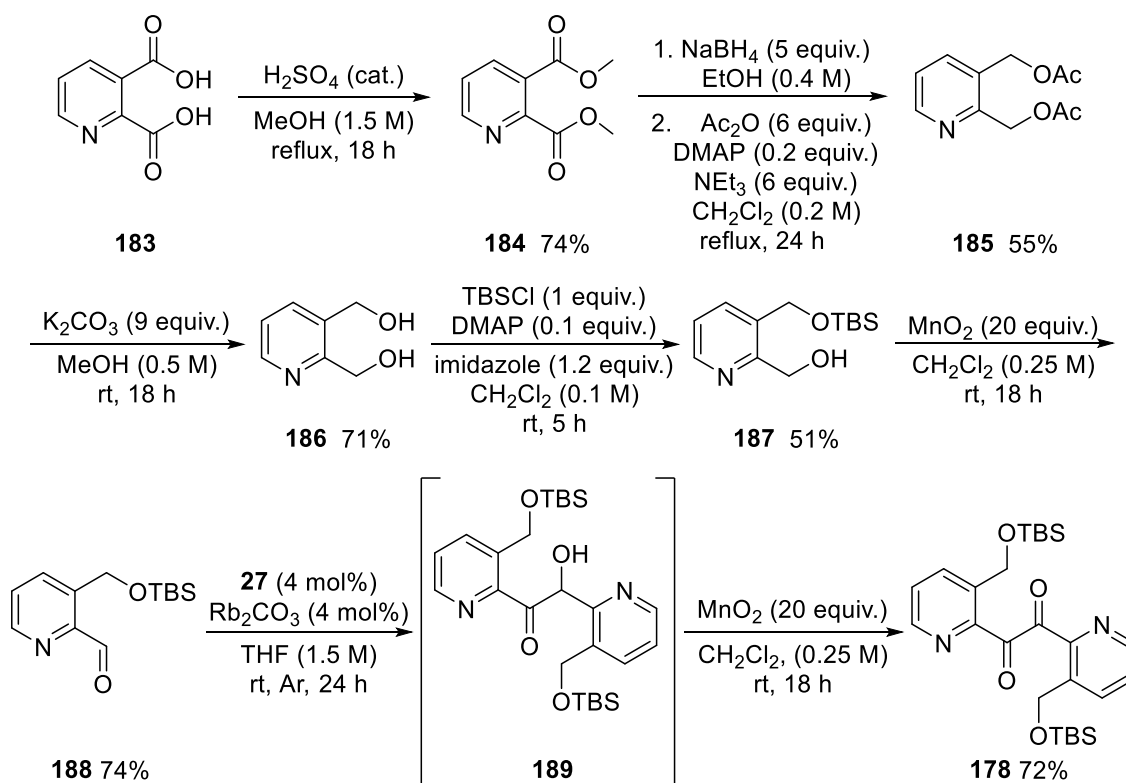
reactions, **180** was not formed. Further optimisations of this reaction have not been carried out at present. Although not a perfect deprotection strategy to obtain protected amine **179**, the acid-mediated protocol, condition set A, was deemed adequate and attention was then turned to the synthesis 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).¹⁶⁷ The reduction of **184** to diol **186** was more challenging than initially anticipated. Following a protocol devised by Yoshiizumi *et al.*,¹⁶⁸ attempts were made to reduce **184** with sodium borohydride (NaBH_4). 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 NaBH_4), 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 (LiAlH_4) and lithium borohydride (LiBH_4) 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 reagents 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_2CO_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**.



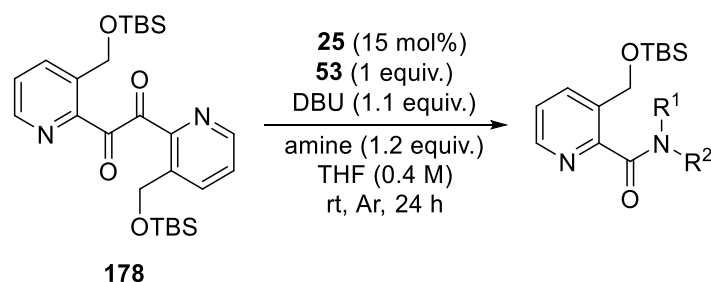
Scheme 51 Synthetic route to **178**

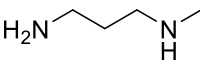
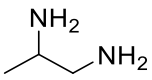
2.3.3 Evaluation of **178** in NHC-catalysed oxidative amidations

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

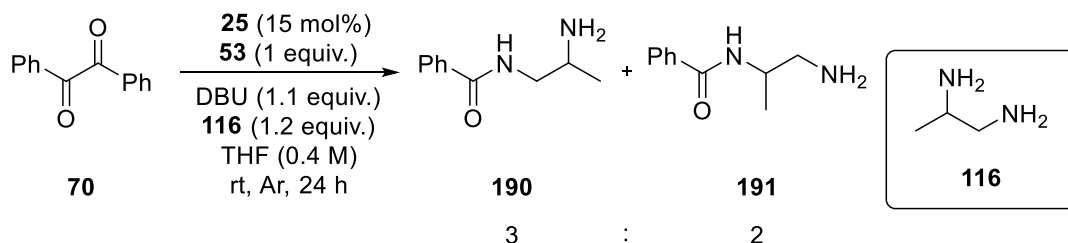


entry	amine	yield (%) ^a	selectivity ^b
1	pyrrolidine	97	n/a
2	piperidine	64	n/a
3	 163	51	100:0
4	 116	63	100:0

^aIsolated yield. ^bRefers 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% selectivity 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 intermediate⁵¹ with trace amounts of oxygen in the reaction flask, likely through an ‘oxygenative’ pathway (see Section 1.4.3).⁷⁴

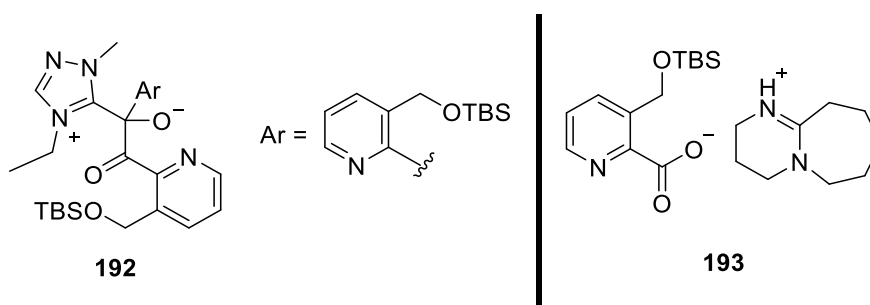
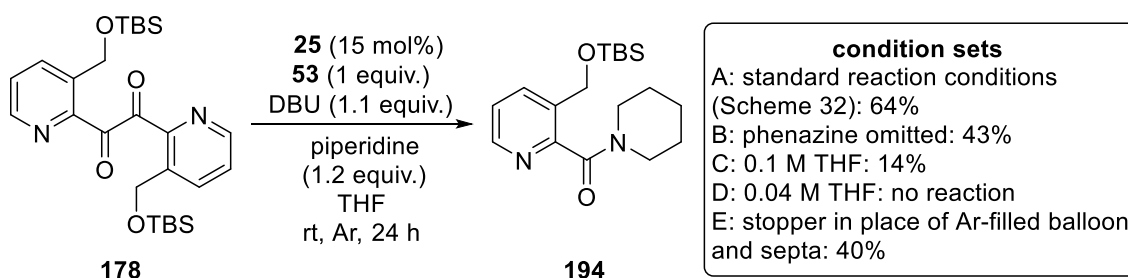


Figure 17 Tetrahedral intermediate **192** and DBU-carboxylate salt **193**

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 μ L) 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.

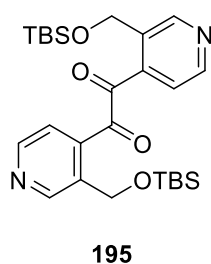
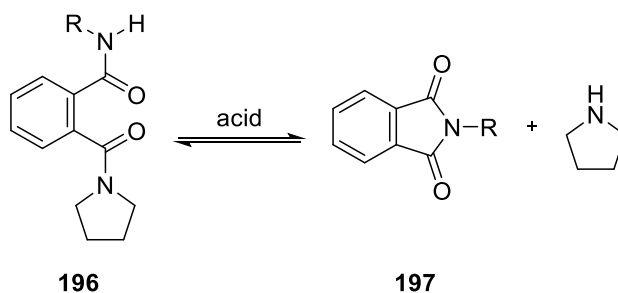


Figure 18 3,4-Substituted pyridil derivative **195**

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 sp^2 -hybridised electron withdrawing group was included in the redesign, for deprotection, as opposed to an sp^3 -hybridised analogue, such as the primary alcohol in **178**. The rationale behind this decision was that a flat sp^2 -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 sp^2 -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).¹⁷⁰ Protecting group **196**, containing a secondary amine, can reversibly form phthalimide (**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.

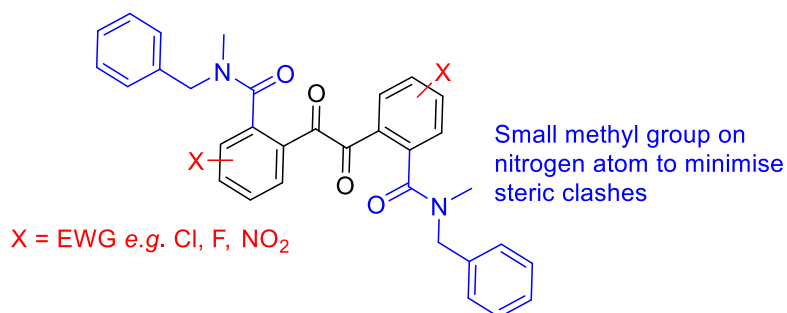


Figure 19 Model compound for second-generation substrate design

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.

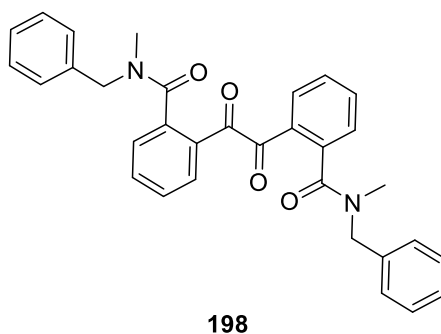
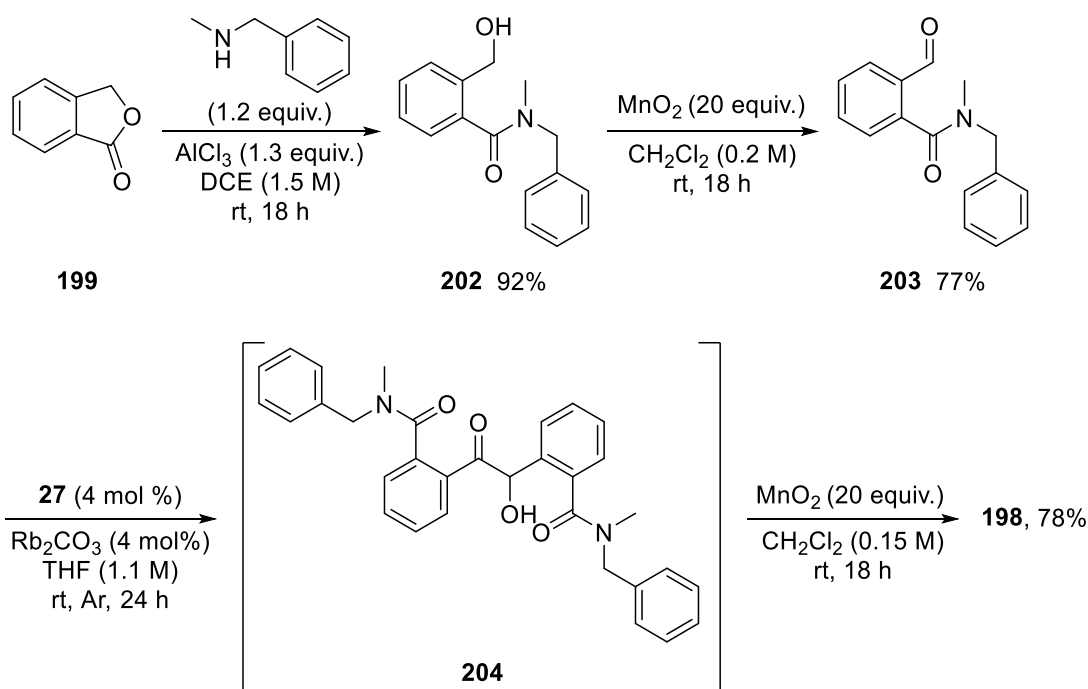


Figure 20 Second-generation prototype substrate **198**

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**, AlCl_3), to form alcohol **202**. Upon oxidation to aldehyde **203**, a benzoin condensation furnished the benzoin derivative **204**, which could be oxidised with MnO_2 to benzil **198**.

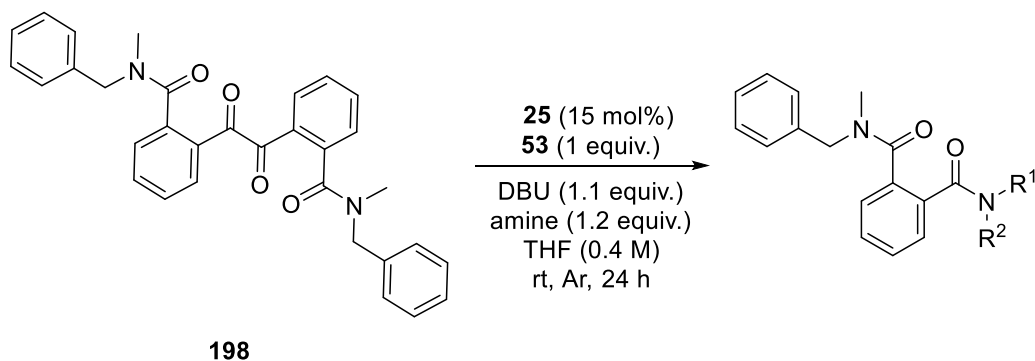


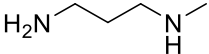
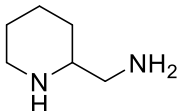
Scheme 55 Synthetic route to substrate **198**

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



entry	amine	yield (%) ^a	selectivity ^b 1° amine:2° amine
1	pyrrolidine	99	n/a
2	piperidine	79	n/a
3	 163	41	100:0
4	 162	53	100:0

^aIsolated yield. ^bRefers 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.

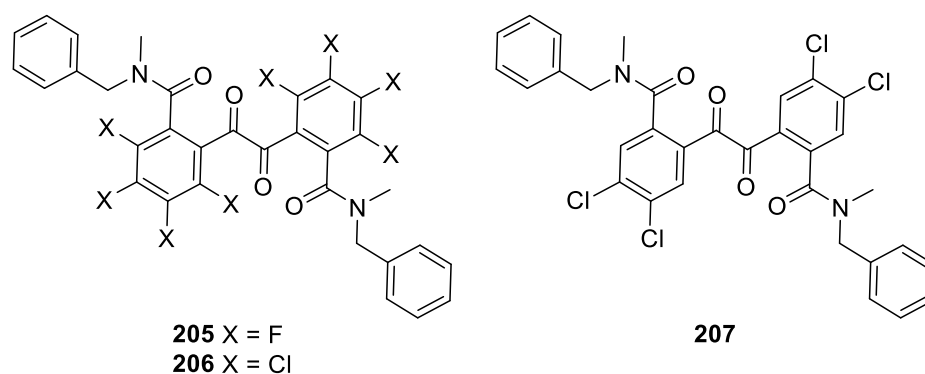
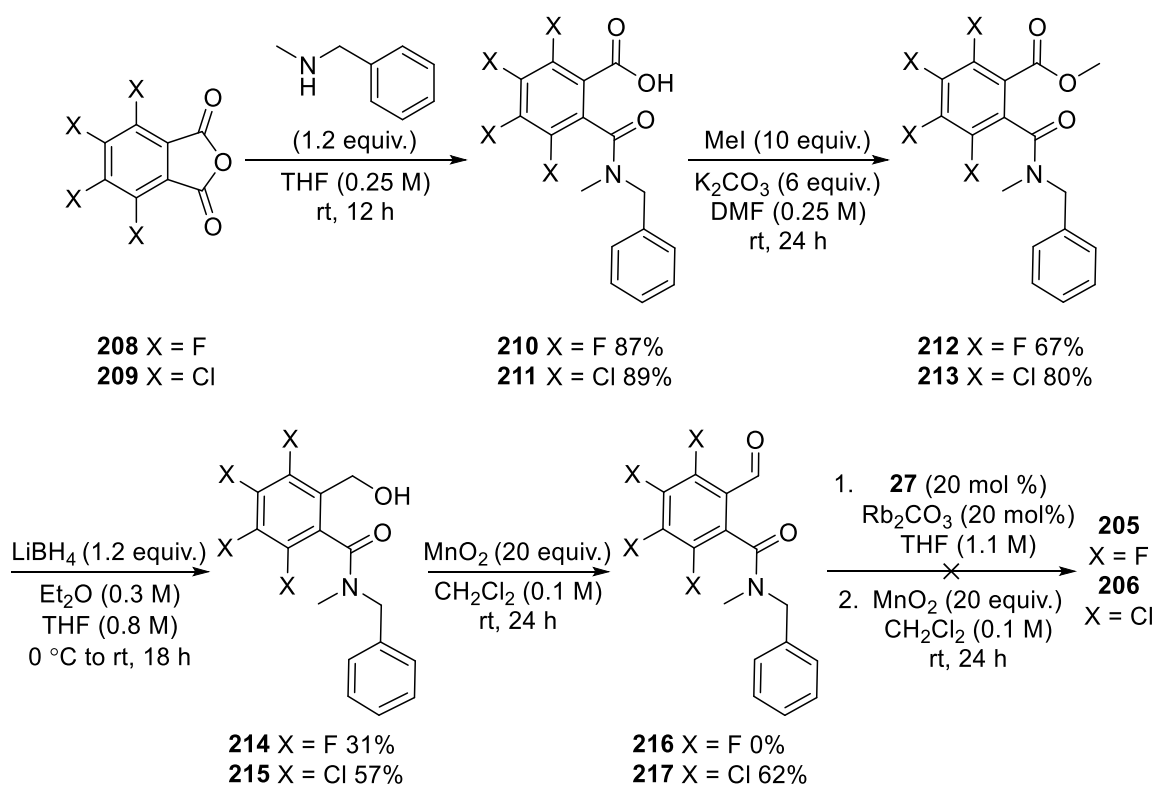


Figure 21 Library of substituted benzils with sp^2 hybridised substituents

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.



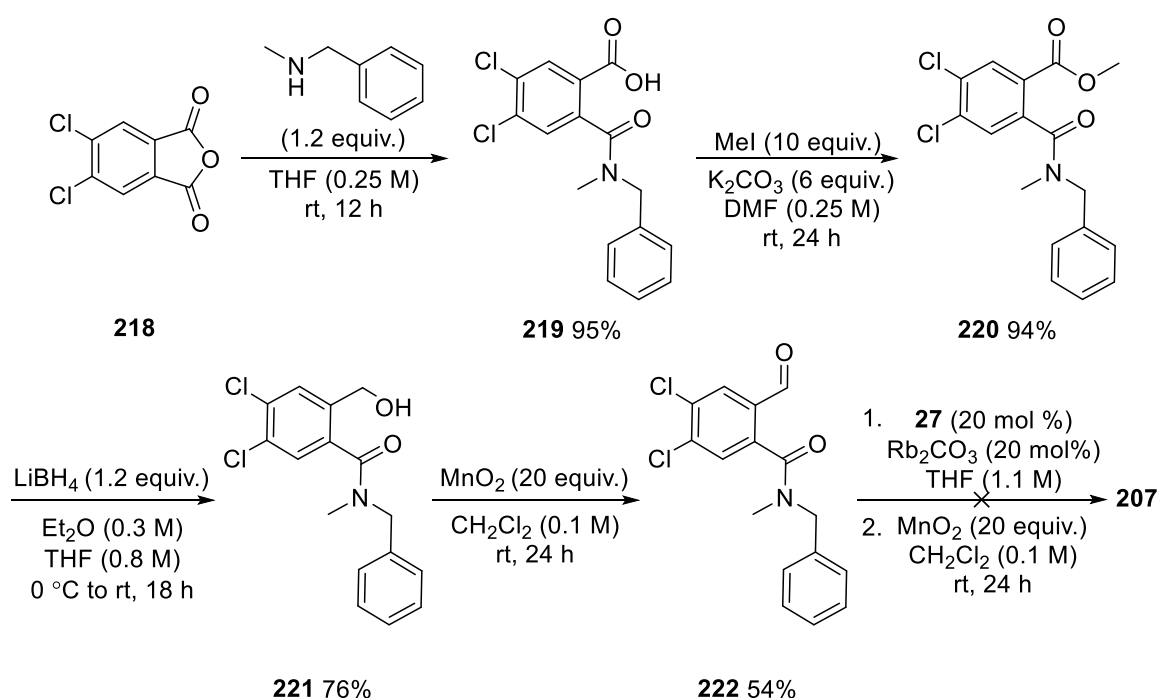
Scheme 56 Synthetic approach towards the synthesis of **205** and **206**

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 ^1H 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).

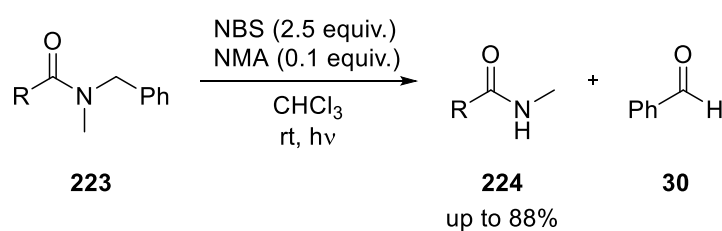


Scheme 57 Attempted synthesis of **207**

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 MnO_2 . 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.

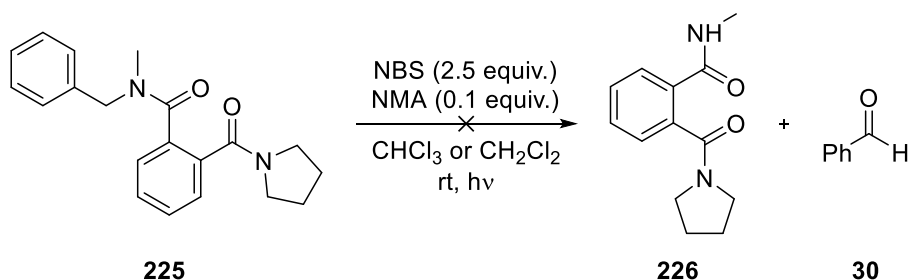
2.4.4 Attempts to cleave the second-generation protecting group

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*-methylacetamide (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 debenzylated 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 ¹H 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).

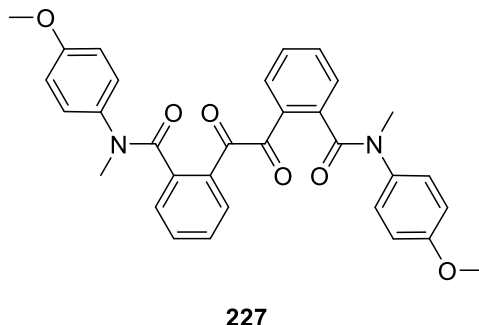
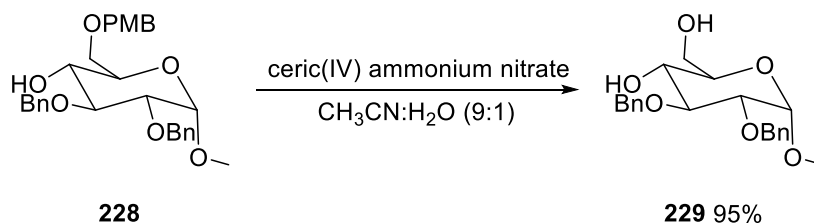


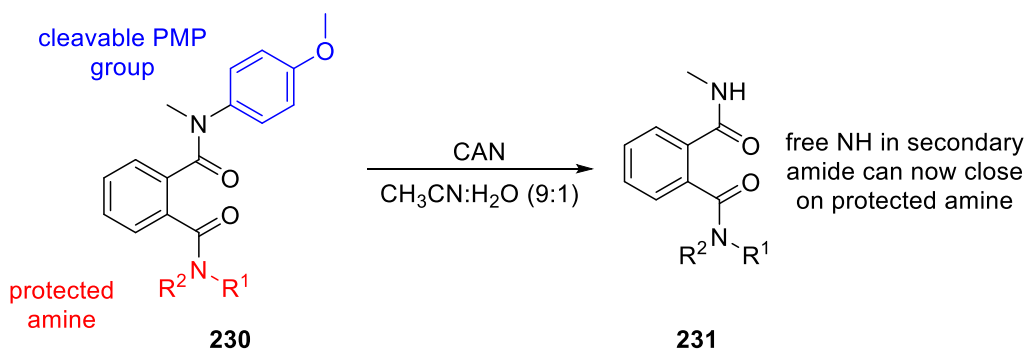
Figure 22 PMP-substituted substrate **227**

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).¹¹²



Scheme 60 PMP deprotection carried out by Sameulsson *et al.*

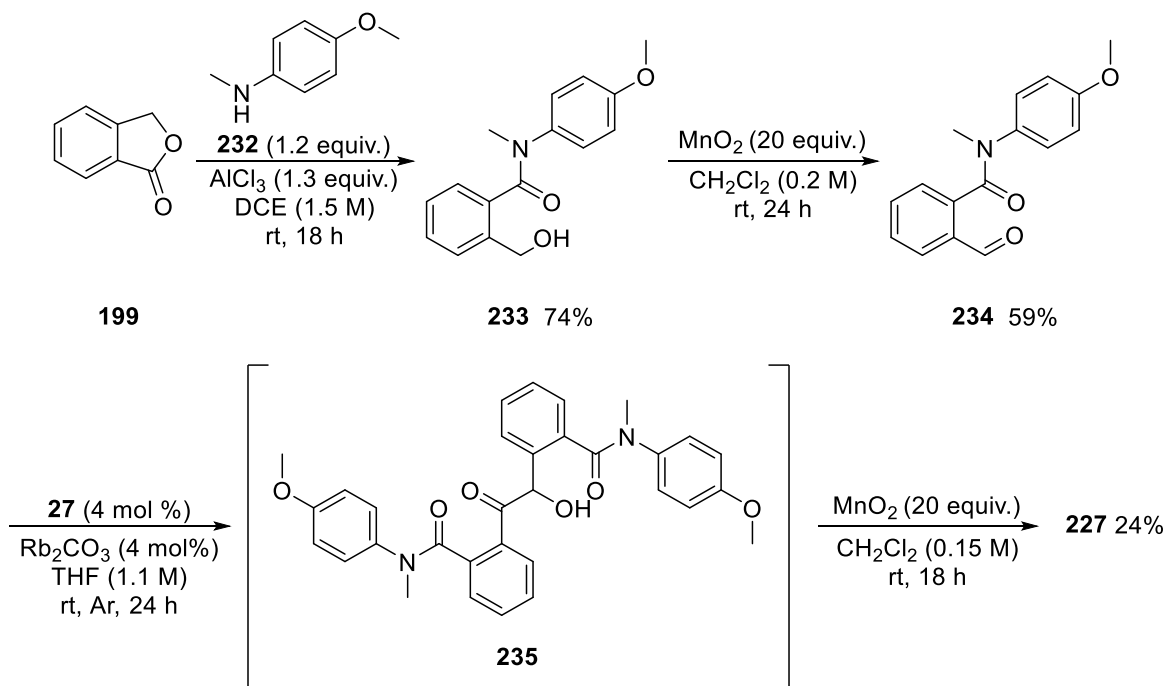
The rationale behind designing substrate **227** was that the PMP group present in the protected amine, such as in **230**, could be cleaved using CAN (at low pHs, in aqueous media) to form the corresponding secondary amide, **231**, which could close upon the protected amine and in doing so, release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



Scheme 61 Proposed deprotection of the protected amine **230** with CAN

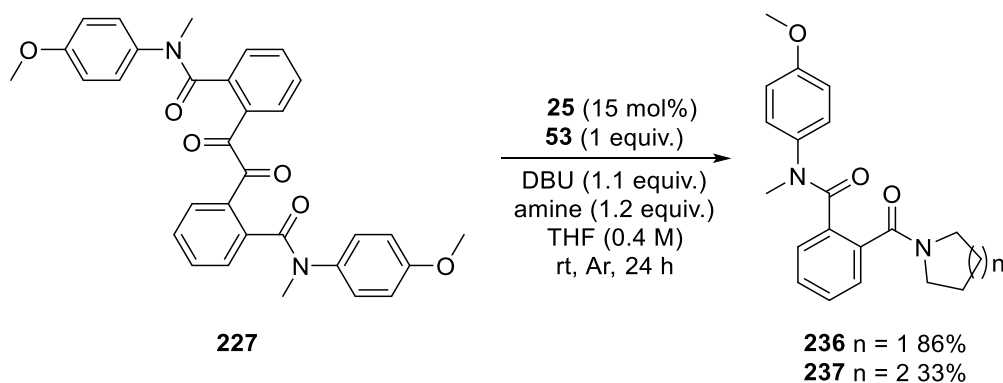
2.5.1 Substrate scope of the third generation protecting group 227

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**

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

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 utmost 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.

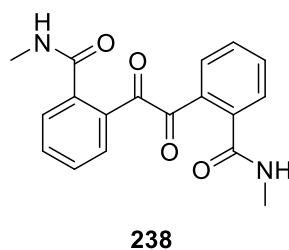


Figure 23 Benzil containing secondary amide

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).

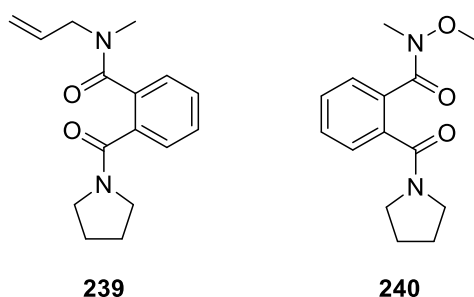
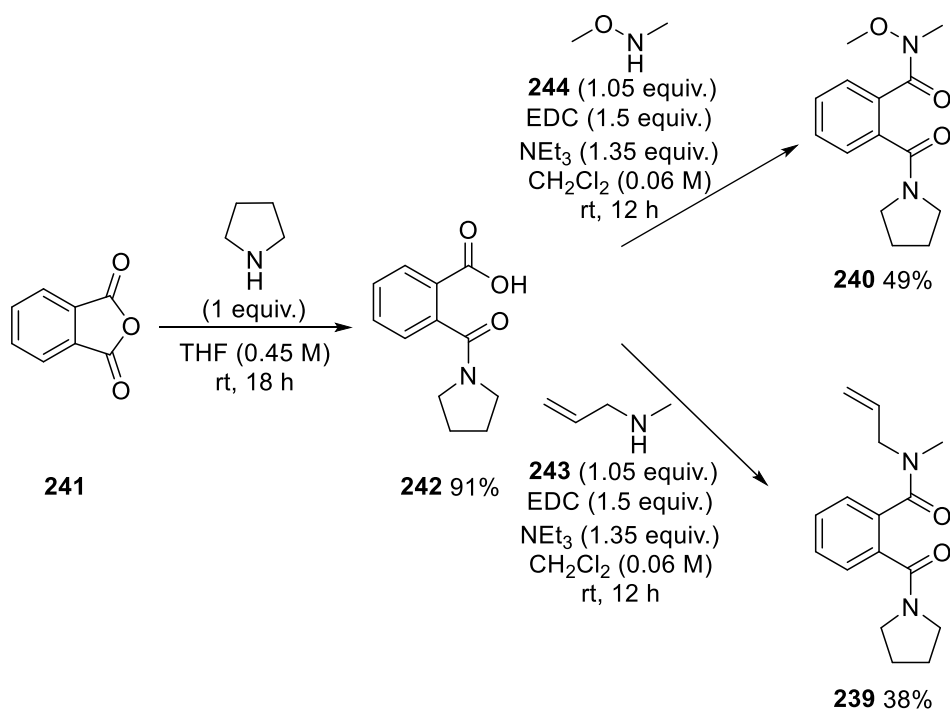


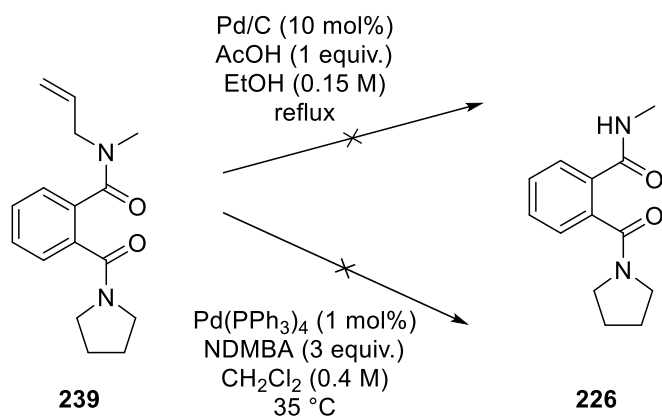
Figure 24 Protected amines **239** and **240**

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).



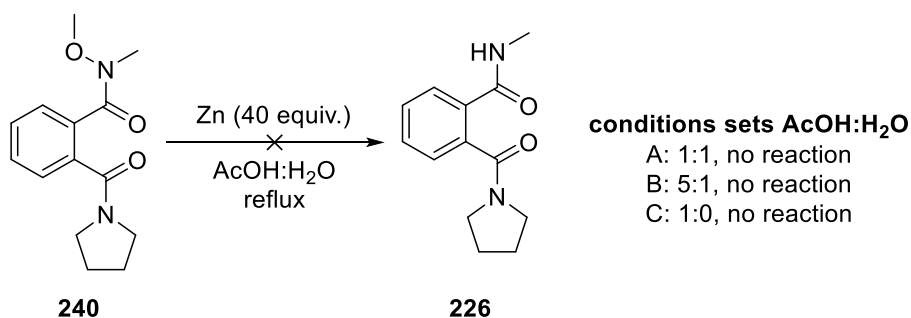
Scheme 64 Synthesis of protected amines **239** and **240**

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)^{172,173} (Scheme 65). 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 ¹H 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 ruthenium¹⁷⁴ and nickel¹⁷⁵) 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**

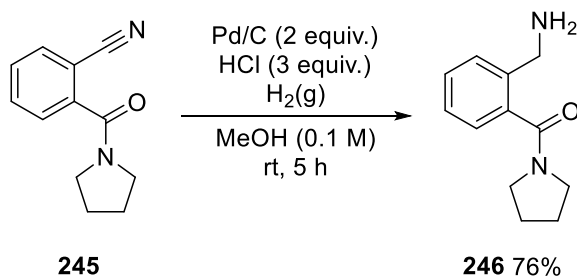
The Weinreb amide was chosen as a cleavable substituent as it has been shown that such alkoxy groups can be reduced from tertiary amines, using activated zinc and acetic acid, to furnish the corresponding secondary amine.¹⁷⁶ Although this example used amines and not amides, the protocol was nevertheless 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 sterically sensitive system (as discussed in Section 2.3.3).



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

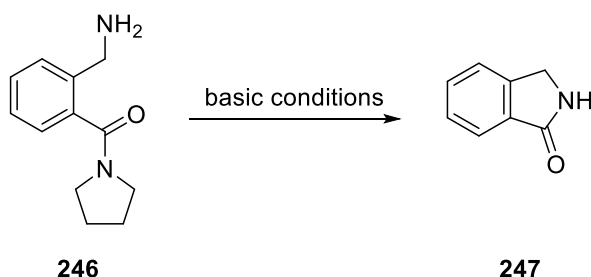
While all the efforts thus far towards the development of a facile deprotection strategy proved unsuccessful, gratifyingly, changing the amide unit *ortho* to the protected amine to a nitrile yielded more promising results. The potential advantages associated with the inclusion of a nitrile substituent 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.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

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

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 *ortho* to the benzil carbonyls.

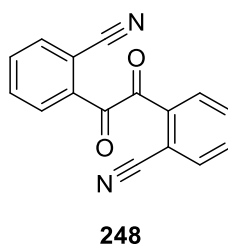
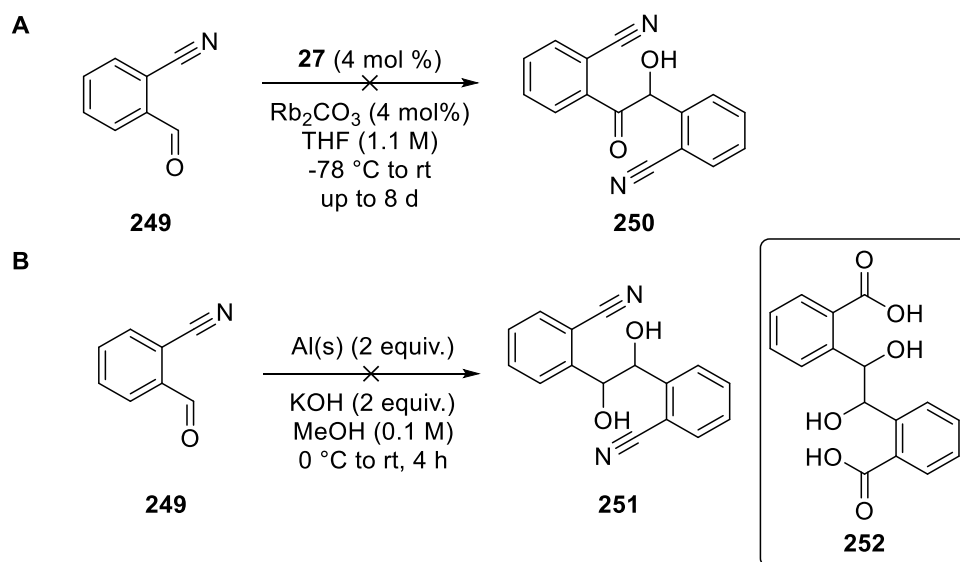


Figure 25 *Ortho*-nitrile substituted benzil **248**

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 $-78\text{ }^{\circ}\text{C}$ and the reaction monitored by ^1H NMR spectroscopy. After 5 days stirring at $-78\text{ }^{\circ}\text{C}$ with no conversion to the benzoin product, the temperature was slowly increased to $-60\text{ }^{\circ}\text{C}$ followed by $-20\text{ }^{\circ}\text{C}$ and $-10\text{ }^{\circ}\text{C}$. 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).



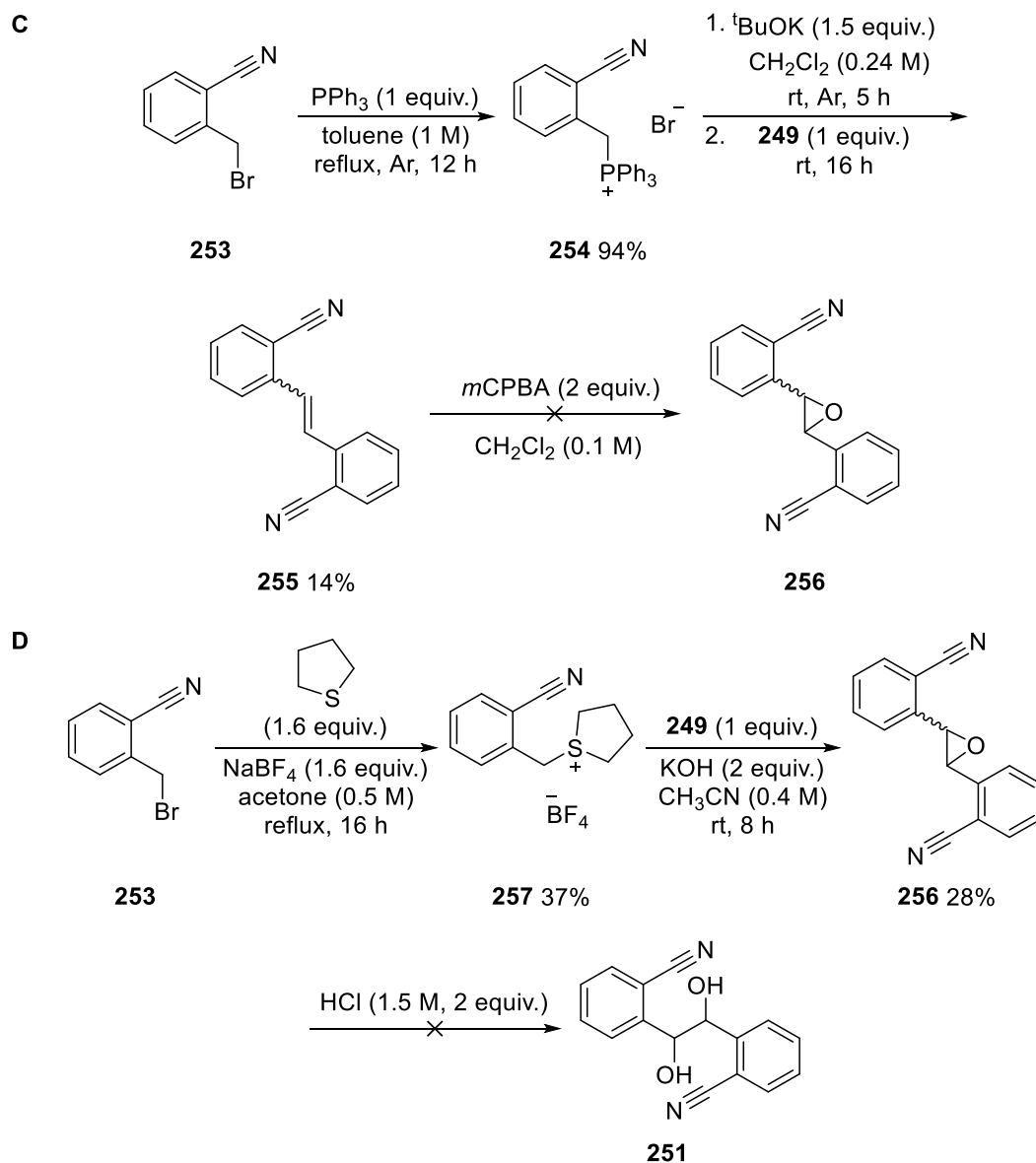
Scheme 69 Attempted synthesis of **248** using coupling reactions

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 triphenylphosphine) (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 (*m*CPBA), 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 ^1H 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 reaction¹⁷⁸ between sulfonium salt **259** and aldehyde **249**; providing the desired product in a low conversion of 28% (determined by ^1H 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).

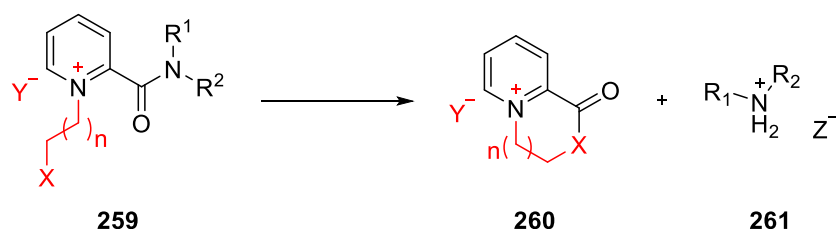
Currently, all efforts towards the synthesis of **248** have proved futile, and even more discouragingly, **249** did not tolerate the benzoin condensation reaction (this is generally an indicator that the corresponding benzil will not withstand the NHC-catalysed oxidative amidation reaction). As a result, it was decided not to pursue the synthesis of **248** any further.



Scheme 70 Attempted synthetic approaches towards **248** via epoxide **256**

2.7 The development of 2,2-pyridil as an acylating agent

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).



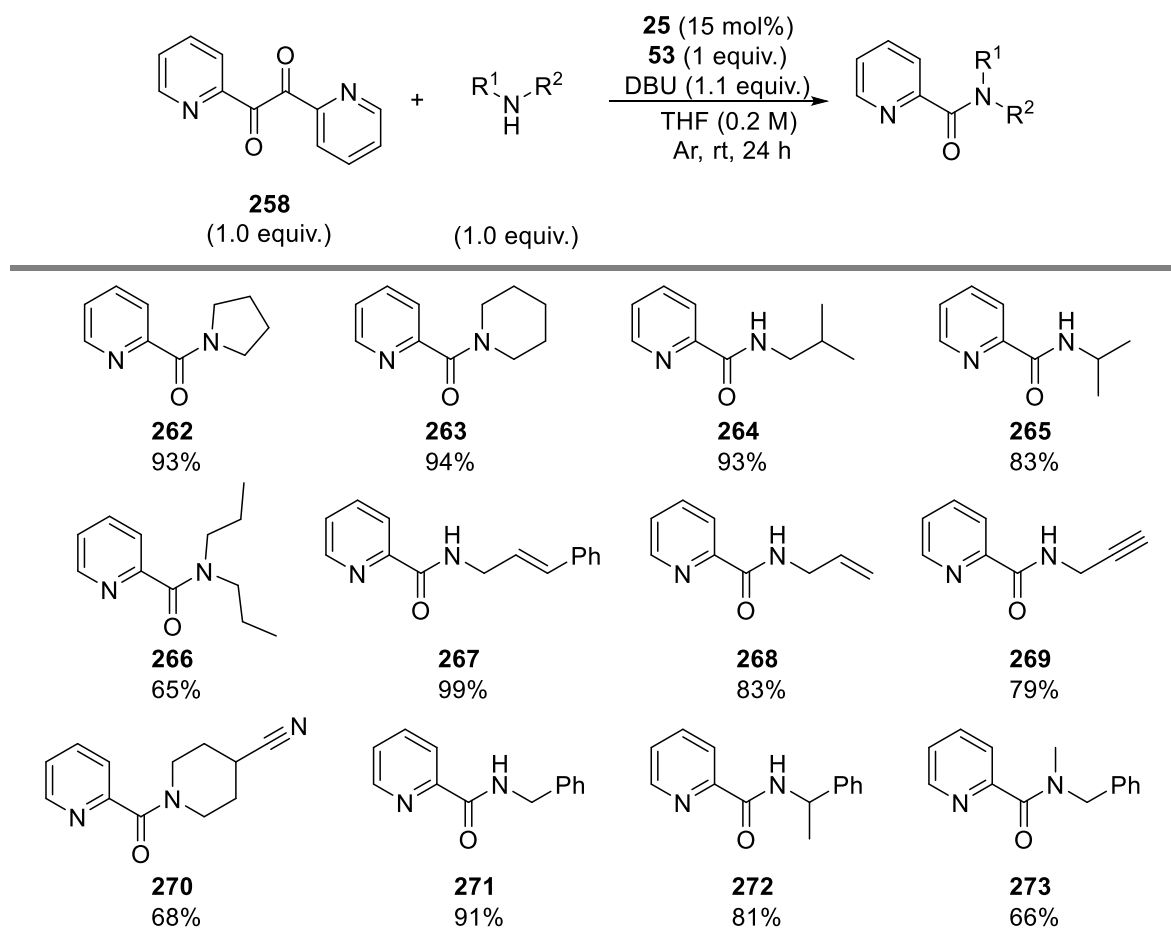
Scheme 71 Postulated modification of the protected amine to allow deprotection

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).

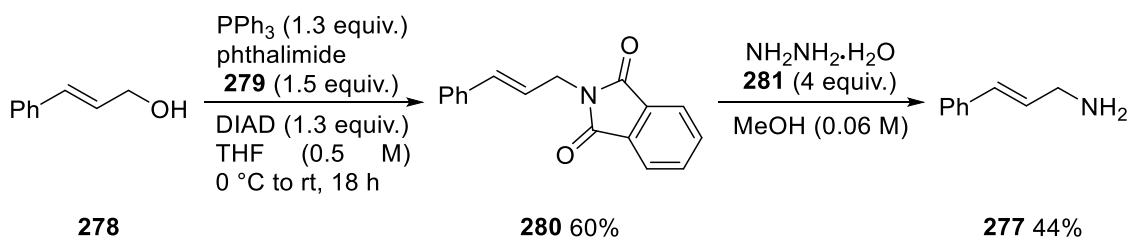
The initial set of amines evaluated were primary and secondary amines. Encouragingly, when the cyclic amines pyrrolidine and piperidine were employed in the reaction, excellent yields of the corresponding amides **262** and **263** (Table 4) were achieved. Comparing these results to the other substrates 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.

Table 4 Substrate scope of 2,2-pyridil (**258**) and various primary and secondary amines



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).¹⁷⁹ Imide **280** was subsequently deprotected using excess hydrazine hydrate (**281**) to render amine **277** in a relatively low yield (Scheme 72).¹⁸⁰



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.

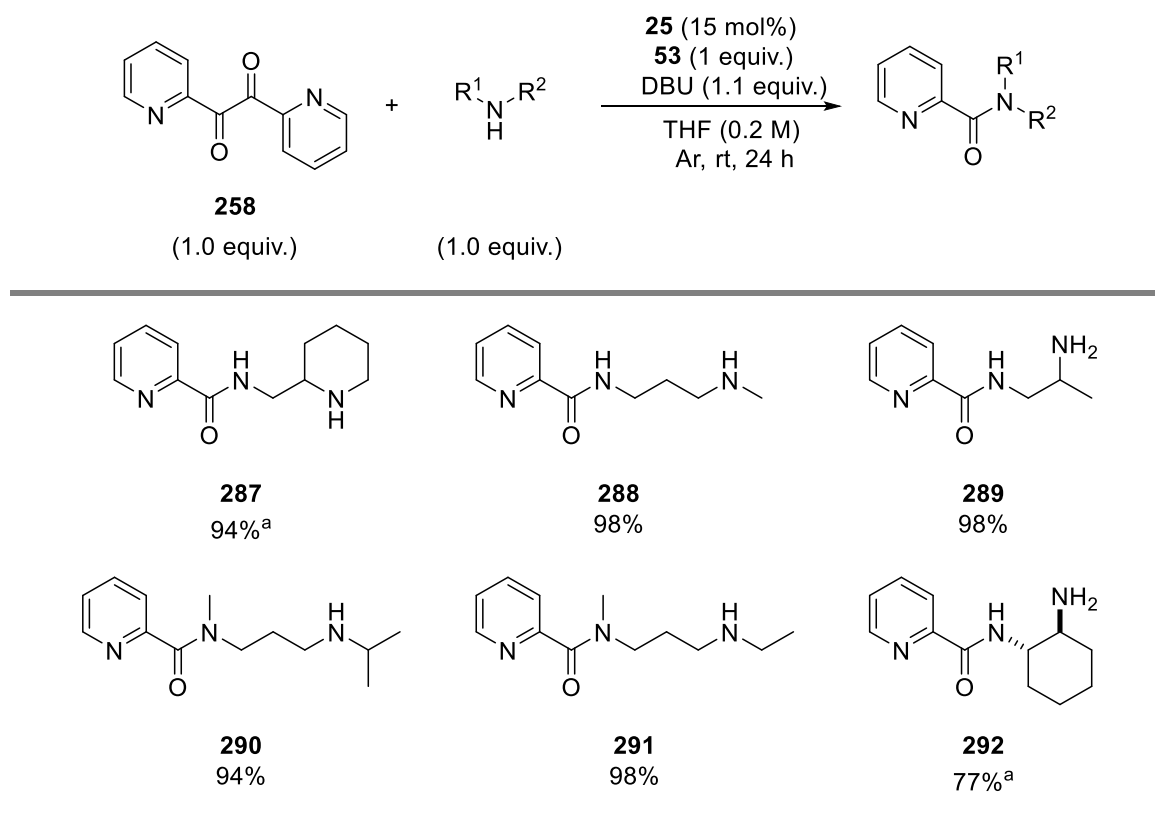
Piperidine-4-carbonitrile (**284**), a cyclic secondary amine containing an electron withdrawing group at the 4-position, was employed in this reaction and produced amide **270** in a somewhat diminished yield (relative to the use of piperidine itself, Table 4). However, these results were pleasing as 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



^a0.5 equivalents of **258** utilised

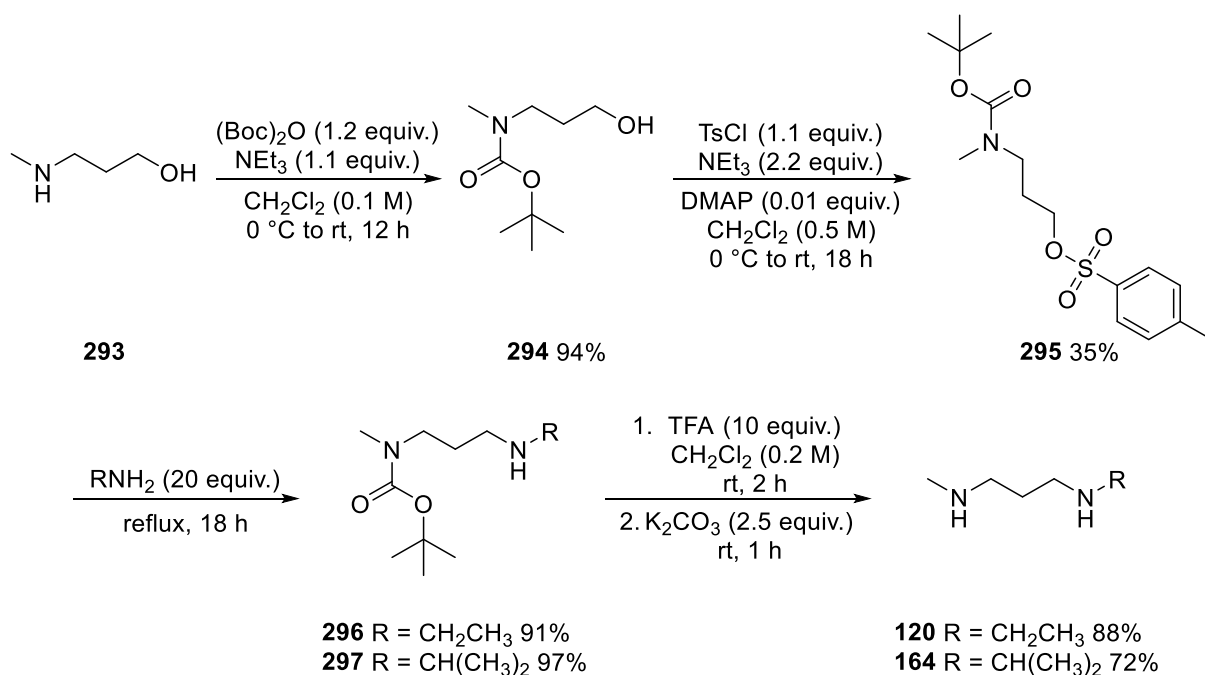
With regard to the reactions involving diamines (Table 5), both the yield of the reaction and the selectivity with regards to the amine being acylated was examined. As it was demonstrated that sterically hindered amines (both primary and secondary) were not tolerated as well as those that are not sterically 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 Synthetic 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 K_2CO_3 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 be 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 ($\pm$)-*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 catalysts^{181,182,183} (e.g. **299** - **301**, Figure 26) and its need to be mono-acylated is of great synthetic interest in catalyst synthesis.

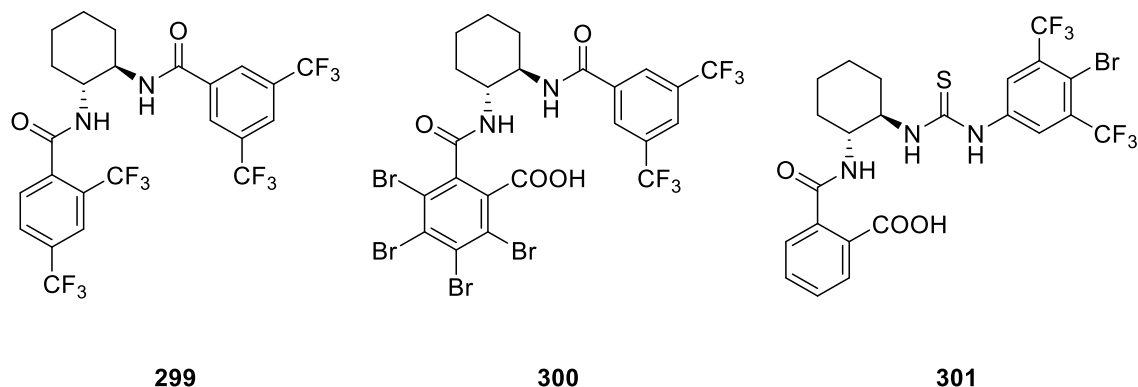
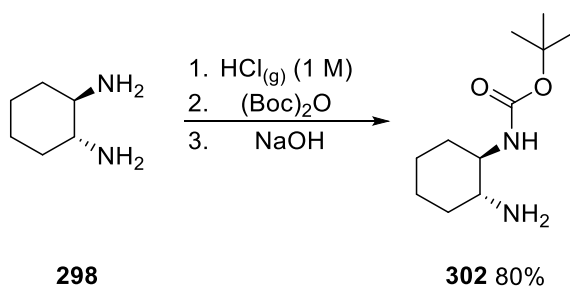


Figure 26 Examples of ($\pm$)-*trans*-1,2-diaminocyclohexane (**298**) cores in asymmetric catalysts

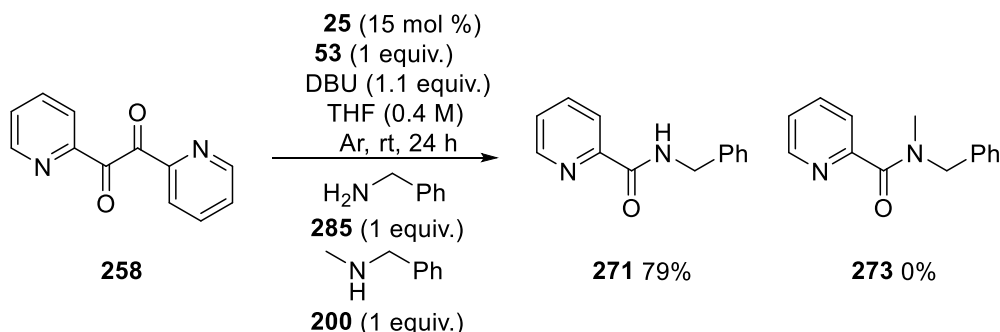
Preparations of mono-acylated **298** have been achieved in the literature however, they require the use of excess **298**, which is undesirable due to its considerable expense. Lee *et al.* reported the mono-Boc protection of **298** in an 80% yield using just one equivalent of the amine and one equivalent 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.*

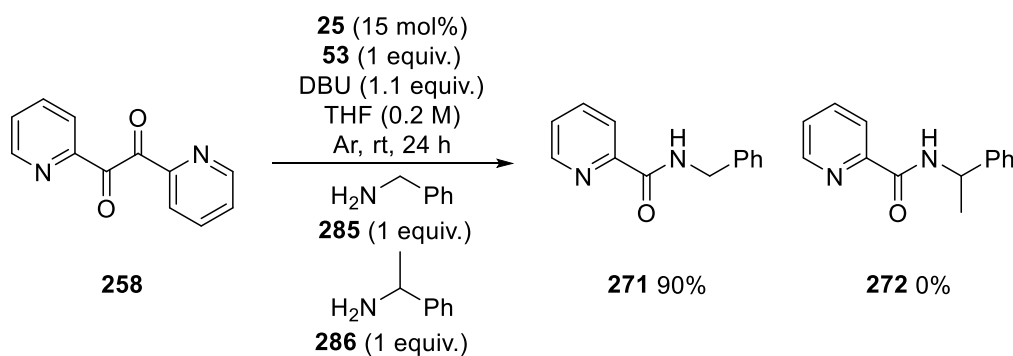
2.7.2 Competition experiments to investigate possible intramolecular hydrogen bonding

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 ¹H 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

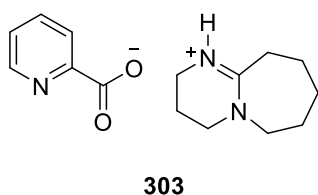


Figure 27 2,2-Pyridil-derived DBU-carboxylate salt **303**

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.

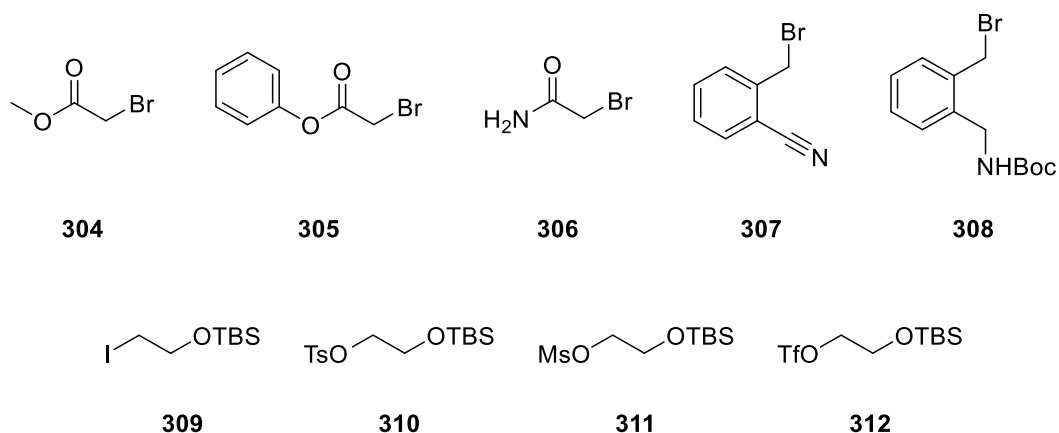
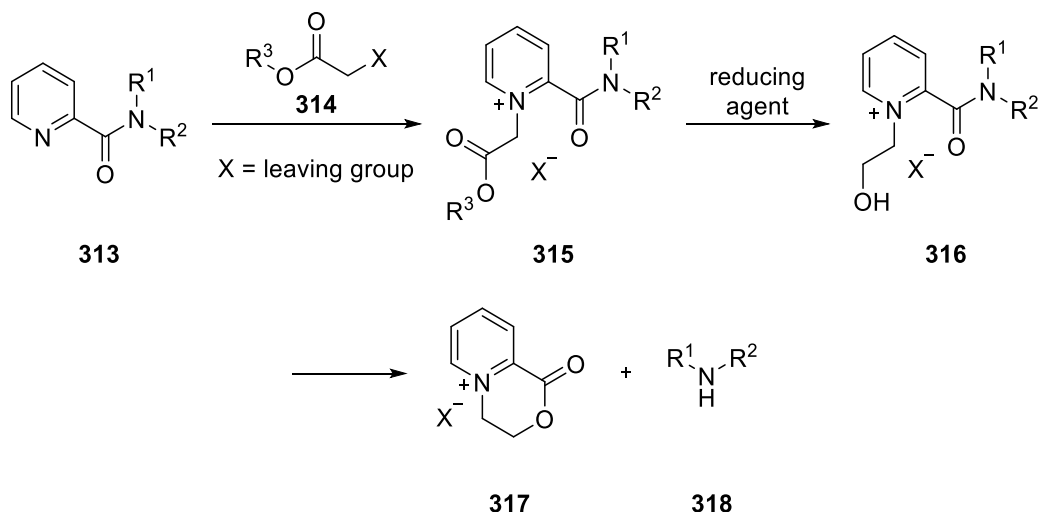


Figure 28 Library of electrophiles tested to promote the cleavage of the pyridoyl moiety

2.8.1 Electrophile screen to promote pyridil cleavage

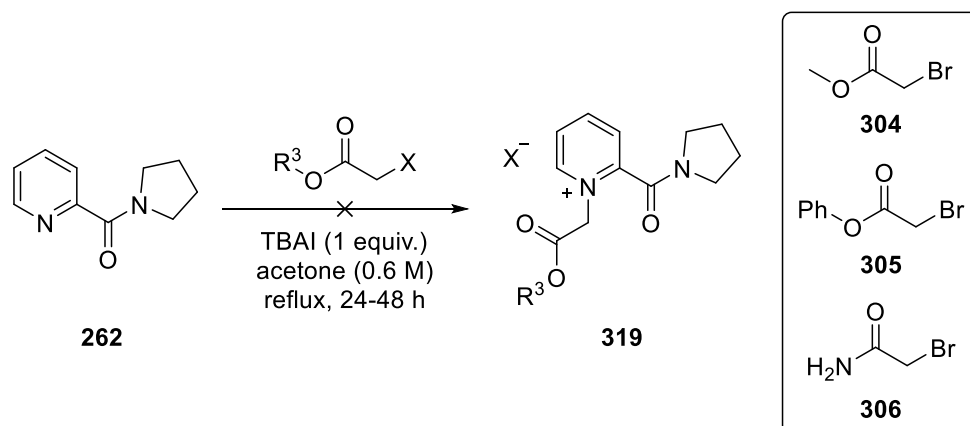
The initial electrophiles screened contained an ester functionality of general structure **314**, the premise being that upon alkylation, the resulting ester **315** could be reduced to alcohol **316** which can attack the carbonyl of the amide, releasing amine **318** (Scheme 77).



Scheme 77 Proposed pyridil cleavage using an ester-containing electrophile

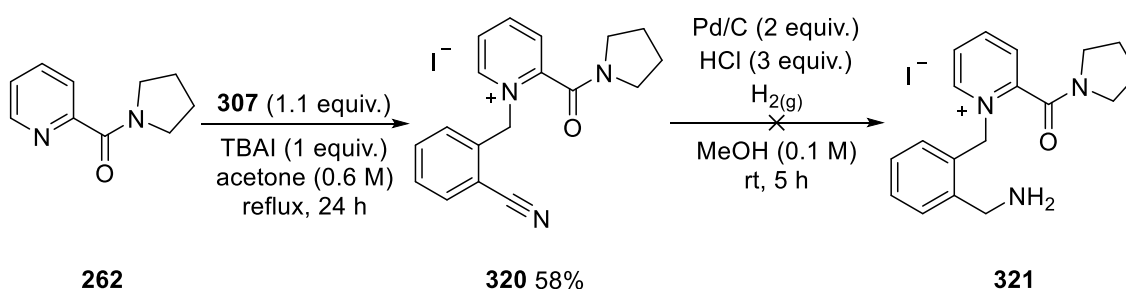
When methyl bromoacetate (**304**) was employed as the electrophile, no reaction between it and the model pyridoyl-protected amine **262** was observed (Scheme 78). The same result was observed when phenyl bromoacetate (**305**) and 2-bromoacetamide (**306**) were utilised (Scheme 78). Heating the reaction 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.



Scheme 78 Electrophiles screened containing ester and amide functionalities

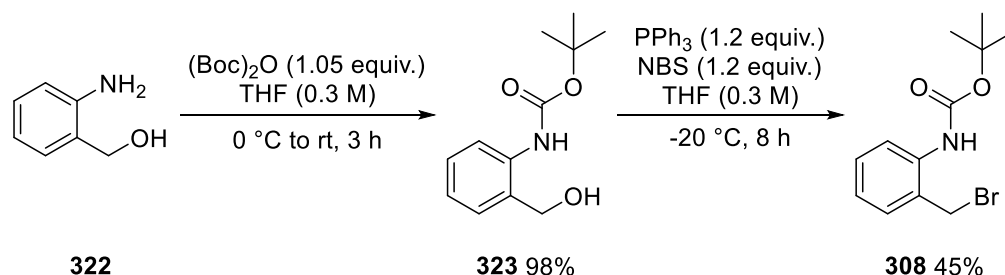
Another electrophile that was screened was 2-(bromomethyl)benzonitrile (**307**). It was postulated that upon alkylation, the nitrile in **320** could be reduced to the corresponding primary amine **321** which could close (possibly facilitated by basic conditions). Reaction of **307** with **262** furnished 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 ¹H NMR spectroscopy and was found to contain multiple compounds, none of which were determined to be the desired product.



Scheme 79 Attempted alkylation approach using electrophile **307**

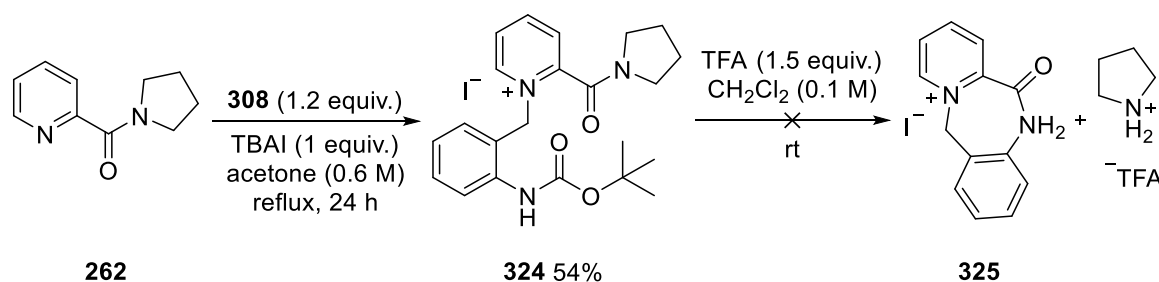
Substituted aromatic benzyl bromide derivative **308** was also evaluated in this alkylation reaction. Incorporating a Boc-protected primary amine *ortho* to the electrophilic site, it was envisaged that once alkylated, removal of the Boc group would render it possible for the primary amine to close 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**

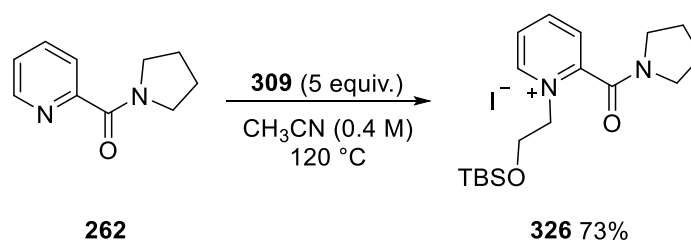
While alkylation of **262** with **308** was possible, albeit in a moderate yield (Scheme 81), problems arose upon deprotection of the Boc group to reveal the primary amine. The use of TFA (a standard deprotection method for removal of Boc groups, see Section 1.6.1.1) to carry out the Boc deprotection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

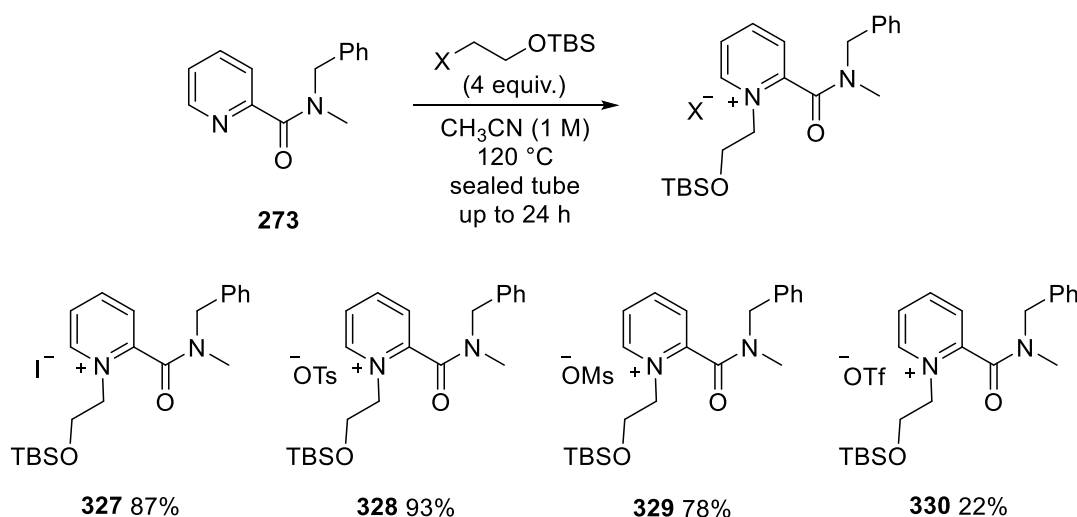
2.8.2 Development of 2-iodoethanol derivatives as electrophiles

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).



Scheme 82 Alkylation of **262** with protected 2-iodoethanol derivative **309**

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 ^1H NMR spectrum which allows the reactions to be easily monitored by ^1H 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.

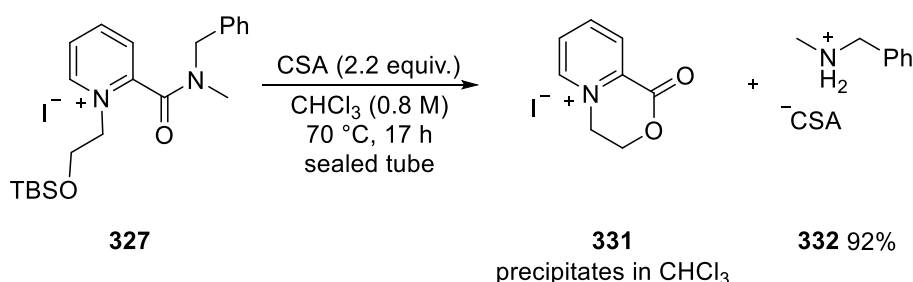


Scheme 83 Evaluation of electrophiles in the alkylation of **273**

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.

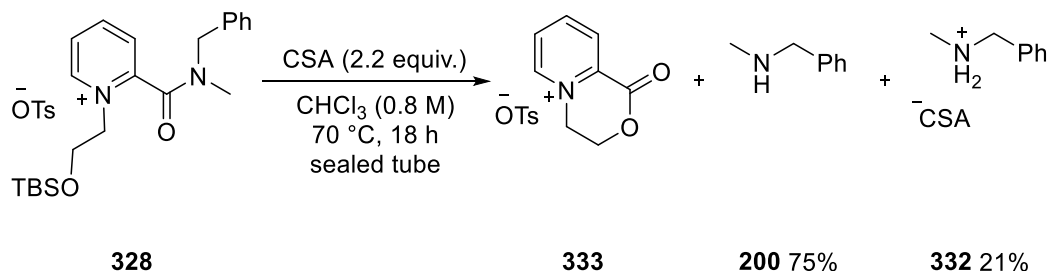
With an alkylating strategy in hand, albeit unoptimised, studies into ring-closure to facilitate amine deprotection were undertaken. Organic iodide salt **327** was first evaluated in the ring-

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 prove 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 ^1H 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 ^1H 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

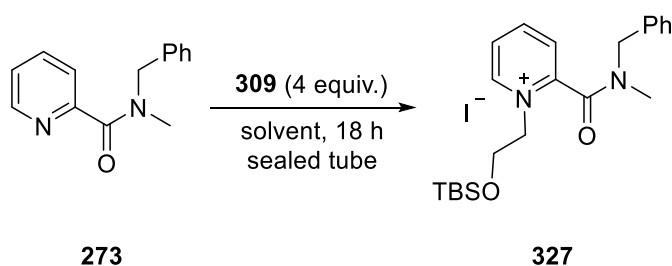
Disappointingly, **333** is soluble in CHCl_3 and so separation of it from **200** and **323** was more cumbersome and required careful extractions. Other solvents were screened in this reaction (CH_2Cl_2 , toluene, DMF, CH_3CN) but yields were highest when CHCl_3 was used. Although tosylate salt **328** 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 S_N2 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

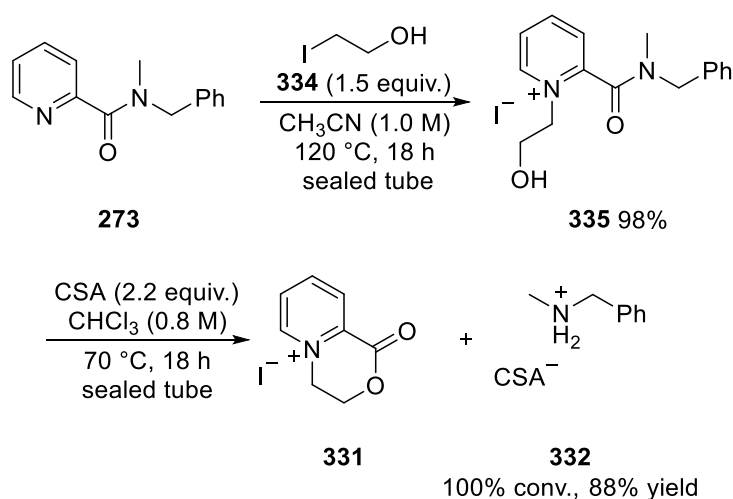


entry	solvent	temperature (°C)	yield ^a (%)
1	CH ₃ CN	120	87
2	acetone	60	20
3	DMF	120	n.d.
4	DMSO	120	n.d.

^aIsolated 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

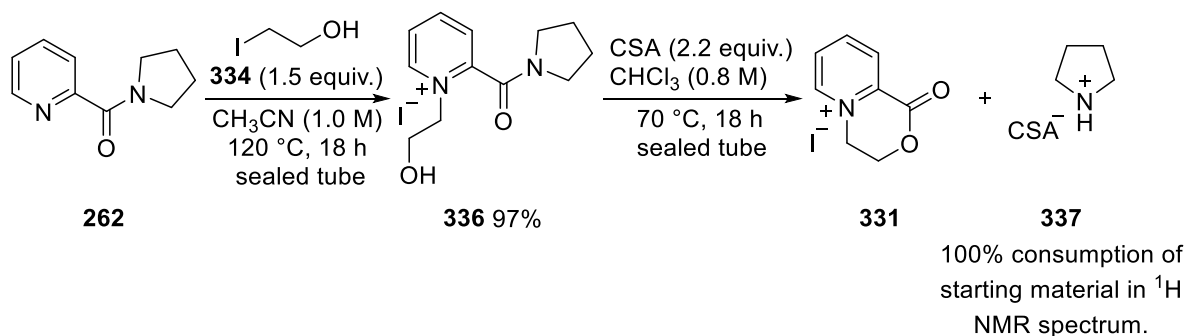
120 °C (boiling point of DMF: 153 °C at s.t.p.), the reaction mixture was complicated to analyse by both TLC analysis and ^1H NMR spectroscopy as many products were observed and it was difficult to identify any discernible amounts of **327**. While DMSO did facilitate alkylation of **273** (68% conversion 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**

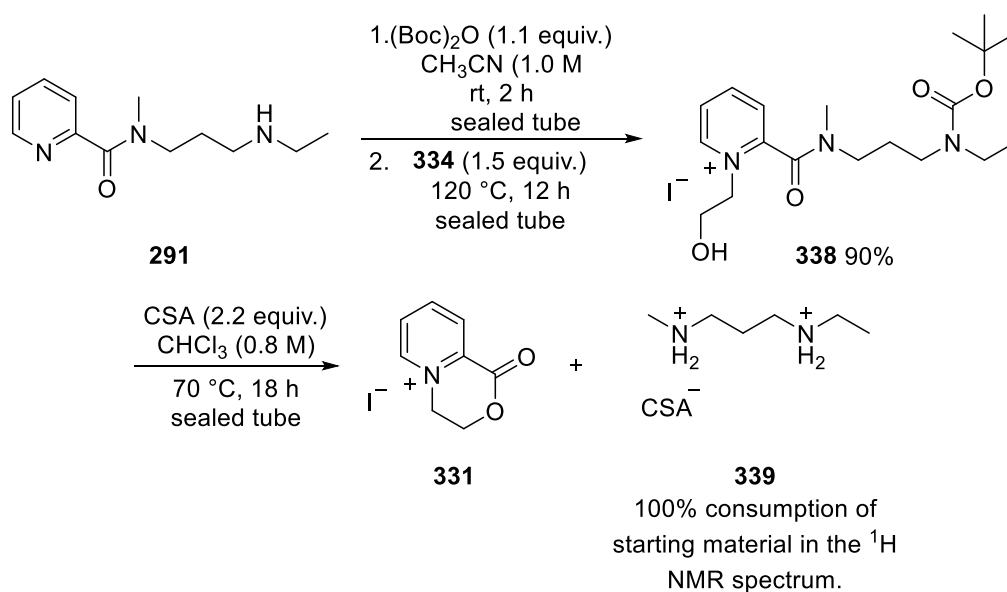
This methodology could be extended to other tertiary amides such as pyrrolidine amide **262** (Scheme 87). Again, alkylation was carried out in an excellent yield and ring-closure was successful with 100% of salt **336** being converted to lactone **331** and the pyrrolidine CSA salt **337** being recovered (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

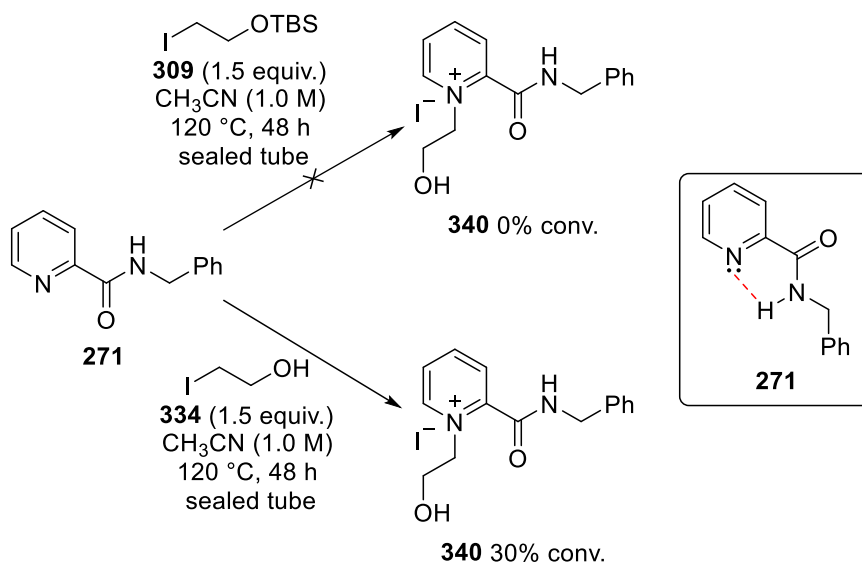
Amides which were the products of the chemoselective acylation such as amide **291** which contains a free amino group, were deprotected using a similar methodology, however, the amino group was first Boc-protected to prevent its possible acylation by **334** (Scheme 88). A one-pot Boc-protection and 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 ^1H 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 ^1H 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

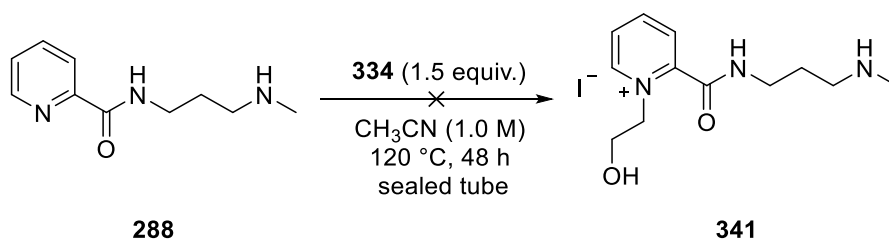
2.8.4 Extending the methodology to amides incorporating free amino groups

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).



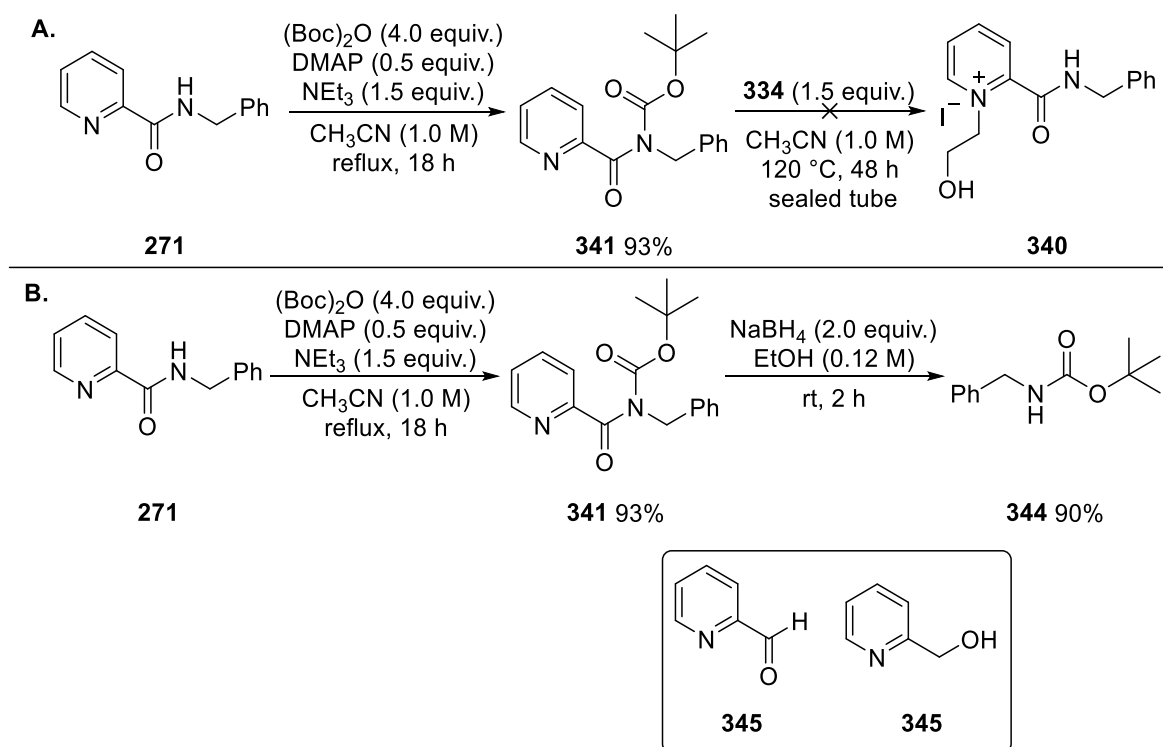
Scheme 89 Attempted alkylation of secondary amide **271**

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**

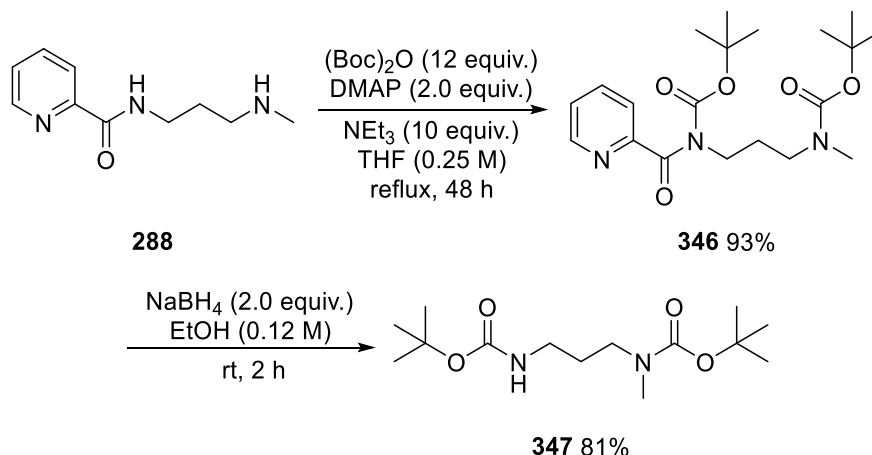
A means to overcome this problem was to protect the free amido unit of **271** with a Boc group and then carry out the alkylation reaction as depicted in Scheme 89A. However, Boc-protection of **271** to furnish **342** did not allow for alkylation to proceed with **334**, presumably due to the additional 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 trivial¹⁸⁸ 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

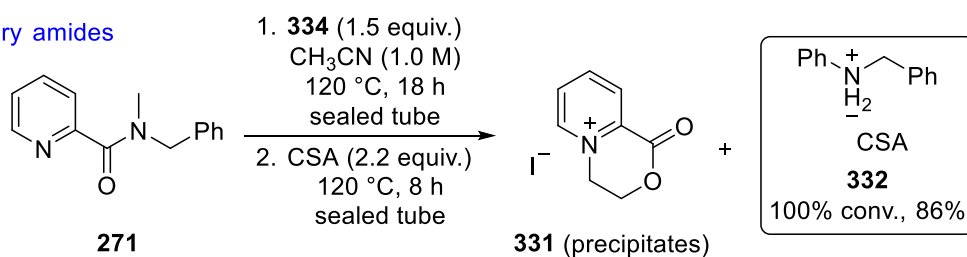
Having previously carried out the NHC-catalysed acylation of diamines using benzil (**70**, Scheme 47), it was observed that this reaction occurred with unprecedented levels of chemoselectivity; the least hindered amine in the system being acylated preferentially. This unexpected result can be explained by the sterically hindered reaction intermediates in the catalytic cycle of this reaction.⁷⁶ 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.

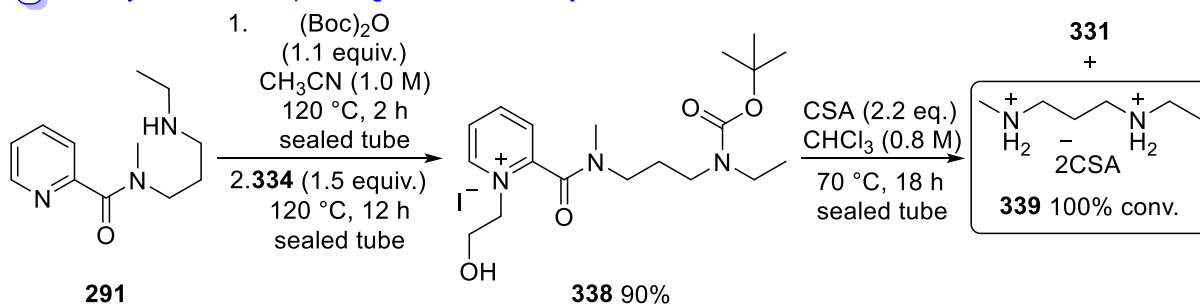
Alkylation of the nitrogen atom of the subsequent pyridoyl amides allowed for the deprotection of the amines. A novel set of conditions was developed to deprotect the monoacylated pyridoyl amines, without requiring the harsh acidic and basic hydrolytic conditions associated with cleaving benzoyl units 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.

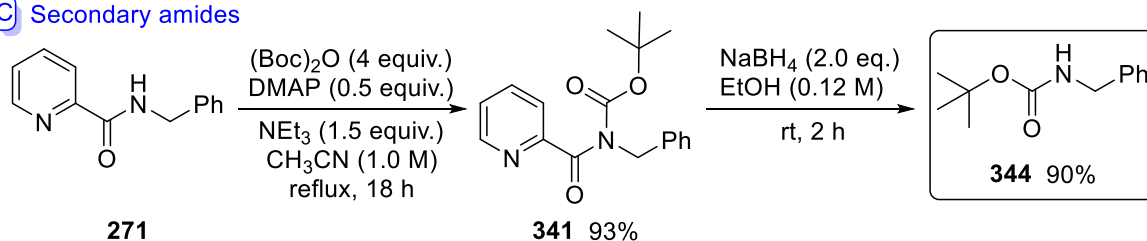
A Tertiary amides



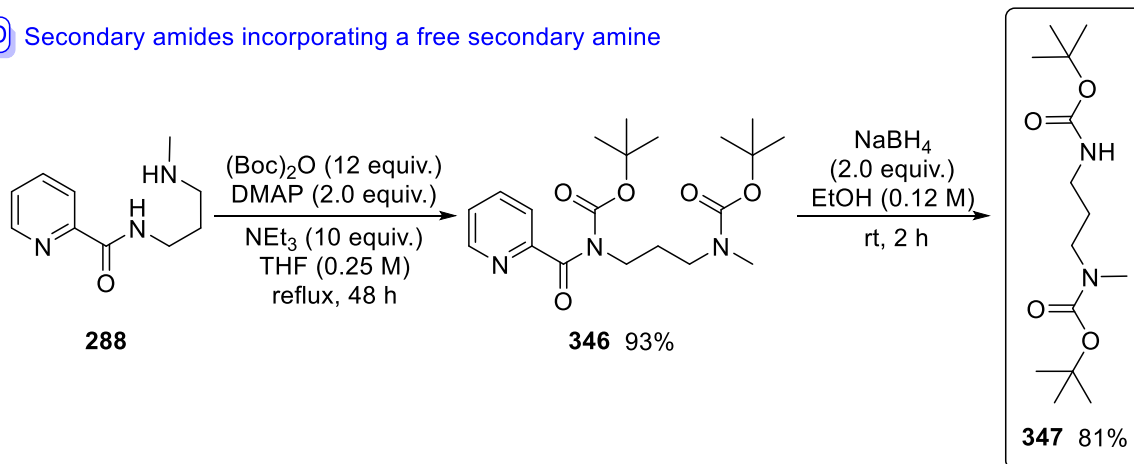
B Tertiary amides incorporating a free secondary amine



C Secondary amides



D Secondary amides incorporating a free secondary amine



Scheme 93 Summary of pyridoyl-amide cleavage

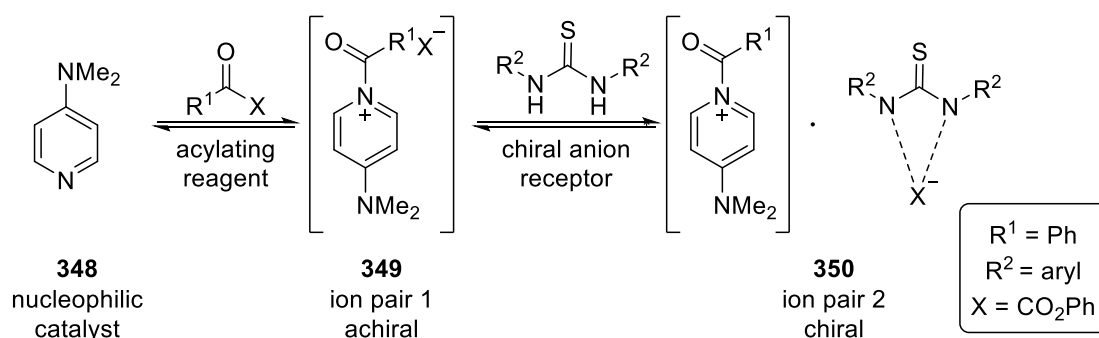
Chapter 3 DKR of azlactones *via* aminolysis

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 a *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

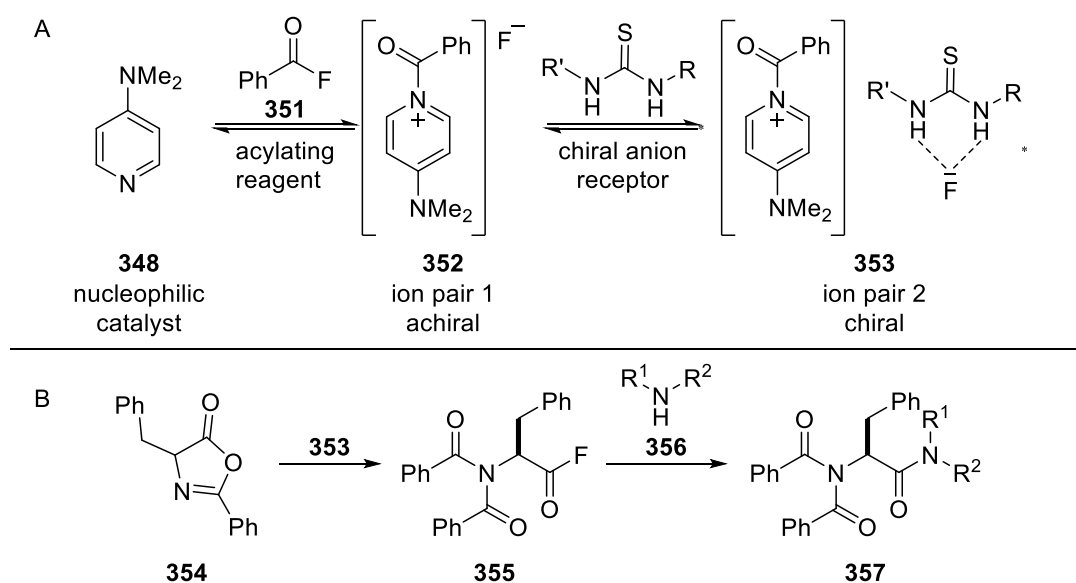


Scheme 94 Seidel's anion-binding concept for asymmetric acyl transfer reactions¹⁹⁰

This chiral acylating agent is generated *in situ* via an interaction between three components: DMAP (**348**), an achiral acylating reagent and a chiral anion receptor/hydrogen bond-donating catalyst.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.

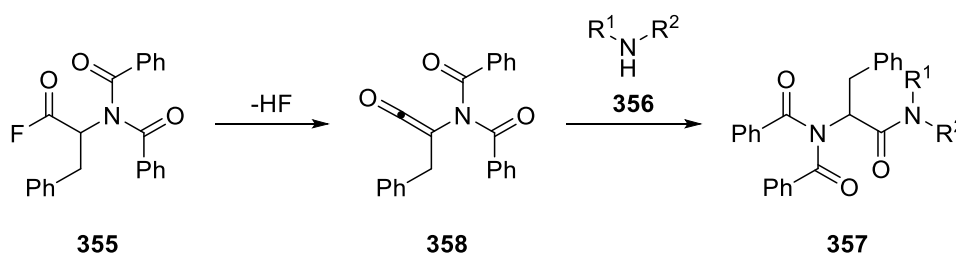
Seidel and co-workers employed this strategy in a range of acyl transfer reactions including: the Steglich rearrangement of *O*-acylated azlactones; the desymmetrisation of *meso*-diamines and the kinetic resolution of various amines.¹⁹⁰ In each case, this novel form of catalysis was carried out utilising 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.



Scheme 95 Aminolysis strategy carried out by Ms. Sarah Cronin

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 benzoyl 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 , ^{13}C 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.



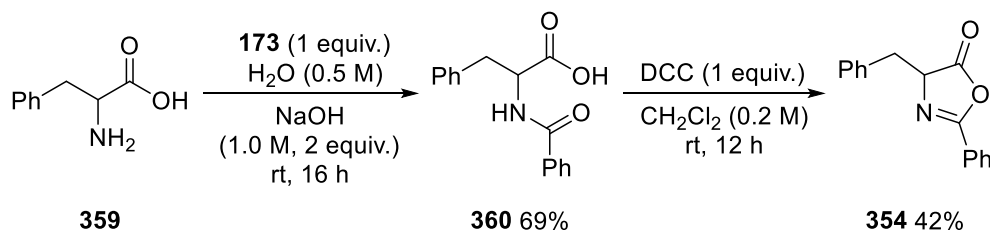
Scheme 96 Elimination of hydrofluoric acid to form ketene **358**

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.

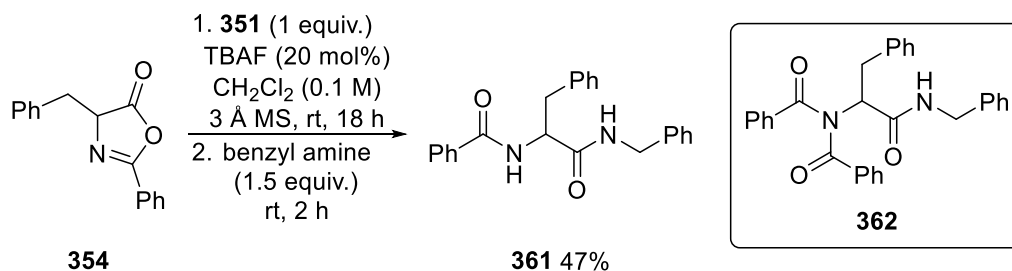
The azlactone used in this racemic study was derived from DL-phenylalanine (**359**). Acylation of the amino group of **359** using benzoyl chloride (**173**), under basic conditions,

produced *N*-benzoyl amide **360**. Intramolecular ring-closure of **360** was carried out using *N,N'*-dicyclohexylcarbodiimide (DCC) to produce azlactone **354** (Scheme 97).



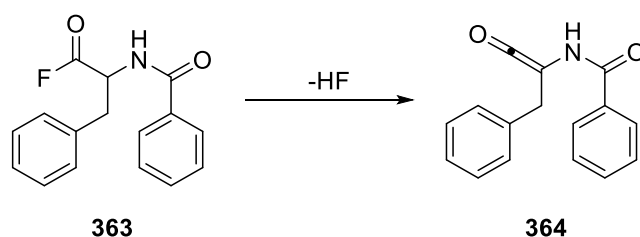
Scheme 97 Synthesis of azlactone **354** derived from DL-phenylalanine (**359**)

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_2Cl_2 as the solvent and with the addition of molecular sieves, to maintain strictly anhydrous conditions (Scheme 98).



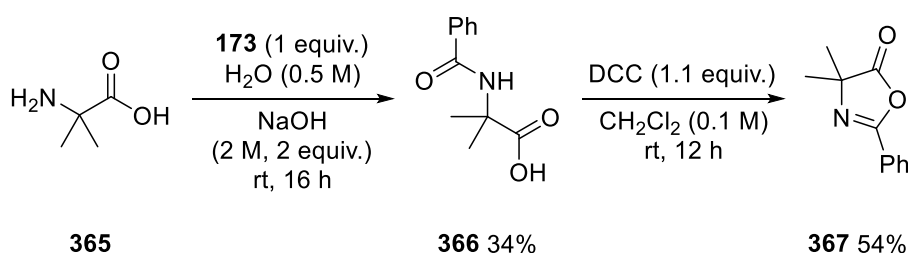
Scheme 98 Initial attempted aminolysis of **354** using PTC conditions

The reaction was carried out at room temperature for 18 hours after which time 100% of **354** was consumed (determined by ^1H 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 ^1H 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 ^1H 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.



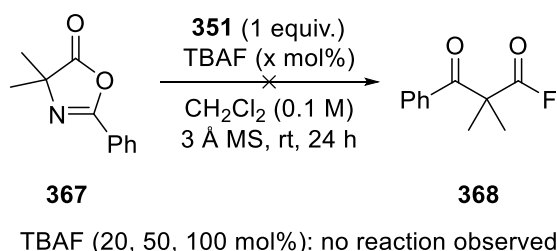
Scheme 99 Elimination of HF from mono-acylated intermediate **363** to form ketene **364**

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).



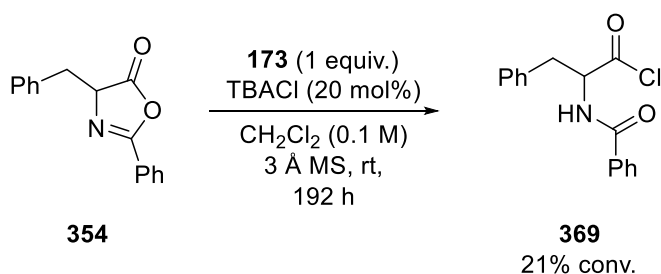
Scheme 101 Attempted fluoride mediated ring-opening of **367**

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

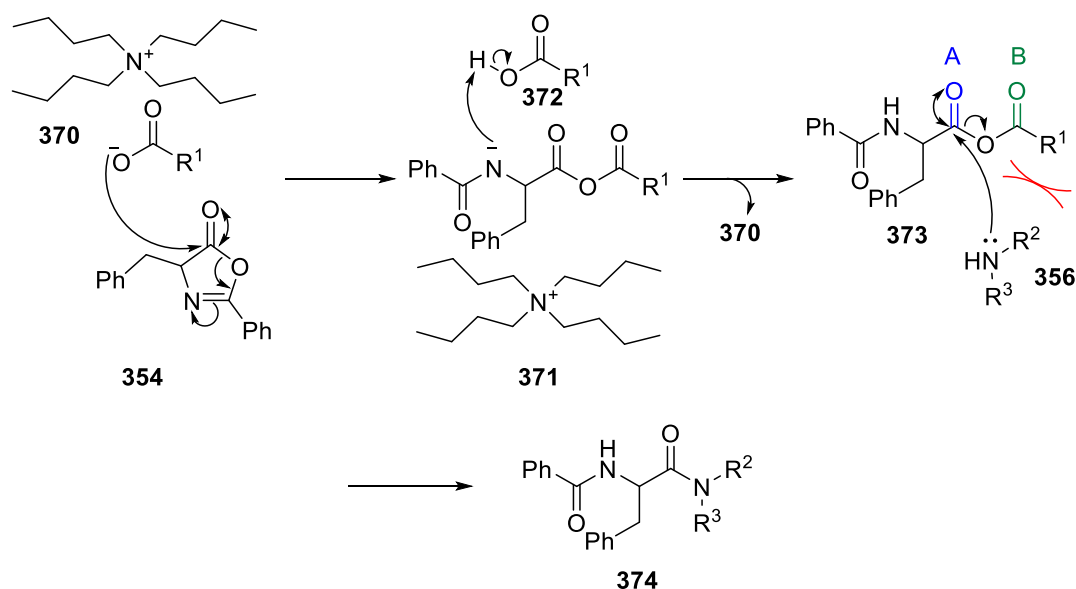
As fluoride was ruled out as an anion to carry out azlactone ring-opening, attention was turned to other (less basic) anions that could potentially be used to carry out this transformation. The other anions tested were chloride, as well as carboxylate anions; acetate, benzoate and pivalate.

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**.



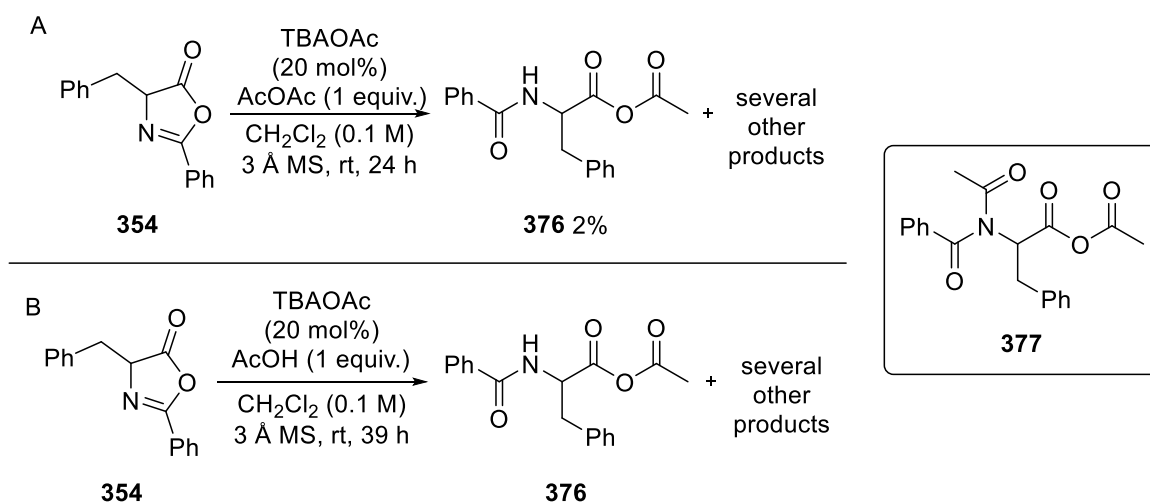
Scheme 102 Attempted ring-opening of **354** using chloride

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 ^1H 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 *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).



Scheme 104 Ring-opening of **354** by an acetate anion

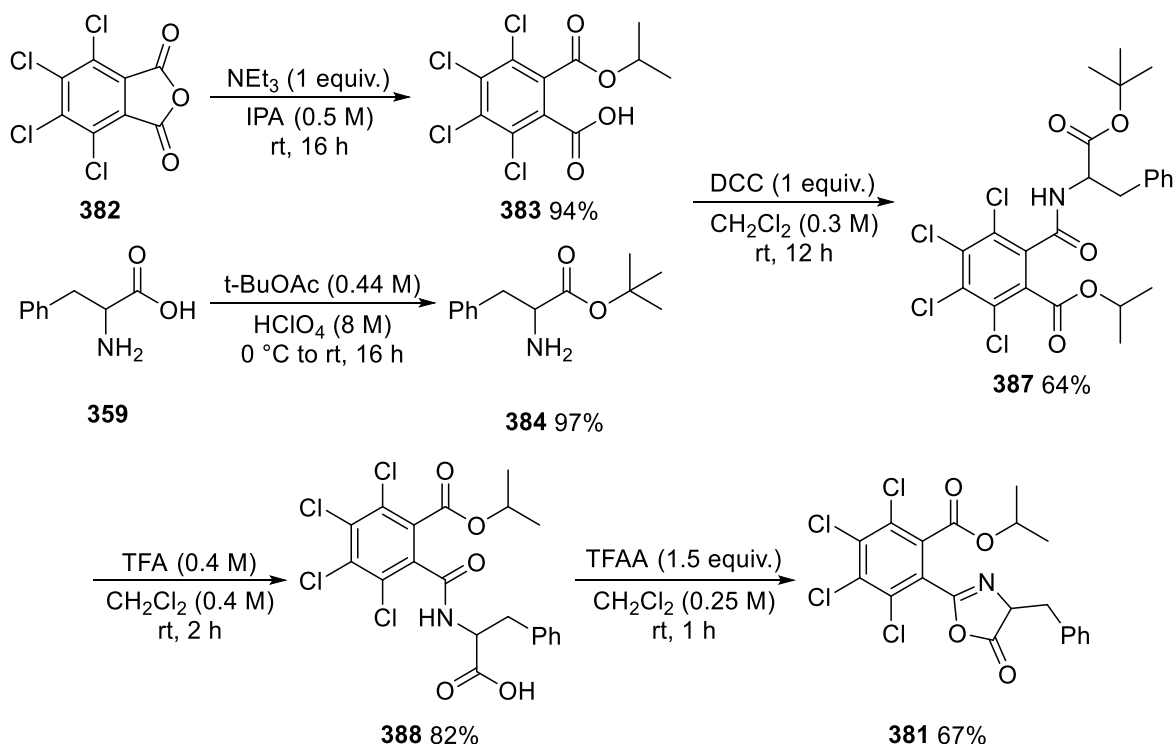
When acetic acid (**378**) was used in the place of **375**, 71% of **354** was consumed after 39 hours, however, analysis of the ^1H NMR spectrum of the crude reaction mixture showed that while **354** was being consumed, again, many products were being formed. Mixed anhydride **376** was tentatively assigned as being formed in 24% yield (determined by analysis of the ^1H 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 ^1H 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 Cannon and co-workers report (Scheme 105).¹⁵⁶ 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 ^1H 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.

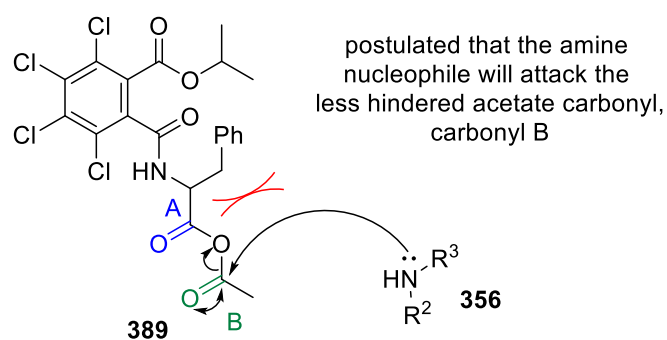
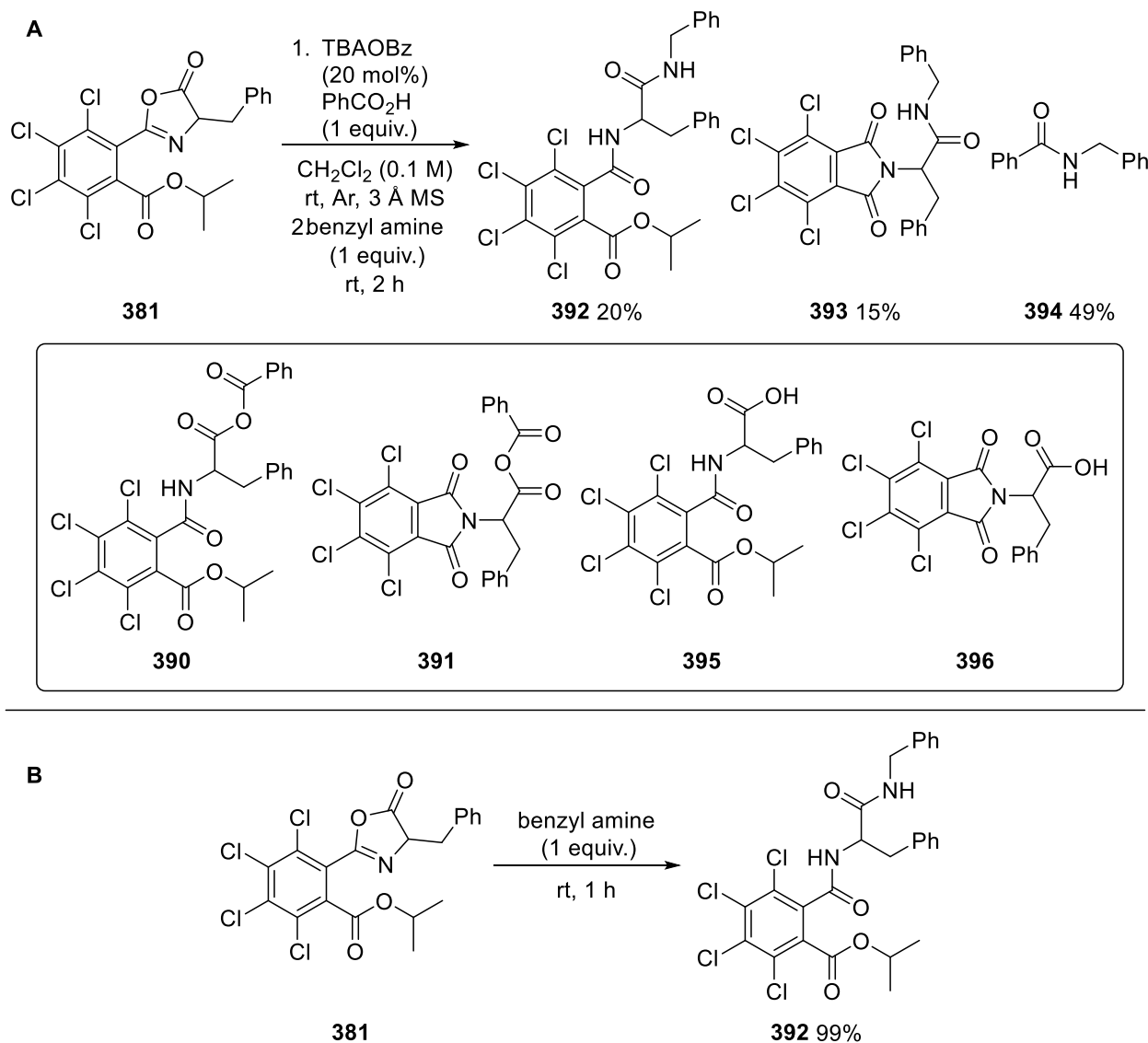


Figure 29 Addition of an amine nucleophile **356** to mixed anhydride **389**

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 CH_2Cl_2 (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 Cannon and co-workers required the addition of an external base (DABCO, 20 mol%) to bring about this ring-closure,¹⁵⁶ 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).

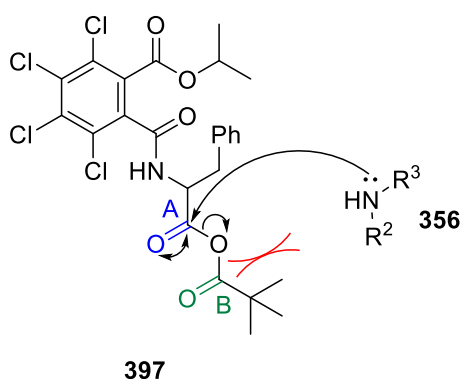
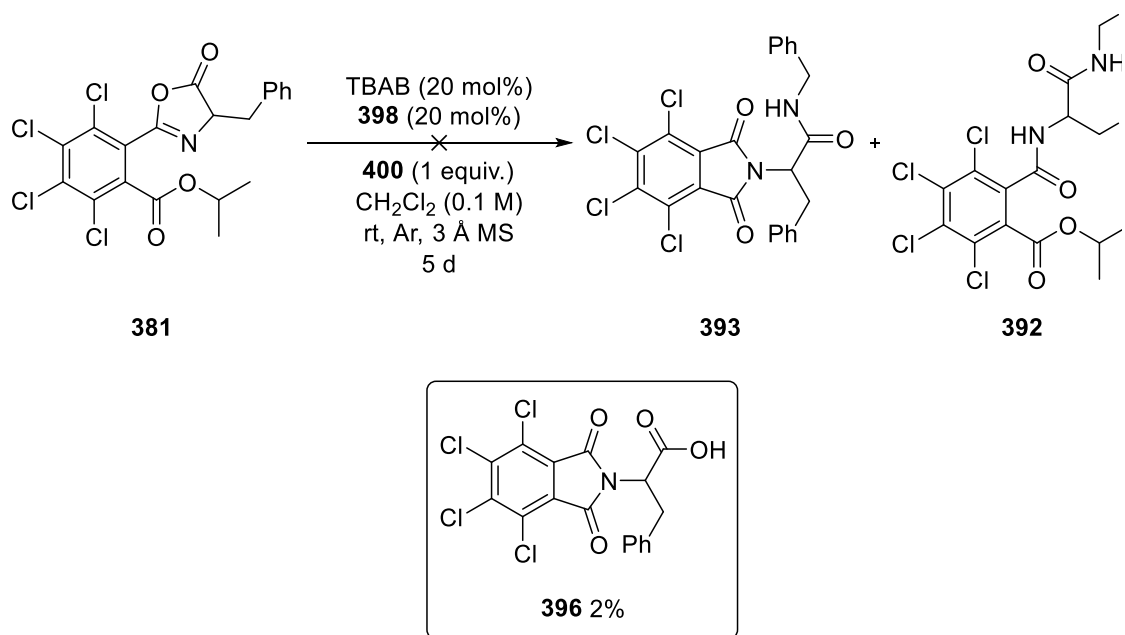


Figure 30 Proposed mixed anhydride **397** which is formed after pivalate anion ring-opening of **381**

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.



Scheme 107 Attempted azlactone ring-opening using a pivalate anion system

Attempts were made to decrease this reaction time; the concentration of CH_2Cl_2 used was increased (0.2 and 0.4 M were screened) and other solvents were tested (THF, CH_3CN , 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

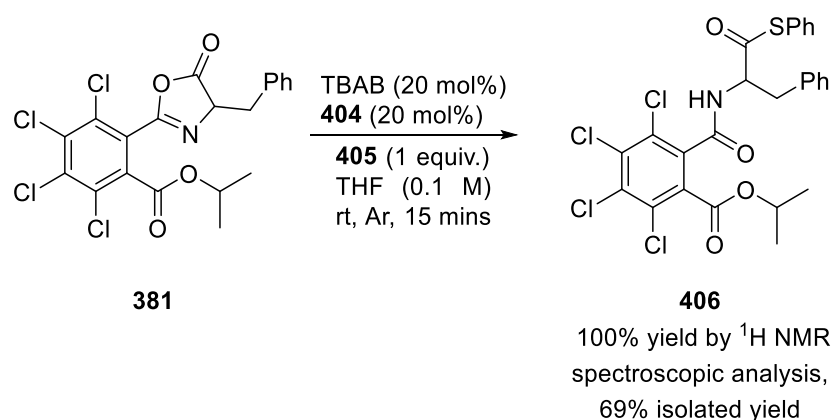
As the carboxylate anion/carboxylic acid system to carry out aminolysis of azlactones up until this point were unsuccessful, other anions were explored in the aminolysis of azlactones. It was decided to investigate phenolate and phenolate-derived ions in this system. This endeavour was undertaken as 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

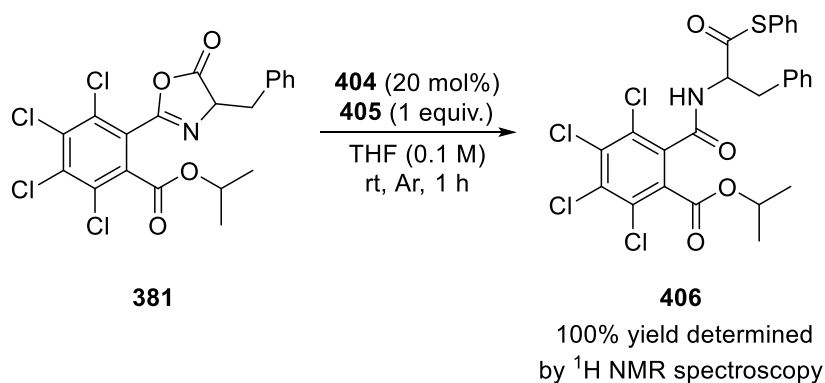
Due to their reduced basicity and increased nucleophilicity in comparison to their phenolate counterparts, thiophenol was first evaluated as a potential method to ring open **381**. Cannon and co-workers have previously carried out the DKR of azlactones *via* thiolysis,^{153,154} these protocols utilised 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 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).

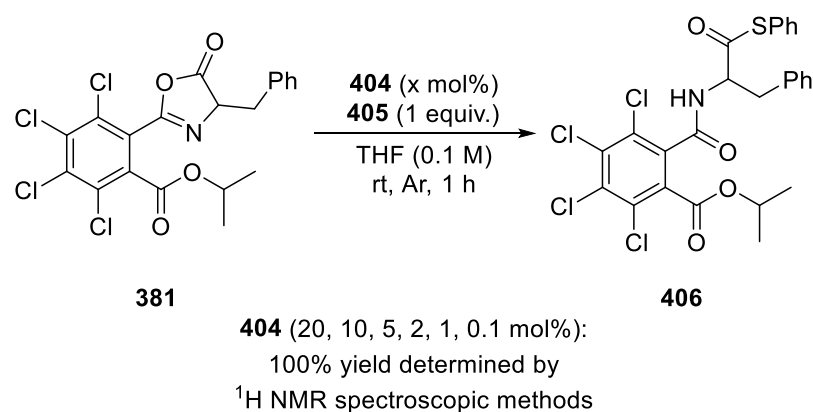


Scheme 109 Thiolysis control reaction of **381** using **404** and **405**

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.

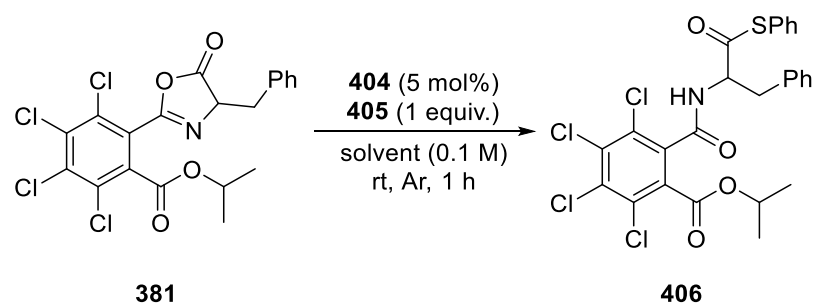
Carrying out the thiolysis control reaction at catalyst loadings of 10 mol%, 5 mol%, 2 mol%, 1 mol% and even as low as 0.1 mol% **404**, in THF, failed to eliminate the background reaction (Scheme 110). In each case, quantitative yield of thioester **406** was observed in the ^1H NMR spectrum of the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

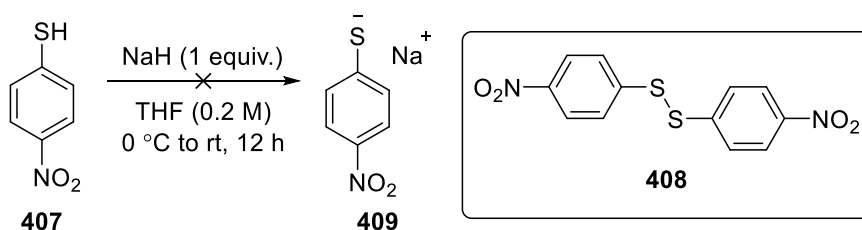


entry	solvent	conversion (%) ^a
1	THF	100
2	CH ₂ Cl ₂	88
3	CH ₃ CN	84
4	Et ₂ O	90
5	MTBE	82
6	toluene	88
7	hexanes	n.d.
8	hexanes: toluene (1:1)	96

^a Determined by ¹H NMR spectroscopy using *p*-iodoanisole as the internal standard.

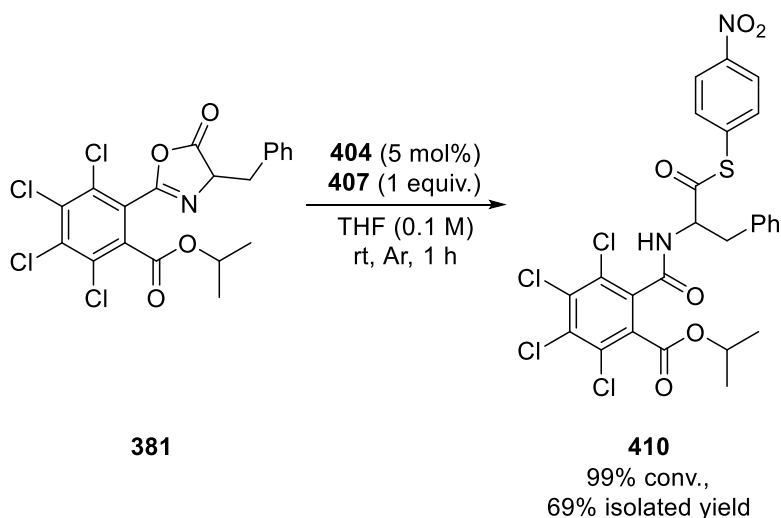
Azlactone **381** was not soluble in hexanes and so no reaction was observed (Table 7, entry 7). A mixture of toluene and hexanes was investigated however, 1:1 hexanes: toluene was required to dissolve **381** and at this solvent ratio, the background reaction was observed (Table 7, entry 8).

Another method investigated to control the thiolysis background reaction was to utilise a different source of thiol, in this case, *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 *p*-nitrophenolate **409**

Further efforts to synthesise sodium *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 *p*-nitrothiophenol (**407**) in stoichiometric quantities (Scheme 112). Disappointingly, almost quantitative conversion of **381** to thioester **410** was observed after 1 hour at room temperature.



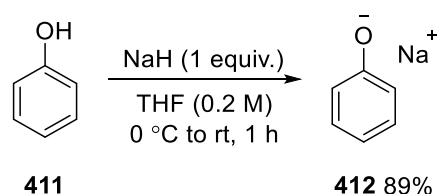
Scheme 112 The thiolysis of **381** with **404** and **407**

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

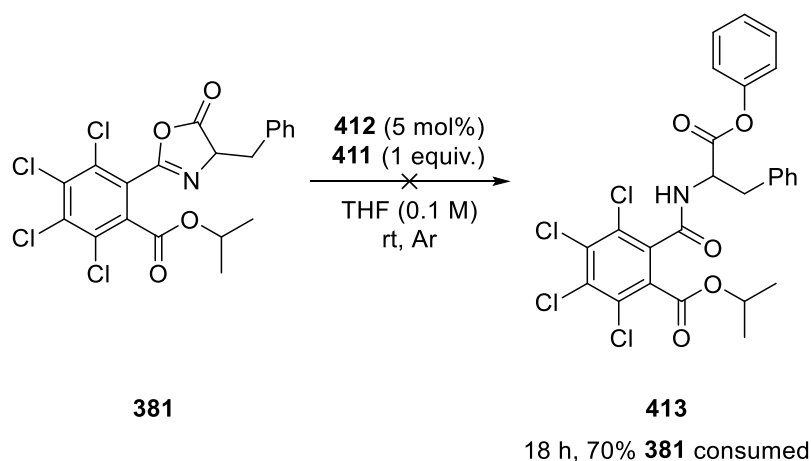
Having briefly explored the thiolysis of azlactones as a means of carrying out aminolysis and observing that the background reaction was going to require careful reaction conditions to be eliminated, formal aminolysis *via* an ester intermediate was next examined. While the alcoholysis of azlactones 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**

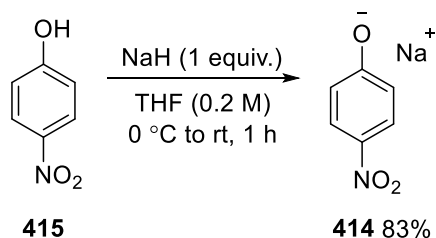
As observed with the thiophenolate system previously discussed (Section 3.5.1), it was imperative to first investigate if the phenolate anion took part in a background reaction, *i.e.* if the alcoholysis reaction proceeds in the absence of a phase-transfer catalyst (TBAB). Azlactone **381** was reacted with **412** (catalytic quantity) and **411** (stoichiometric) using THF as the reaction solvent (Scheme 114).



Scheme 114 Background reaction between **381** and **412**

After 1 hour, 34% of **381** had been consumed, but no discernible product resonance signals were observed in the ^1H NMR spectrum of the crude reaction mixture. The reaction was allowed to continue and was monitored by ^1H NMR spectroscopic methods. Following 18 hours stirring at room temperature (under an atmosphere of argon) 70% of **381** had been consumed and the ^1H 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 ^1H 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.

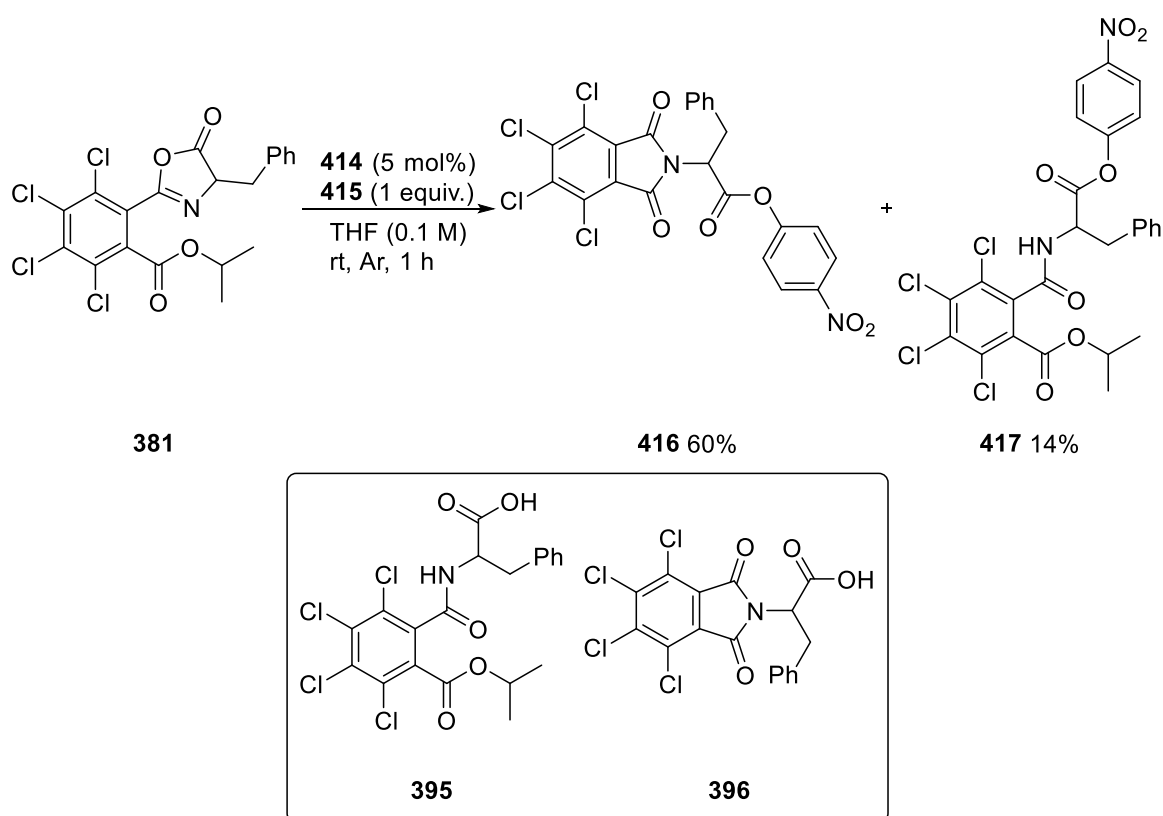
The next phenolate anion investigated in this reaction was sodium *p*-nitrophenolate (**414**). Sodium salt **414** was synthesised analogously to phenolate salt **412** from *p*-nitrophenol (**415**), again using NaH (Scheme 115).



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.



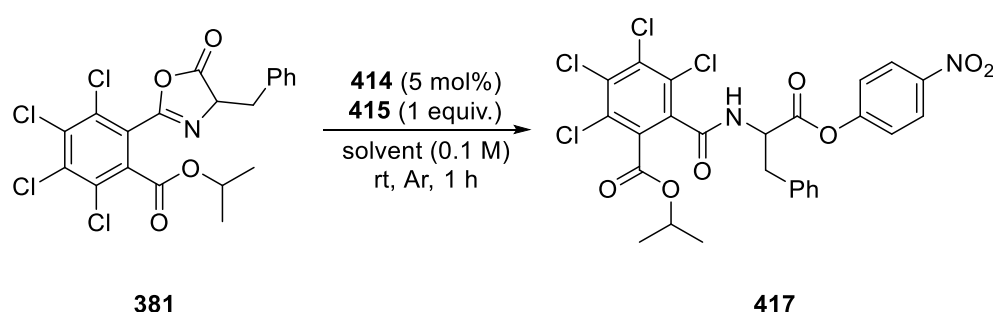
Scheme 116 The background reaction between **381** and **414** in THF

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 ^1H 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 ^1H NMR spectrum of the crude reaction mixture.

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



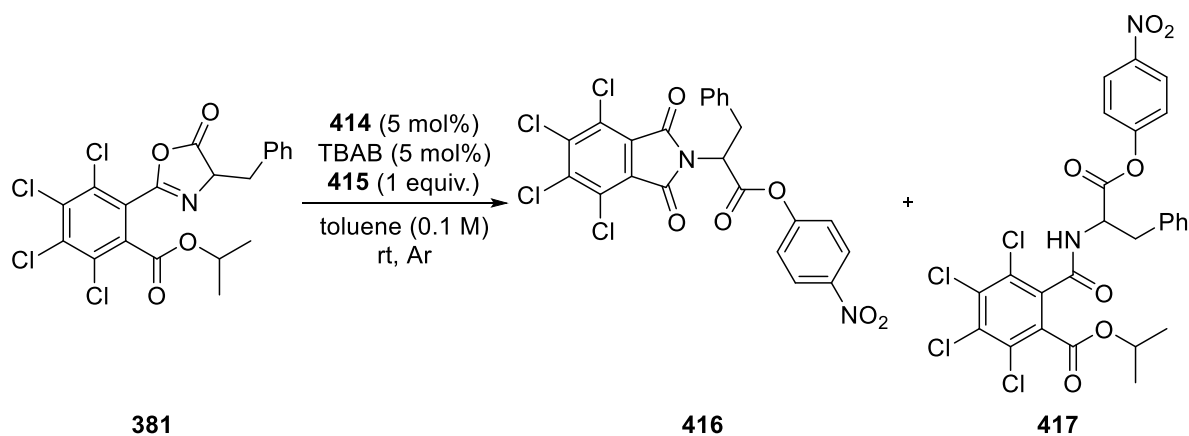
entry	solvent	conversion (%) ^a
1	THF	100
2	CH ₂ Cl ₂	94
3	MTBE	100
4	Et ₂ O	54
5	toluene	0

^aDetermined by ^1H 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**

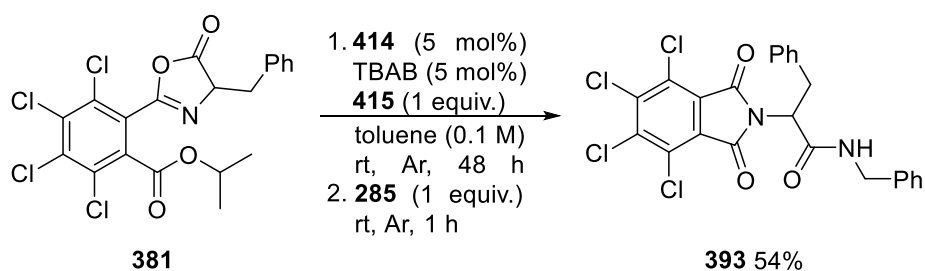


entry	time (h)	conversion to 416 (%) ^a	conversion to 417 (%) ^a
1	1	0	40
2	3	0	74
3	18	48	34
4	24	67	33
5	48	92	6
6	72	100	0

^aDetermined by ¹H NMR spectroscopy using *p*-iodoanisole as the internal standard.

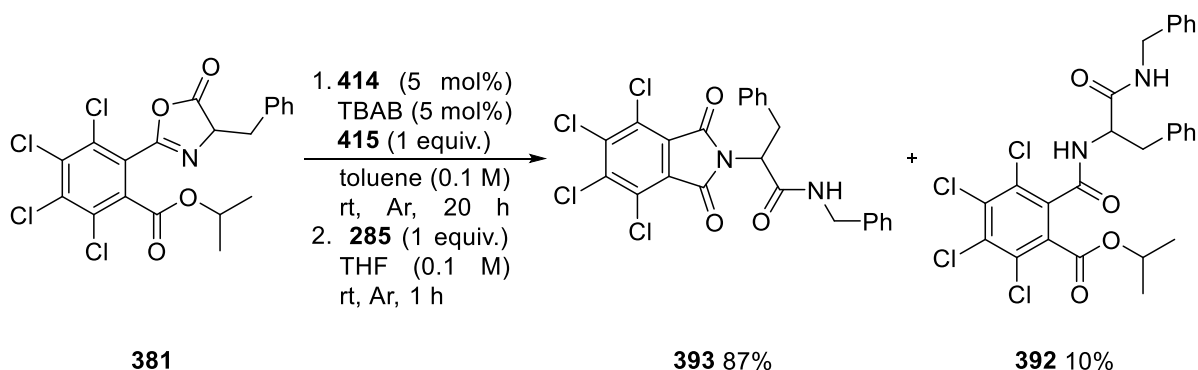
It was now imperative to demonstrate that the addition of an amine to phenolic ester **416** (or even isopropyl ester **417**, which can undergo a simple base-catalysed ring-closure to form the desired amide product) would form the amide coupling product; in doing so aminolysis would be achieved (which 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 ¹H NMR spectroscopy using *p*-iodoanisole as the internal standard), benzylamine (**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 ^1H 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

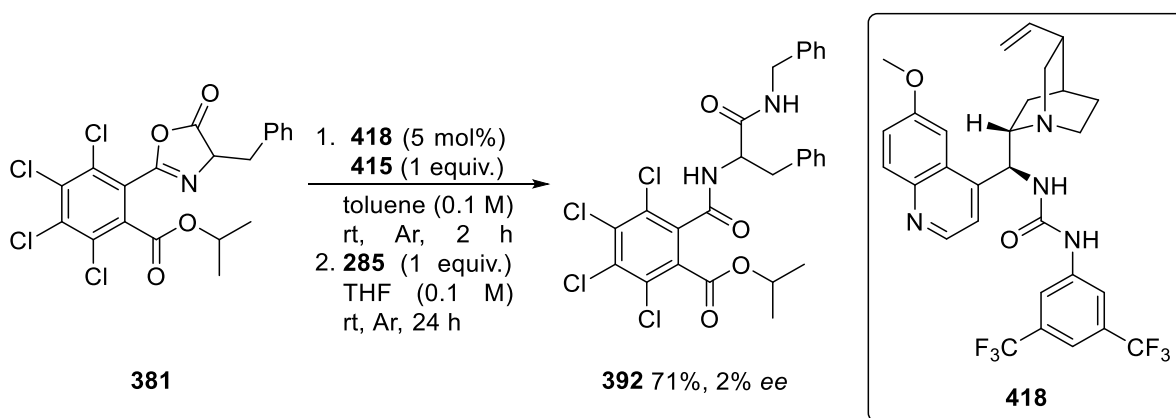
The alcoholysis reaction was quenched after 20 hours (upon complete conversion to **417** as determined by ^1H NMR spectroscopy) by the addition of THF to the reaction mixture, a few minutes before the addition of benzylamine. With these improved, although unusual reaction conditions in hand, *N*-protected **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 Cannon and co-workers to carry out the alcoholysis and thiolysis of azlactones in 2008)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.



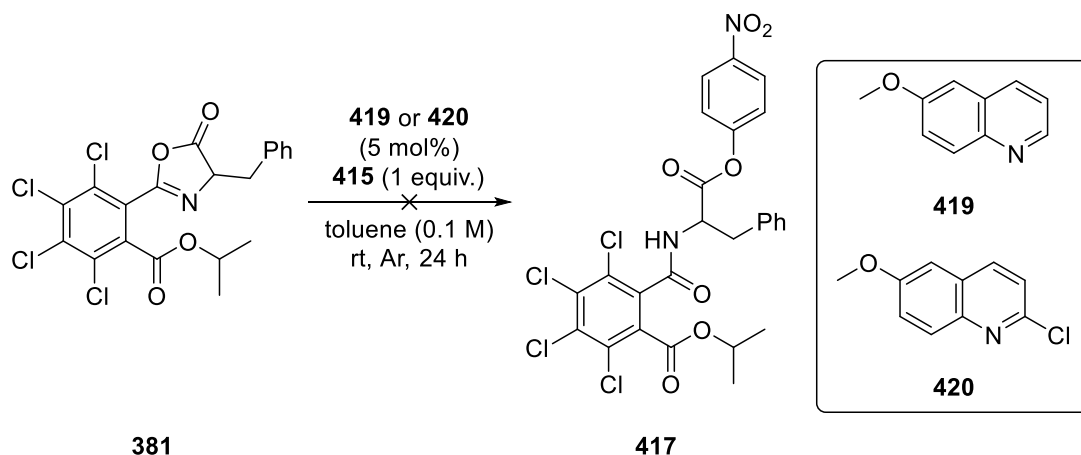
Scheme 119 Evaluation of bifunctional catalyst **418** in the DKR **381**

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.

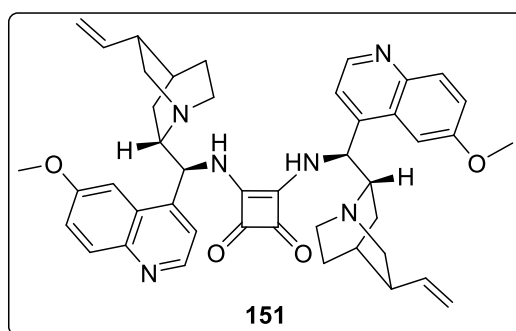
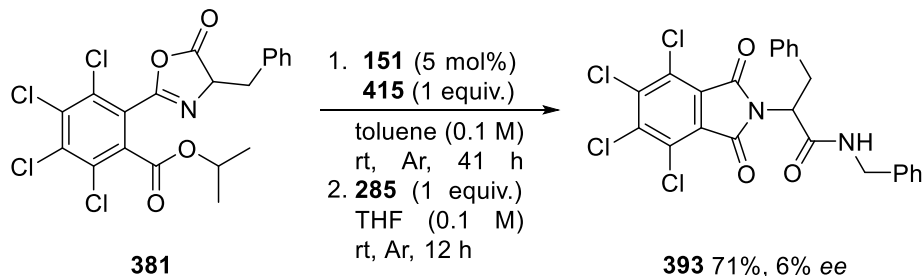
In the first experiment, catalyst **418** was replaced with 6-methoxyquinoline (**419**), which did not result in the formation any product, even when the reaction was left to proceed for up to 24 hours (Scheme 120). In a concurrent reaction, 2-chloro-6-methoxyquinoline (**420**) was employed as the 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 Investigations into quinoline as a potential catalyst to promote the alcoholysis of **381**

The next organocatalyst evaluated in this reaction, was Song's C_2 -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.^{132,156} 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.

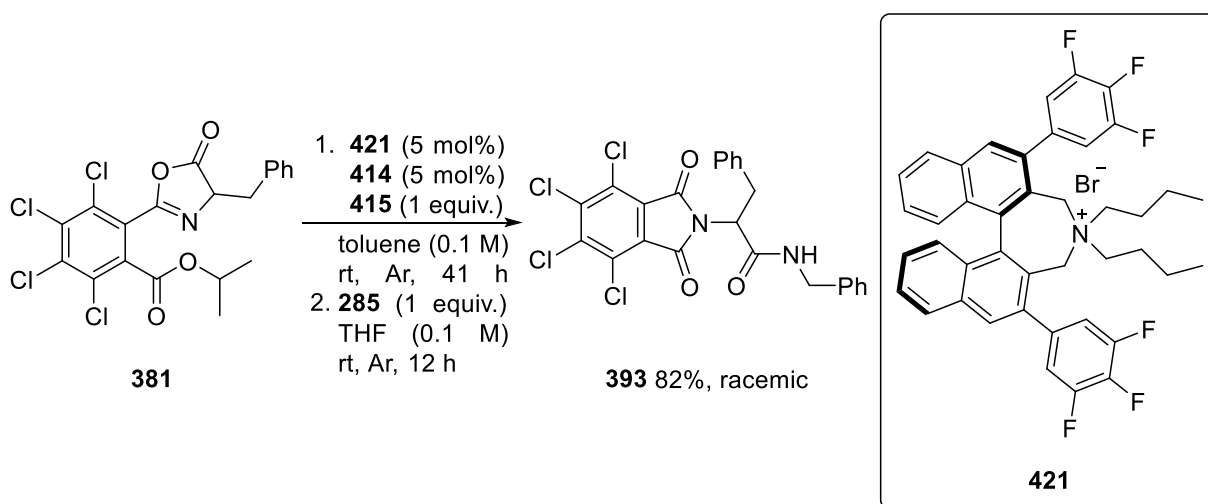
3.6.2 Evaluation of chiral phase-transfer catalysts in the DKR of azlactone **381**

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

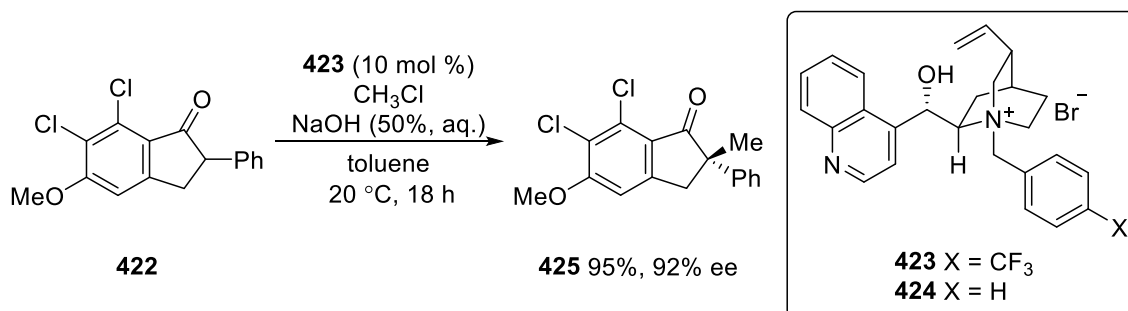
addition of **414** to **381** in a chiral environment to form ester intermediate **417**, which would be quenched with an amine to form the formal aminolysis product, *N*-protected **393**.

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%).^{191,192} 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 1976.¹⁹³ 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).¹⁹⁴



Scheme 123 Asymmetric phase-transfer catalysed alkylation of **422**¹⁹⁴

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.

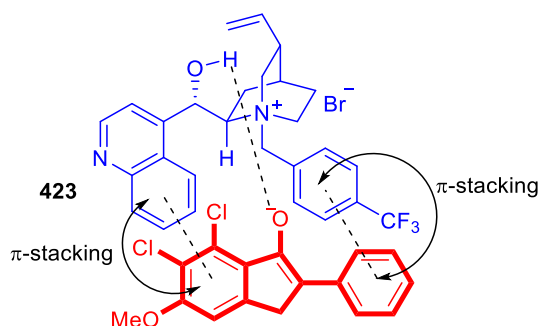


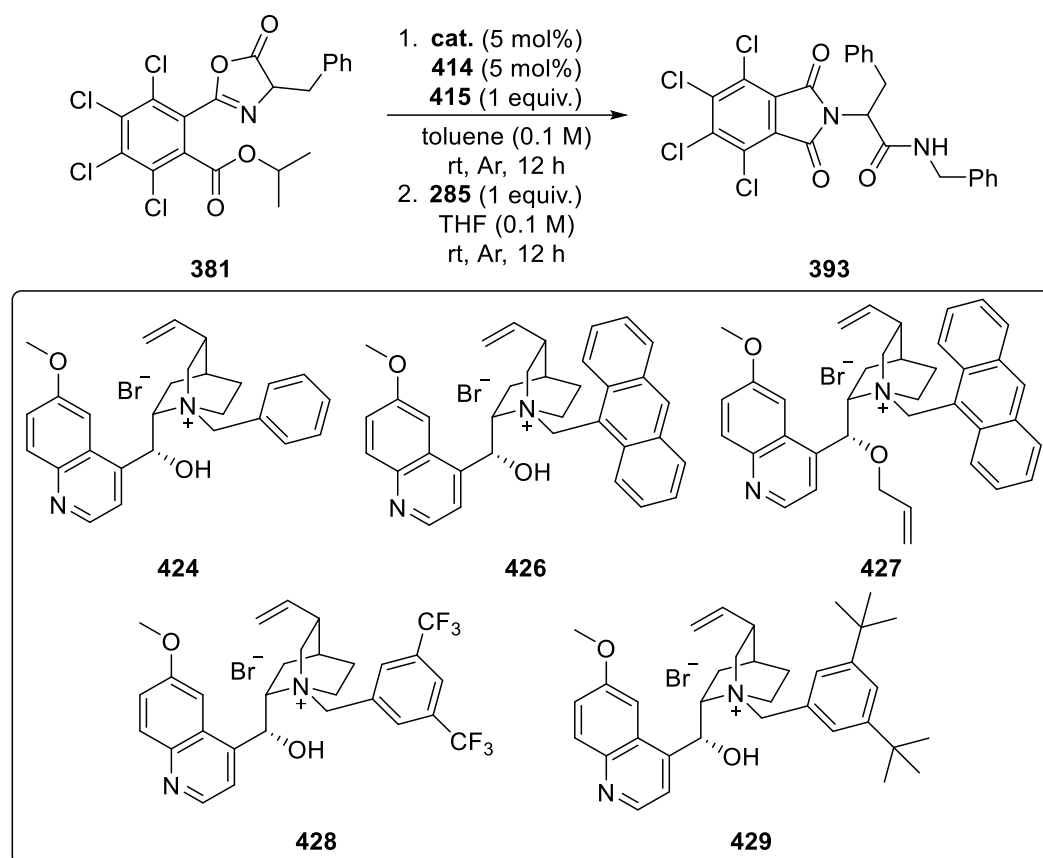
Figure 31 Pre-transition state assembly for asymmetric PTC alkylation proposed by Dolling *et. al.*¹⁹⁴

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.¹⁹⁴ 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 catalyst^{195,196} **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**



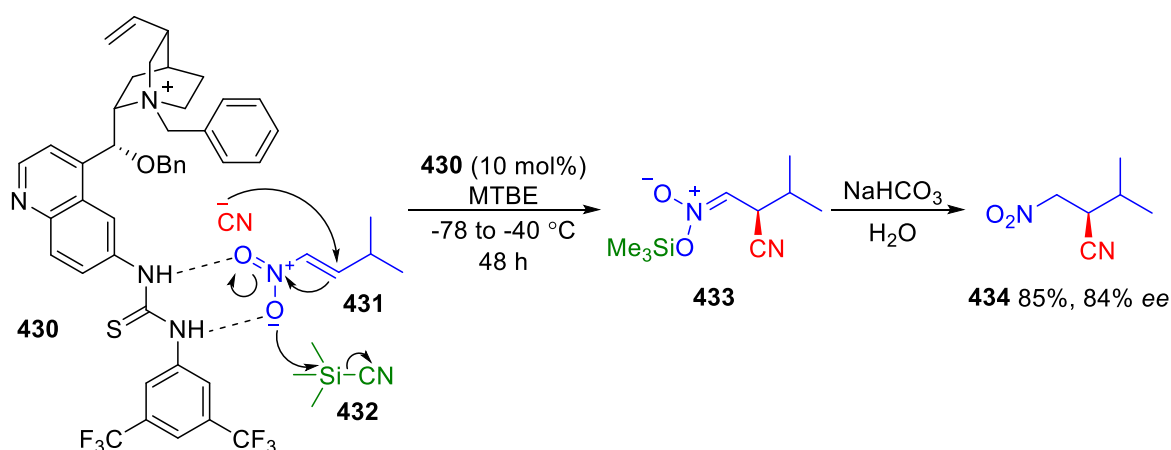
entry	catalyst	conversion (%) ^a	ee (%) ^a
1	424	97	0
2	426	96	0
3	427	91	0
4	428	92	16
5	429	94	20

^aDetermined by ¹H NMR spectroscopy using *p*-iodoanisole as the internal standard. ^bDetermined by CSP-HPLC analysis after isolation by column chromatography.

Catalyst **428** - bearing an *N*-benzyl unit substituted with electron-withdrawing groups in the *meta* 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 *ee* when catalyst **429** was utilised (Table 10, entry 5). Although the *ee* 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*.

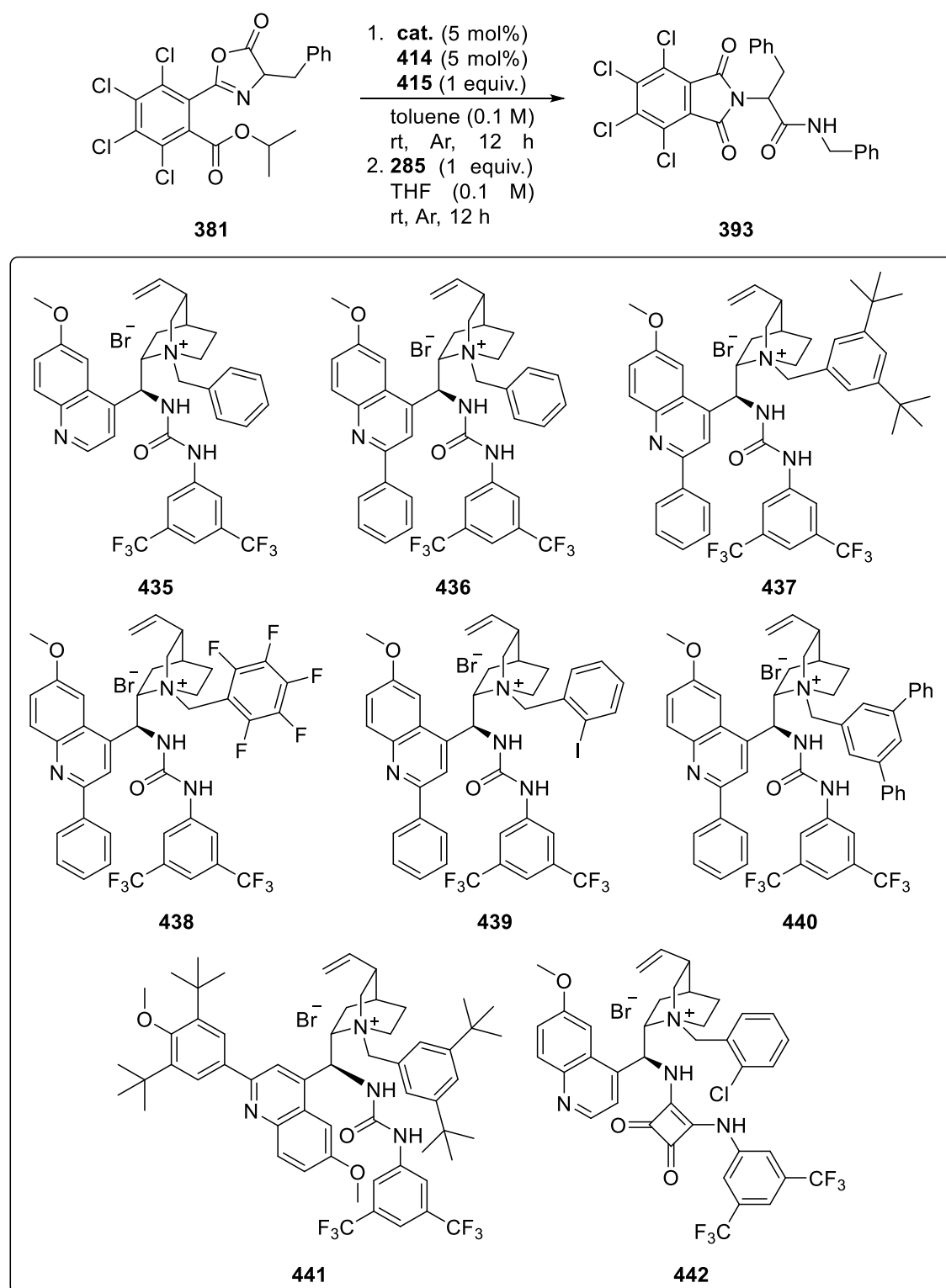


Scheme 124 1,4-Addition of cyanide to nitroalkanes catalysed by bifunctional PTC **430**¹⁹⁷

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



entry	catalyst	conversion (%) ^a	ee (%) ^a
1	435	96	10
2	436	94	11
3	437	99	17
4	438	98	19
5	439	93	23
6	440	100	7
7	441	97	8
8	442	100	10

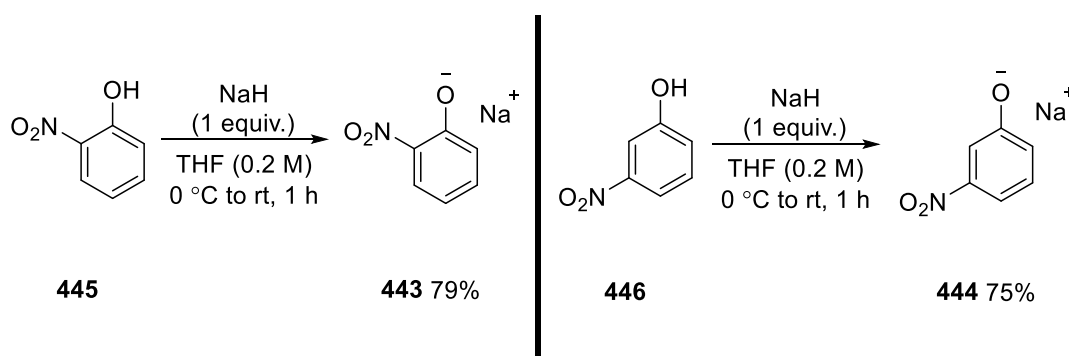
^aDetermined by ¹H NMR spectroscopy using *p*-iodoanisole as the internal standard. ^bDetermined by CSP-HPLC analysis after isolation by column chromatography.

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

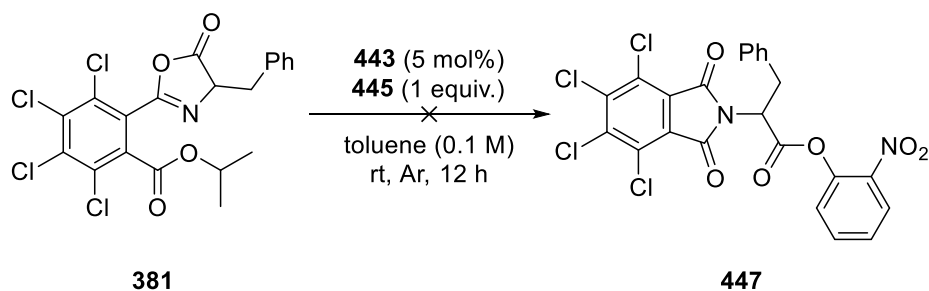
on the results obtained with the other hydrogen bond donating, bifunctional PTCs but still only slightly higher than the use of catalyst **429** (Table 10, entry 5), which again has a more simplistic catalyst design (and synthesis). Catalyst **440**, which incorporates additional steric bulk to the *N*-benzyl moiety in the form of *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 *motif*. In this structure the *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 *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 *ee* would occur. Both *o*-nitrophenolate (**443**) and *m*-nitrophenolate (**444**) were synthesised by treating the appropriate phenol with NaH, under strictly anhydrous conditions (Scheme 125).



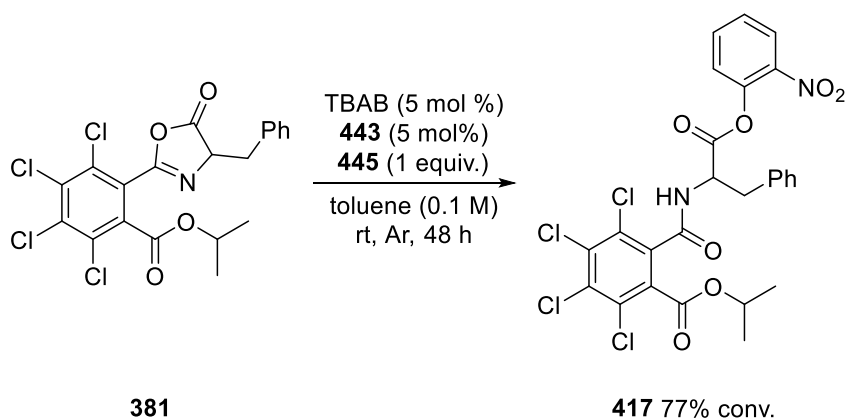
Scheme 125 Synthesis of salts **443** and **444**

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).



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).



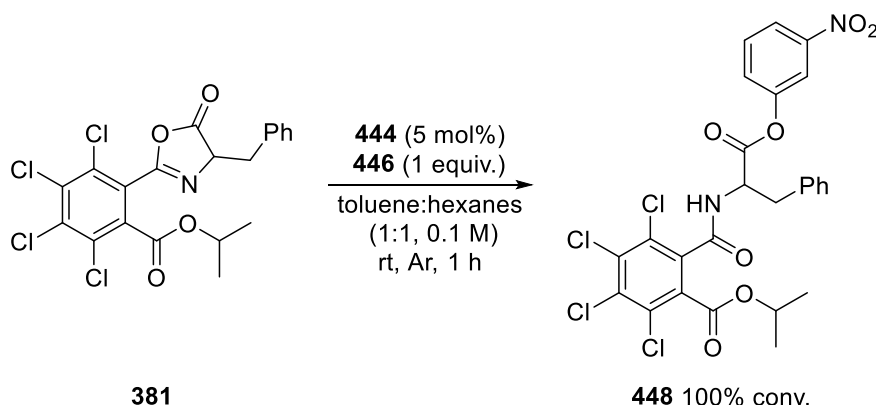
Scheme 127 Evaluation of *o*-nitrophenolate salt **443** in the alcoholysis of **381**

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).

Carrying out the reaction using **443** in other solvents (THF, CH₂Cl₂ and MTBE) failed to increase the rate of reaction. Currently no further attempts to optimise the reaction between **381** and phenolate **443** have been carried out.

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 thiolysis reaction between **381** and sodium thiophenolate (**404**)) also failed to eliminate the background reaction.



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

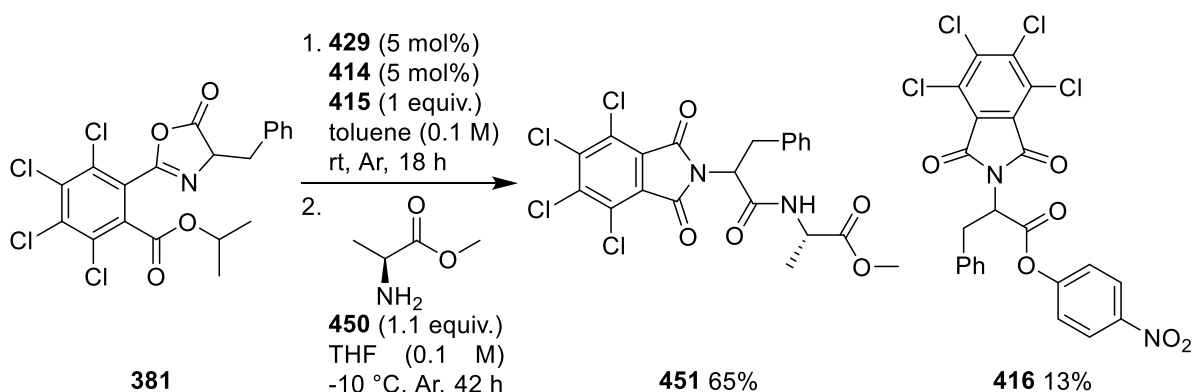
As it had now been demonstrated that it is possible to carry out the aminolysis of azlactones (*via* formation of an ester intermediate using a substituted phenolate anion) under the control of phase-transfer catalysis, to furnish products with a small degree of enantioselectivity. Attention was next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

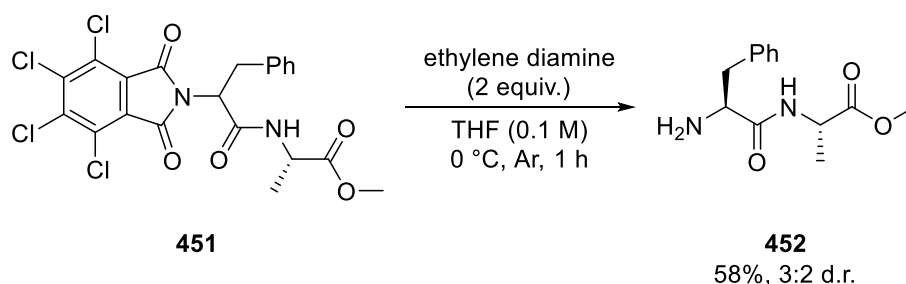
Following synthesis of the racemates, the alcoholysis of **381** using phenolate **414** and **415** was facilitated by PTC **429** (one of the most successful catalysts employed in the DKR reaction section 3.6.2, Table 10, entry 5). Ester intermediate **417** formed from the alcoholysis reaction was 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 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**, ^1H NMR spectroscopic techniques were employed. To carry this out, it was first necessary to deprotect the *N*-protected phthalimido group of **451**, which was carried out using ethylene diamine at low temperature to produce amino ester **452** in a moderate yield (Scheme 130).¹⁵⁶



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 ^1H NMR spectrum of deprotected dipeptide **452** against a literature ^1H NMR spectrum of *L*-phenylalanine *L*-alanine methyl ester (**453**).¹⁹⁸ Through analysis of the ^1H 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.¹⁵⁶

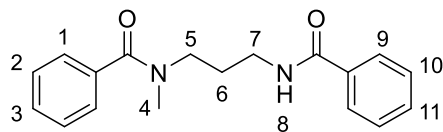
Chapter 4 Experimental procedures and data

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_3OD and referenced relative to residual CHCl_3 ($\delta = 7.26$ ppm) DMSO ($\delta = 2.50$ ppm) or CH_3OH ($\delta = 3.31$ 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_3CN), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and diethyl ether (Et_2O) 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_3OH), 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 ^1H 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 μ L, 1 mmol), NEt_3 (175 μ L, 1.25 mmol) and THF (2.5 mL). *N*-methyl-1,3-propanediamine (**163**, 125 μ L, 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_2Cl_2 :MeOH, 100:2.5) to afford **174** as a white solid (145.2 mg, 49%). M.p. 122-125 $^\circ\text{C}$.

δ_{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).

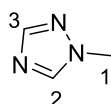
δ_{C} (100 MHz, CDCl_3): 172.8 (C=O), 167.1 (C=O), 136.0 (q), 134.5 (q), 131.3, 129.8, 128.6, 128.5, 127.1, 126.7, 44.2, 37.3, 35.5, 26.2.

ν_{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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2$ Requires: 297.1598.

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

1-Methyl-1*H*-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 $^\circ\text{C}$ in a H_2O /ice bath. Iodomethane

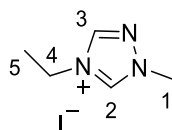
(9.04 mL, 20.61 g, 155.0 mmol) was added dropwise *via* syringe. Stirring was continued for 5 minutes at 0 °C before warming to room temperature. The reaction mixture was stirred for a further 2 h under argon before equipping a reflux condenser to the flask and heating it to 60 °C for 20 h. Upon cooling, 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

δ_{H} (400 MHz, CDCl₃): 7.93 (1 H, s, H-2), 7.78 (1 H, s, H-3), 3.80 (3 H, s, H-1).

HRMS (*m/z* - ESI): Found: 84.0564 (M+H)⁺ C₃H₆N₃ Requires: 84.0562.

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



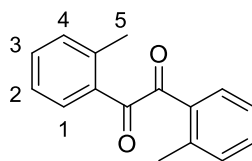
To an oven-dried 50 mL round-bottomed flask, equipped with a magnetic stirring bar, septum seal and argon-filled balloon, was charged 1-methyl-1*H*-1,2,4-triazole (**454**, 4.2 g, 50.5 mmol). The vessel was placed under an atmosphere of argon and ethyl iodide (17.3 g, 8.9 mL, 111 mmol) was added *via* 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

δ_{H} (400 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* - ESI): Found: 112.0874 (M)⁺ C₅H₁₀N₃ Requires: 112.0875.

1,2-di-*o*-tolylethane-1,2-dione (175)



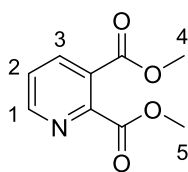
To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged sequentially Rb_2CO_3 (1.21 g, 5.22 mmol), 4-ethyl-1-methyl-1*H*-1,2,4-triazol-4-ium iodide (**25**, 1.14 g, 4.77 mmol), *o*-tolualdehyde (**176**, 3.0 mL, 25.9 mmol) and THF (15 mL). The flask was fitted with 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_2Cl_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_2Cl_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

δ_{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**)



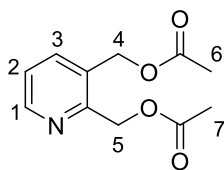
An oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with 2,3-pyridinedicarboxylic acid (**183**, 10.01 g, 59.91

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-diylbis(methylene) diacetate (**185**)

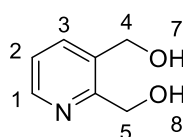


To an oven-dried 250 mL round-bottomed flask containing a magnetic stirring bar, under an argon atmosphere, was charged with dimethyl 2,3-pyridinecarboxylate (**184**, 7.32 g, 40.40 mmol) and ethanol (100 mL). Sodium borohydride (7.72 g, 202.0 mmol) was added portion wise to the stirring solution under 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).

δ_{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.
ν_{max} (neat)/ cm^{-1} :	2960, 1738 (C=O), 1579, 1443, 1378, 1222, 1028, 968, 921, 796, 606.
HRMS (m/z - ESI):	Found: 246.0312 ($\text{M}+\text{Na}$) ⁺ $\text{C}_{11}\text{H}_{13}\text{NNaO}_4$ Requires: 246.0737.

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



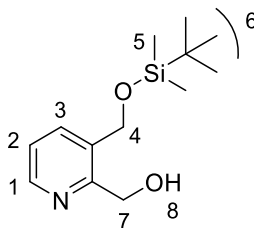
To a stirred solution of **185** (3.73 g, 16.7 mmol) in anhydrous MeOH (70 mL) at 0 °C, under an argon atmosphere, in a 250 mL round-bottomed flask equipped with a magnetic stirring bar, sodium methoxide (2.73 g, 50.5 mmol) was added portion wise. The reaction mixture was warmed to room temperature and 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_2Cl_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

δ_{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).
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* The protic signals H-7 and H-8 are not visible in CDCl_3 .

(3-(tert-butyldimethylsilyl)oxy)methylpyridin-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 CH₂Cl₂ (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 (CH₂Cl₂:EtOAc, 15:1) to furnish **187** as a colourless oil (1.34 g, 51%).

δ_{H} (400 MHz, CDCl₃): 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).

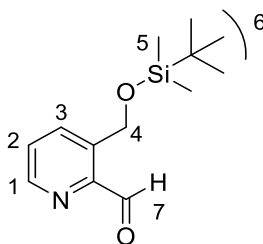
* The protic signal (H-8) is not visible in CDCl₃.

δ_{C} (100 MHz, CDCl₃): 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)⁺ C₁₃H₂₄NO₂Si Requires: 254.1571.

3-(tert-butyldimethylsilyl)oxy)methylpicolinaldehyde (188)



To a stirred solution of **187** (0.857 g, 3.38 mmol) in CH₂Cl₂ (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.

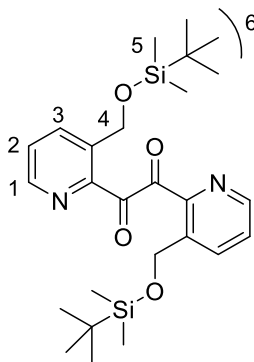
ν_{max} (neat)/cm⁻¹: 2954, 2930, 2857, 1707 (C=O), 1568, 1463, 1255, 1122, 1077, 835, 776, 663.

HRMS (*m/z* - APCI): Found: 252.1411 (M+H)⁺ C₁₃H₂₂NO₂Si 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-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)ethane-1,2-dione (178)



Prepared according to general procedure I using THF (0.9 mL), Rb_2CO_3 (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, CDCl_3): 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).

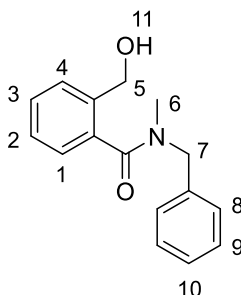
δ_{C} (100 MHz, CDCl_3): 198.8 (C=O), 146.9 (q), 146.8, 141.1 (q), 137.7, 127.1, 61.4, 26.0, 18.4 (q), -5.1.

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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{Si}_2$ Requires: 501.2599.

Synthesis of second-generation substrate

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



To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged AlCl_3 (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*-methybenzylamine (**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.

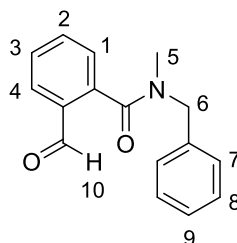
δ_H (400 MHz, CDCl₃): Major rotamer: 7.47-7.39 (8 H, m, H-1, H-3, H-4, H-8, H-9, H-10), 7.11 (1 H, d, *J* 7.2, H-2), 4.78 (2 H, s, H-7), 4.56 (2 H, s, H-5), 2.82 (3 H, s, H-6).

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)**



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 MnO₂ (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 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 **203** as a colourless oil (3.45g, 77%).

Spectral data for this compound were consistent with those in the literature.²⁰²

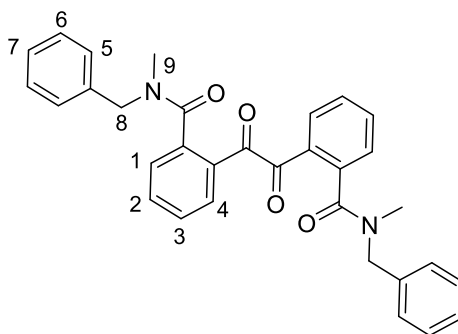
*A non-degenerate mix of rotamers is observed in the ¹H NMR spectrum of this compound.

δ_{H} (400 MHz, CDCl₃): 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)⁺ C₁₆H₁₅NNaO₂ Requires: 276.0995.

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



Prepared according to general procedure I using THF (0.9 mL), Rb₂CO₃ (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 (CH₂Cl₂: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.

δ_{H} (400 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).

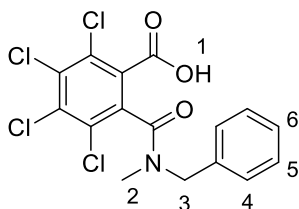
δ_{C} (100 MHz, CDCl_3): 192.6 (C=O), 192.5 (C=O), 192.4 (C=O), 192.3 (C=O), 171.0 (C=O), 170.9 (C=O), 170.6 (C=O), 138.4 (q), 138.4 (q), 138.2 (q), 138.1 (q), 136.8 (q), 136.8 (q), 136.3 (q), 136.3 (q), 133.8, 133.7, 133.7, 132.7, 132.7, 132.6, 132.5, 131.6 (q), 131.4 (q), 131.3 (q), 131.1 (q), 129.5, 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.

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

HRMS (m/z - ESI): Found: 505.2138 ($\text{M}+\text{H}$) $^+$ $\text{C}_{32}\text{H}_{29}\text{N}_2\text{O}_4$ 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. *N*-methylbenzylamine (**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 *in vacuo*. The corresponding residue was extracted into CH_2Cl_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_H (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).

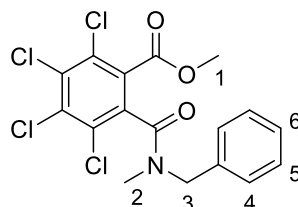
δ_C (100 MHz, CDCl₃): Major rotamer: 167.1 (C=O), 166.5 (C=O), 135.5 (q), 134.4 (q), 133.8 (q), 133.4 (q), 130.3 (q), 130.0 (q), 129.7, 128.8 (q), 128.2, 127.8, 55.2, 35.6.

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.

$\nu_{\max}$ (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)⁺ C₁₆H₁₂NO₃Cl₄ Requires: 405.9566.

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



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%).

δ_{H} (400 MHz, CDCl₃): 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).

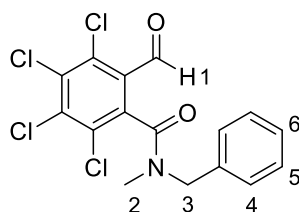
δ_{C} (100 MHz, CDCl₃): Major rotamer: 164.6 (C=O), 164.3 (C=O), 135.9 (q), 135.4 (q), 135.2 (q), 134.8 (q), 134.3 (q), 131.1 (q), 130.7 (q), 128.7, 128.6, 127.8, 53.3, 50.6, 35.2.

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.

ν_{max} (neat)/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)⁺ C₁₇H₁₄Cl₄NO₃ Requires: 419.9722.

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



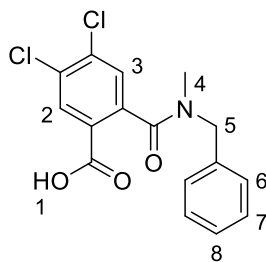
An oven-dried 100 mL round-bottomed flask was equipped with a magnetic stirring bar and was flushed with argon. An argon balloon and septum were fitted to the flask following which, LiBH₄ (0.20 g, 9.1 mmol) was added. The flask was cooled to 0 °C in a H₂O/ice bath and anhydrous Et₂O (26 mL) was charged 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.

δ_{H} (400 MHz, CDCl ₃):	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).
δ_{C} (100 MHz, CDCl ₃):	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.
ν_{max} (neat)/cm ⁻¹ :	1767 (C=O), 1698, 1648 (C=O), 1523, 1449, 1344, 1226, 1204, 1169, 1089, 967, 843, 777, 695, 576.
HRMS (<i>m/z</i> - ESI):	Found: 389.9614 (M+H) ⁺ C ₁₆ H ₁₂ NO ₂ Cl ₄ 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 CH₂Cl₂ (3 x 25 mL) and the combined organic extracts were washed with brine (2 x 25 mL). The combined organic layers were dried over MgSO₄ 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 ¹H and ¹³C NMR spectra of this compound.

δ_{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).

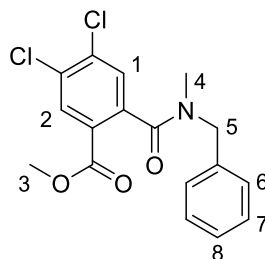
δ_{C} (100 MHz, DMSO-*d*₆): Major rotamer: 168.2 (C=O), 165.7 (C=O), 139.2 (q), 137.5 (q), 136.0 (q), 132.3, 131.9 (q), 129.5 (q), 128.9, 128.4, 127.8, 127.6, 49.8, 36.1.

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.

ν_{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.

δ_H (600 MHz, DMSO- d_6): 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).

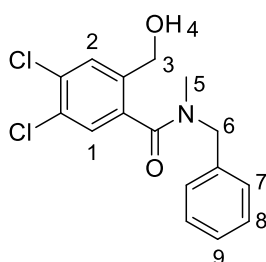
δ_C (100 MHz, DMSO- d_6): Major rotamer: 167.3 (C=O), 164.1 (C=O), 138.4 (q), 136.9 (q), 136.0 (q), 131.8, 131.7 (q), 129.1, 128.5, 128.1, 127.3, 52.8, 49.5, 35.7.

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.

$\nu_{\max}$ (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)⁺ C₁₇H₁₆Cl₂NO₃ Requires: 352.0502.

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



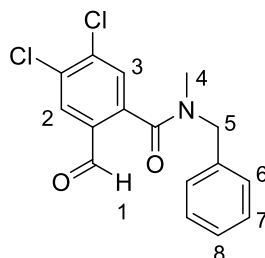
An oven-dried 50 mL round-bottomed flask was equipped with a magnetic stirring bar and was flushed with argon. An argon balloon and septum were attached to the flask following which LiBH₄ (0.23 g, 10.4 mmol) was added. The flask was cooled to 0 °C in a H₂O/ice bath and anhydrous Et₂O (30 mL) was charged 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 LiBH₄/Et₂O 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 Et₂O (3 x 30 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH₂Cl₂:MeOH, 100:1) to afford **221** as a colourless oil (2.13 g, 76%).

*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: 7.59-7.57 (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).
δ_{C} (100 MHz, CDCl_3):	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
ν_{max} (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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{16}\text{H}_{16}\text{NO}_2\text{Cl}_2$ 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 CH_2Cl_2 (25 mL) was charged to the flask followed by MnO_2 (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 CH_2Cl_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 **222** as a colourless oil (1.08 g, 54%).

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

δ_{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).

δ_{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.

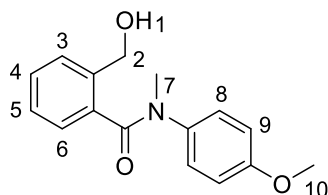
Minor rotamer: 189.8 (C=O), 166.6 (C=O), 137.4 (q), 137.1 (q), 136.4 (q), 133.2, 132.5 (q), 132.3 (q), 129.3, 128.6, 127.9, 127.3, 53.7, 32.5.

ν_{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 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{NNaO}_2$ 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_2O /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 CH₂Cl₂ (3 x 15 mL). The organic extract was washed with brine (2 x 10 mL). The combined organic layers were dried over MgSO₄ 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%).

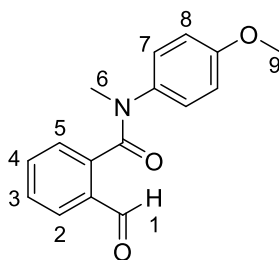
δ_{H} (400 MHz, CDCl₃): 7.31 (1 H, d, *J* 7.2, H-3), 7.20 (1 H, app. t, H-4), 7.01-6.87 (4 H, m, H-5, H-6, H-8), 6.69 (2 H, d, *J* 8.6, H-9), 4.64 (2 H, d, *J* 5.6, H-2), 3.93 (1 H, t, *J* 5.6, H-1), 3.72 (3 H, s, H-7), 3.49 (3 H, s, H-10).

δ_{C} (100 MHz, CDCl₃): 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.

ν_{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)⁺ C₁₆H₁₈NO₃ 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 CH₂Cl₂ (42 mL) was charged to the flask followed by MnO₂ (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 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, 1:1) to afford **234** as a brown oil (1.64 g, 59%).

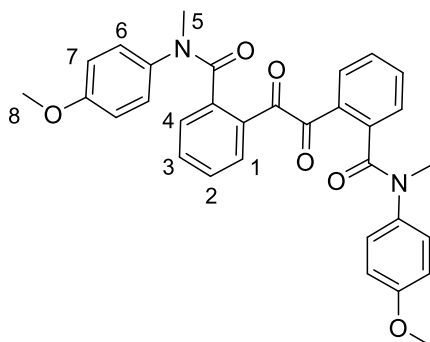
δ_{H} (400 MHz, CDCl_3): 10.09 (1 H, s, H-1), 7.73 (1 H, d, J 7.5, H-2), 7.44 (1 H, td, J 7.5, 1.2, H-4), 7.37 (1 H, td, J 7.5, 1.2, H-3), 7.29-7.26 (1 H, m, H-5), 6.95 (2H, d, J 8.9, H-7), 6.66 (2 H, d, J 8.9, H-8), 3.71 (3 H, s, H-6), 3.53 (3 H, s, H-9).

δ_{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.

ν_{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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{16}\text{H}_{16}\text{NO}_3$ Requires: 270.1125.

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



Prepared according to general procedure I using THF (2 mL), Rb_2CO_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 $^{\circ}\text{C}$.

δ_{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).

δ_{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.

ν_{max} (neat)/ cm^{-1} : 3002, 1691 (C=O), 1615 (C=O), 1510, 1441, 1385, 1246, 1207, 1174, 1030, 837, 814, 758, 616, 581.

Found: 537.2025 (M+H)⁺ C₃₂H₂₉N₂O₆ Requires: 537.2020

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.

Chemical structure of compound 6, showing a pyridine ring substituted with a pyrrolidine ring and a tert-butyldimethylsilyl group. The numbering indicates the atoms: 1 (pyridine N), 2 (pyridine C2), 3 (pyridine C3), 4 (pyridine C4), 5 (Si), 6 (tert-butyl methyls), 7 (pyrrolidine N), 8 (pyrrolidine C2), 9 (pyrrolidine C3).

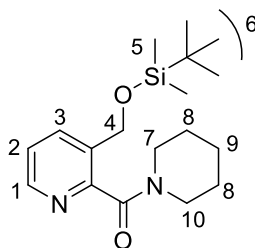
Prepared according to general procedure II using THF (0.5 mL), **178** (98.8 mg, 0.194 mmol), **53** (35.0 mg, 0.194 mmol) and **25** (6.96 mg, 0.0291 mmol, 15 mol%), DBU (32 μ L, 0.213 mmol) and pyrrolidine (20.5 μ L, 0.233 mmol). Purified by flash column chromatography (CH_2Cl_2 :MeOH, 95:5) to afford **455** as a brown oil (60.5 mg, 97%).

δ_{H} (400 MHz, CDCl_3): 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, CDCl_3): 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.

ν_{max} (neat)/ cm^{-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 ₁₇ H ₂₉ N ₂ O ₂ Si Requires: 321.1993.

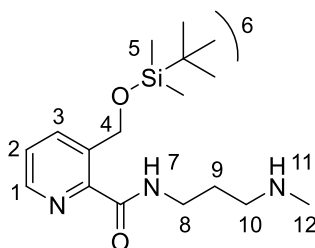
(3-(Tert-butyldimethylsilyl)oxy)methylpyridin-2-yl)(piperidin-1-yl)methanone (456, Table 2, entry 2)



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 (CH₂Cl₂:MeOH, 95:5) to afford **456** as a brown oil (41.5 mg, 64%).

δ_{H} (400 MHz, CDCl 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), 3.76-3.68 (2 H, m, H-10), 3.16 (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).
δ_{C} (100 MHz, CDCl 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.
ν_{max} (neat)/ cm^{-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 ₁₈ H ₃₁ N ₂ O ₂ Si Requires: 335.2149.

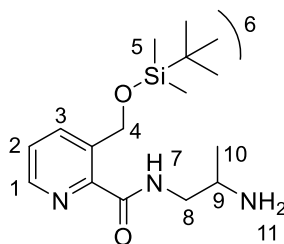
3-(Tert-butyldimethylsilyl)oxy)methyl)-N-(3-(methylamino)propyl)picolinamide (457, Table 2, entry 3)



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 μ L, 0.213 mmol) and *N*-methyl-1,3-diaminopropane (**163**, 24.5 μ L, 0.233 mmol). Purified by flash column chromatography (CH_2Cl_2 :MeOH: NEt_3 , 100:1:1) to afford **457** as a brown oil (35.4 mg, 51%).

δ_{H} (400 MHz, CDCl_3):	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, CDCl_3):	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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{17}\text{H}_{32}\text{N}_3\text{O}_2\text{Si}$ 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 μ L, 0.185

mmol) and 1,2-diaminopropane (**116**, 17 μ L, 0.202 mmol). Purified by flash column chromatography (CH_2Cl_2 :MeOH: NEt_3 100:1:1) to afford **458** as a brown oil (34.5 mg, 63%).

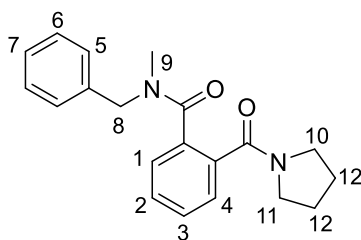
δ_{H} (400 MHz, CDCl_3): 8.64-8.56 (1 H, m, H-7), 8.42 (1 H, dd, J 4.5, 1.0, H-1), 8.24 (1 H, dd, J 7.8, 1.0, H-3), 7.46 (1 H, dd, J 7.8, 4.5, H-2), 5.28 (2 H, s, H-4), 3.66 (2 H, br s, H-11), 3.58-3.50 (1 H, m, H-8a), 3.41-3.29 (2 H, m, H-8b, H-9), 1.25 (3 H, d, J 6.0, H-10), 0.97 (9 H, s, H-6), 0.14 (6 H, s, H-5).

δ_{C} (100 MHz, CDCl_3): 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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{16}\text{H}_{30}\text{N}_3\text{O}_2\text{Si}$ Requires: 324.2102.

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



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 μ L, 0.213 mmol) and pyrrolidine (19.5 μ L, 0.233 mmol). Purified by flash column chromatography (CH_2Cl_2 :MeOH, 95:5) to afford **459** as a brown oil (74.7 mg, 99%).

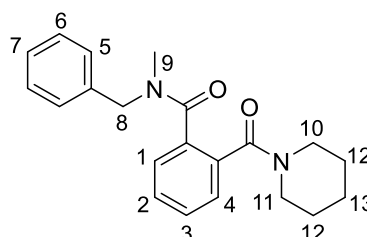
*A non-degenerate mix of rotamers is observed in the ^1H and ^{13}C NMR spectra of this compound.

δ_{H} (400 MHz, CDCl_3): 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-

	3.31 (2 H, m, H-10), 2.95 (3 H, s, H-9), 1.97-1.79 (4 H, m, H-12).
δ_{C} (100 MHz, CDCl_3):	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.
ν_{max} (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 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{20}\text{H}_{22}\text{N}_2\text{NaO}_2$ 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 (CH_2Cl_2 :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 ^{13}C NMR spectra of this compound.

δ_{H} (400 MHz, CDCl_3):	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-
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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).

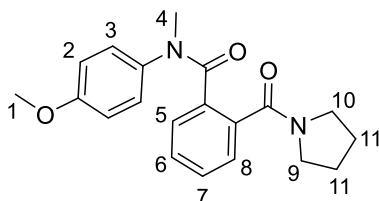
δ_{C} (100 MHz, CDCl_3): Major rotamer: 170.4 (C=O), 168.7 (C=O), 136.9 (q), 135.1 (q), 134.8 (q), 128.8, 128.7, 128.0, 127.5, 127.3, 127.1, 126.4, 50.5, 48.7, 42.8, 36.9, 26.2, 25.5, 24.5.

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.

ν_{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 ($\text{M}+\text{Na}^+$) $\text{C}_{21}\text{H}_{24}\text{N}_2\text{NaO}_2$ Requires: 359.1729.

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



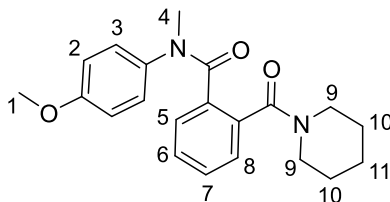
Prepared according to general procedure II using THF (0.27 mL), **227** (58.3 mg, 0.109 mmol), **25** (3.9 mg, 0.0164 mmol, 15 mol%), **53** (19.7 mg, 0.109 mmol), DBU (18.0 μL , 0.120 mmol) and pyrrolidine (11.0 μL , 0.131 mmol). Purified by flash column chromatography (hexanes:EtOAc, 8:2) to afford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

δ_{H} (400 MHz, CDCl_3): 7.32 (2 H, d, J 7.5, H-3), 7.27-7.16 (2 H, m, H-6, H-8), 7.17 (1 H, app. t, H-7), 6.92 (1 H, d, J 7.2, H-5), 6.71 (2 H, d, J 7.5, H-2), 3.72 (3 H, s, H-4), 3.66 (2 H, t, J 6.4, H-9), 3.43 (3 H, s, H-1), 3.37 (3 H, t, J 6.4, H-10), 2.04-1.88 (4 H, m, H-11).

δ_{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.

ν_{max} (neat)/ cm^{-1} :	2935, 1627 (C=O), 1580 (C=O), 1432, 1321, 1243, 1179, 1108, 837, 789, 776, 639, 579.
HRMS (m/z - ESI):	Found: 339.1707 ($M+H$) ⁺ C ₂₀ H ₂₃ N ₂ O ₃ Requires: 339.1703.

***N*-(4-methoxyphenyl)-*N*-methyl-2-(piperidine-1-carbonyl)benzamide (237)**

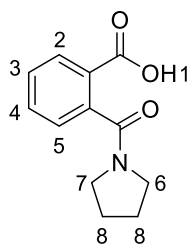


Prepared according to general procedure II using THF (0.3 mL), **227** (62.4 mg, 0.116 mmol), **25** (4.2 mg, 0.0174 mmol, 15 mol%), **53** (21.0 mg, 0.116 mmol), DBU (19.0 μL , 0.128 mmol) and piperidine (14 μL , 0.139 mmol). Purified *via* flash column chromatography (hexanes:EtOAc, 8:2) to afford **237** as a white solid (13.6 mg, 33%). M.p. 127-130 °C.

δ_{H} (400 MHz, CDCl_3):	7.40 (2 H, d, J 8.5, H-3), 7.33 (2 H, d, J 8.5, H-2), 7.21-7.15 (2 H, m, H-5, H-8), 7.04-6.99 (1 H, m, H-6), 6.91 (1 H, app. d, H-7), 3.79-3.68 (7 H, m, H-4, H-9), 3.52 (3 H, s, H-1), 1.78-1.58 (6 H, m, H-10, H-11).
δ_{C} (100 MHz, CDCl_3):	170.6 (C=O), 170.0 (C=O), 157.8 (q), 137.7 (q), 136.7, 136.6 (q), 136.1 (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.
ν_{max} (neat)/ cm^{-1} :	3056, 1633 (C=O), 1594 (C=O), 1444, 1368, 1286, 1088, 1001, 954, 889, 705, 668.
HRMS (m/z - ESI):	Found: 375.1685 ($M+\text{Na}$) ⁺ C ₂₁ H ₂₄ N ₂ NaO ₃ Requires: 375.1679.

Synthesis of protected amines to investigate deprotection methodologies

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



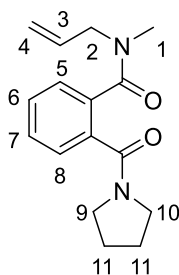
To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged phthalic anhydride (**241**, 8.04 g, 54.0 mmol) followed by THF (120 mL). The vessel was placed under a protective atmosphere of argon. The flask was fitted with a septum seal and argon balloon. Pyrrolidine (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 CH₂Cl₂ (3 x 50 mL) and the organic extract was washed with brine (2 x 30 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 **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

δ_{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*-methylallyl 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%).

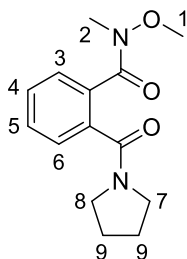
δ_{H} (400 MHz, CDCl₃): 7.45-7.29 (4 H, m, H-5, H-6, H-7, H-8), 5.87-5.67 (1 H, m, H-3), 5.25-5.09 (2 H, m, H-4a, H-4b), 4.09 (1 H, d, *J* 5.6, H-2a), 3.81 (1 H, d, *J* 5.6, H-2b), 3.55 (2 H, td, *J* 6.8, 3.2, H-9), 3.32 (2 H, q, *J* 6.4, H-10), 2.98 (3 H, s, H-1), 1.96-1.78 (4 H, m, H-11).

δ_{C} (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.

ν_{max} (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.

HRMS (*m/z* - ESI): Found: 273.1599 (M+H)⁺ C₁₆H₂₁N₂O₂ Requires: 273.1597.

***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 (CH₂Cl₂:EtOAc, 10:1) to yield the title product **240** as a colourless oil (1.2 g, 49%).

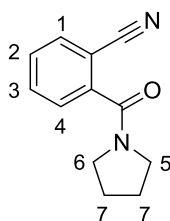
δ_{H} (400 MHz, CDCl₃): 7.51-7.34 (4 H, m, H-3, H-4, H-5, H-6), 3.65-3.56 (5 H, m, H-1, H-7), 3.34 (2 H, t, *J* 6.6, H-8), 3.29 (3 H, s, H-2), 1.99-1.83 (4 H, m, H-9).

δ_{C} (100 MHz, CDCl₃): 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.

ν_{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)⁺ C₁₄H₁₉N₂O₃ Requires: 263.1390.

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



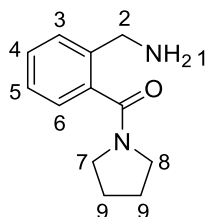
To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar under an atmosphere of argon maintained using an argon-filled balloon and septum was charged CH₂Cl₂ (28 mL), NEt₃ (0.27 mL, 1.92 mmol), EDC (0.41 g, mmol) and pyrrolidine (0.12 g, 1.5 mmol). The vessel was cooled to 0 °C in a H₂O/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 (CH₂Cl₂: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, CDCl_3): 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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$ 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, CDCl_3): 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).

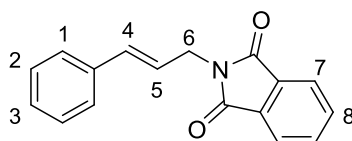
δ_{C} (100 MHz, CDCl_3): 169.4 (C=O), 137.2 (q), 136.8 (q), 128.2, 127.8, 127.5, 127.4, 64.7, 49.7, 46.3, 26.4, 24.5.

ν_{max} (neat)/ cm^{-1} : 3409, 2968, 2875, 1602 (C=O), 1562, 1514, 1425, 1339, 1252, 1018, 905, 840, 761, 669, 630, 573.

HRMS (m/z - APCI): Found: 205.1338 ($\text{M}+\text{H}$) $^+$ $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}$ Requires: 205.1335.

Synthesis of amines and diamines: procedures

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

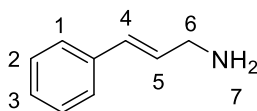


To an oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with THF (12 mL) and cinnamyl alcohol (**278**, 0.77 mL, 6.0 mmol) under an atmosphere of argon. Triphenylphosphine (2.05 g, 7.8 mmol), and phthalimide (**199**, 1.32 g, 9.0 mmol) was charged to the reaction mixture 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 *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 MgSO₄ 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

δ_{H} (400 MHz, CDCl₃): 7.87 (2H, dd, *J* 5.5, 3.1, H-7), 7.72 (2 H, dd, *J* 5.5, 3.1, H-8), 7.37-7.32 (2 H, m, H-1), 7.31-7.27 (2 H, m, H-2), 7.24-7.21 (1 H, m, H-3), 6.66 (1 H, d, *J* 15.8, H-4), 6.26 (1 H, dt, *J* 15.8, 6.5, H-5), 4.45 (2 H, dd, *J* 6.5, 1.1, H-6).

(*E*)-3-phenylprop-2-en-1-amine (**277**)



To a solution of 2-cinnamylisoindoline-1,3-dione (**280**, 0.94 g, 3.6 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 mL, 14.4 mmol) at room temperature. The mixture was stirred overnight at room temperature after which time the mixture was

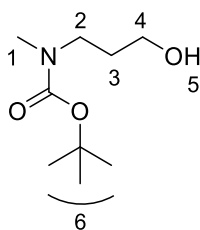
concentrated *in vacuo*. The resulting residue was diluted with CH₂Cl₂ (30 mL) and KOH (1 M, 30 mL) and the aqueous phase was extracted into EtOAc (3 x 30 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure to yield **277** as a pale-yellow oil (0.21 g, 44%).

Spectral data for this compound were consistent with those in the literature.¹⁸⁰

δ_{H} (400 MHz, CDCl₃): 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/z* - ESI): Found: 134.0956 (M+H)⁺ C₉H₁₂N 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 NEt₃ (3.50 mL, 24.9 mmol) in CH₂Cl₂ (200 mL), was charged a solution of di-*tert*-butyl dicarbonate (5.97 g, 27.2 mmol) in CH₂Cl₂ (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 MgSO₄, filtered and concentrated under reduced pressure to yield **294** as a colourless oil (4.05 g, 94%).

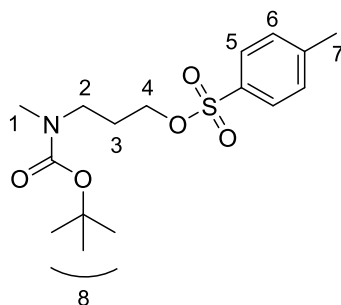
Spectral data for this compound were consistent with those in the literature.²⁰⁶

δ_{H} (400 MHz, CDCl₃): 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 CDCl₃.

HRMS (*m/z* - ESI): Found: 212.1261 (M+Na)⁺ C₉H₁₉NNaO₃ Requires: 212.1257.

3-(*Tert*-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (**295**)



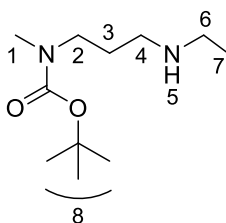
A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with *tert*-butyl (3-hydroxypropyl)(methyl)carbamate (**294**, 5.67 g, 30.0 mmol), CH₂Cl₂ (60 mL) and NEt₃ (9.5 mL, 65.9 mmol). The flask was cooled to 0 °C followed which tosyl chloride (6.28 g, 33.0 mmol) and DMAP (0.37 g, 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 (2 H, d, *J* 8.2, H-6), 4.04 (2 H, t, *J* 6.5, H-4), 3.24 (2 H, t, *J* 6.9, H-2), 2.79 (3 H, s, H-1), 2.45 (3 H, s, H-7), 1.87 (2 H, quin., *J* 6.5, H-3), 1.42 (9 H, s, H-8).

HRMS (*m/z* - ESI): Found: 366.1353 (M+Na)⁺ C₁₆H₂₅NNaO₅S 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.

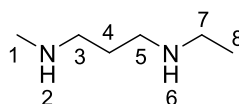
δ_{C} (100 MHz, DMSO-d₆): 155.4 (C=O), 78.8 (q), 66.6, 46.9, 46.8, 46.6, 46.3, 46.0, 43.7, 34.3, 28.5, 27.8, 27.2, 14.8.

*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.

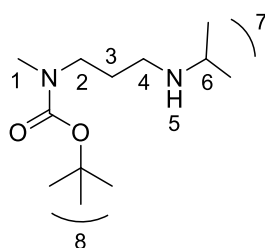
δ_{H} (400 MHz, CDCl₃): 2.72-2.61 (6 H, m, H-3, H-5, H-7), 2.44 (3 H, s, H-1), 1.69 (2 H, quin., *J* 7.0, H-4), 1.31 (2 H, br s, H-2, H-6), 1.11 (3 H, t, *J* 7.1, H-8).

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.

LRMS (*m/z* - ESI): Found: 59.1 (M+2H)⁺ C₆H₁₈N₂ Requires: 59.1.

***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-*d*₆): 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).

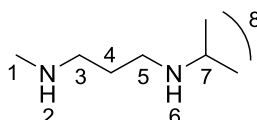
δ_C (100 MHz, DMSO- d_6): 154.6 (C=O), 78.0 (q), 47.9, 43.5, 40.7, 33.5, 27.9, 27.5, 22.1.

*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.

$\nu_{\max}$ (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 ($M+H$) $^+$ $C_{12}H_{27}N_2O_2$ 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_2Cl_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_2O until a white precipitate was observed. This precipitate (0.60 g, 1.67 mmol) was stirred in CH_2Cl_2 and K_2CO_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_2O (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.

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

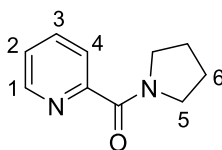
HRMS (m/z - APCI): Found: 131.1549 ($M+H$) $^+$ $C_7H_{19}N_2$ Requires: 131.1543.

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 μ L, 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**)**



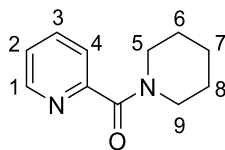
Prepared according to general procedure III using **258** (212.2 mg, 1 mmol) and pyrrolidine (84 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 1% MeOH to 10% MeOH in CH_2Cl_2) to produce **262** as a brown oil (176.4 mg, 93%).

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

δ_{H} (400 MHz, CDCl_3): 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).

HRMS (m/z - ESI): Found: 199.0837 ($\text{M}+\text{Na}$)⁺ $\text{C}_{10}\text{H}_{12}\text{N}_2\text{NaO}$ Requires: 199.0842.

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



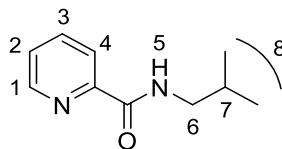
Prepared according to general procedure III using **258** (212.3 mg, 1 mmol) and piperidine (99 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 1% MeOH to 10% MeOH in CH_2Cl_2), to produce **263** as a brown oil (166.3 mg, 94%).

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

δ_{H} (400 MHz, CDCl_3): 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 ($\text{M}+\text{Na}$)⁺ $\text{C}_{11}\text{H}_{14}\text{N}_2\text{NaO}$ Requires: 213.0998.

N-isobutylpicolinamide (264)



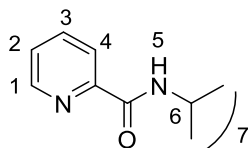
Prepared according to general procedure III using **258** (212.3 mg, 1 mmol) and isobutyl amine (100 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to produce **265** as a brown oil (165.1 mg, 93%).

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

δ_{H} (400 MHz, CDCl_3): 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 ($\text{M}+\text{H}$)⁺ $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}$ Requires: 179.1179.

***N*-isopropylpicolinamide (265)**



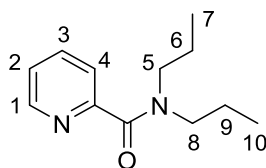
Prepared according to general procedure III using **258** (212.1 mg, 1 mmol) and isopropyl amine (100 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **265** as a brown oil (136.2 mg, 83%).

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

δ_{H} (400 MHz, CDCl_3): 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 ($\text{M}+\text{H}$)⁺ $\text{C}_9\text{H}_{13}\text{N}_2\text{O}$ Requires: 165.1022.

***N,N*-dipropylpicolinamide (266)**



Prepared according to general procedure III using **258** (212.2 mg, 1 mmol) and dipropyl amine (137 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 10:1 to 1:1, CH_2Cl_2 :EtOAc) to isolate **266** as a pale-yellow oil (135.0 mg, 65%).

δ_{H} (400 MHz, CDCl_3): 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).

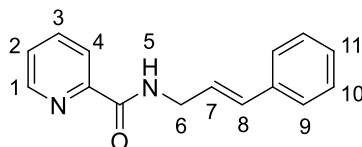
δ_{C} (100 MHz, CDCl_3): 169.0 (C=O), 155.4 (q), 148.3, 136.8, 124.0, 123.2, 50.4, 47.4, 22.1, 20.8, 11.5, 11.1.

ν_{max} (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%).

δ_H (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.

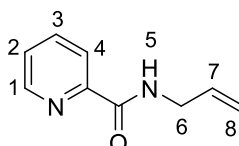
δ_C (100 MHz, CDCl₃): 164.2 (C=O), 149.8 (q), 148.1, 137.4, 136.6 (q), 132.2, 128.6, 127.7, 126.4, 126.3, 125.4, 122.4, 41.5.

ν_{max} (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)**



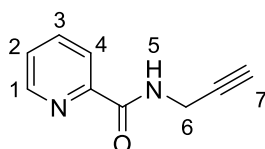
Prepared according to general procedure III using **258** (212.3 mg, 1 mmol) and allyl amine (75 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **268** as a brown oil (136.2 mg, 83%).

Spectral data for this compound were consistent with those in the literature.²¹¹

δ_{H} (400 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 ($\text{M}+\text{H}$)⁺ $\text{C}_9\text{H}_{11}\text{N}_2\text{O}$ Requires: 163.0866.

***N*-(prop-2-yn-1-yl)picolinamide (269)**



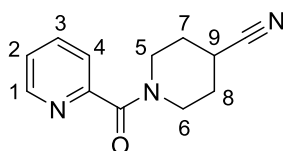
Prepared according to general procedure III using **258** (212.2 mg, 1 mmol) and propargyl amine (64 μL , 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 10:1 hexanes:EtOAc) to isolate **269** as an off-white solid (127.1 mg, 79%).

Spectral data for this compound were consistent with those in the literature.²¹²

δ_{H} (400 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 ($\text{M}+\text{H}$)⁺ $\text{C}_9\text{H}_9\text{N}_2\text{O}$ Requires: 161.0709.

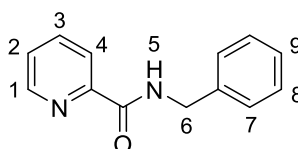
1-Picolinoylpiperidine-4-carbonitrile (270)



Prepared according to general procedure III using **258** (212.2 mg, 1 mmol) and piperidine-4-carbonitrile (112 μL , 1 mmol). Purified by flash chromatography (eluting in gradient from 1% MeOH to 10% MeOH in CH_2Cl_2) to isolate **270** as a colourless oil (147.3 mg, 68%).

δ_{H} (400 MHz, 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).
δ_{C} (100 MHz, 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.
ν_{max} (neat)/ cm^{-1} :	2962, 925, 2236 (CN), 1639 (C=O), 1577, 1308, 1047, 806, 760, 719, 655, 618.
HRMS (m/z - ESI):	Found: 216.1129 ($\text{M}+\text{H}$) $^+$ $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}$ Requires: 216.1131.

N-benzylpicolinamide (271)

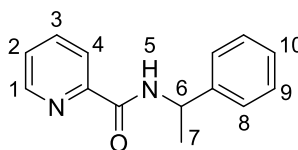


Prepared according to general procedure III using **258** (212.2 mg, 1 mmol) and benzylamine (110 μL , 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **271** as a pale yellow solid (194.0 mg, 91%). M.p. 86-89 $^{\circ}\text{C}$ (lit.,²¹³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

Spectral data for this compound were consistent with those in the literature.²¹³

δ_{H} (400 MHz, 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).
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N-(1-phenylethyl)picolinamide (272)



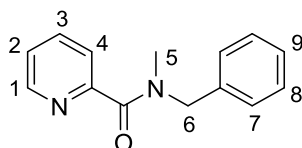
Prepared according to general procedure III using **258** (212.3 mg, 1 mmol) and α -methyl benzylamine (129 μ L, 1 mmol). Purified by flash chromatography (eluting in gradient from 100% hexanes to 30% EtOAc in hexanes) to isolate **272** as a white solid (183.0 mg, 81%).

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

δ_{H} (400 MHz, CDCl_3): 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 ($\text{M}+\text{H}$)⁺ $\text{C}_{14}\text{H}_{15}\text{NO}$ 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 μ L, 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 ^1H spectrum of this compound.

δ_{H} (400 MHz, $\text{DMSO}-d_6$): 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).

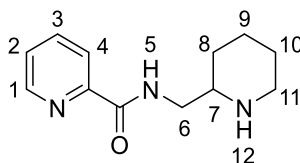
HRMS (m/z - ESI): Found: 227.1168 ($\text{M}+\text{H}$)⁺ $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ Requires: 227.1179.

Table 5: Experimental data

General procedure IV: Substrate evaluation in the NHC-catalysed oxidative amidation between 258 and various diamines (Table 5).

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 μ L, 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)picolinamide (**287**)**



Prepared according to general procedure IV using **258** (106.1 mg, 0.5 mmol) and 2-(aminomethyl)piperidine (146 μ L, 1.2 mmol). Purified by flash chromatography, (eluting in 96:3:1 CH₂Cl₂:MeOH:NEt₃) to isolate **287** as an orange oil (206.8 mg, 94%).

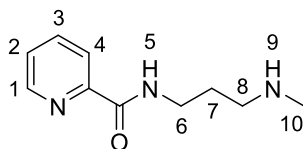
δ_H (400 MHz, CDCl₃): 8.53 (1 H, d, *J* 4.4, H-1), 8.45 (1 H, br. s, H-5), 8.16 (1 H, d, *J* 7.7, H-4), 7.83 (1 H, app. t, *J* 7.7, H-3), 7.44-7.38 (1 H, m, H-2), 4.08 (1 H, br. s, H-12), 3.67-3.57 (1 H, m, H-6a), 3.56-3.46 (1 H, m, H-6b), 3.24 (1 H, d, *J* 12.1, H-11a), 3.07-2.98 (1 H, m, H-7), 2.73 (1 H, td, *J* 12.0, 2.0, H-11b), 1.93-1.76 (2 H, m, H-8a, H-9a), 1.74-1.64 (1 H, m, H-10a), 1.63-1.32 (3 H, m, H-8b, H-9b, H-10b).

δ_C (100 MHz, CDCl₃): 165.1 (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.

ν_{max} (neat)/ cm^{-1} : 3346, 2929, 2796, 1655 (C=O), 1589, 1568, 1528, 1434, 1022, 1087, 1054, 746, 670, 618, 579.

HRMS (m/z - ESI): Found: 220.1444 ($M+H$)⁺ C₁₂H₁₈N₃O Requires: 220.1444.

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



Prepared according to general procedure IV using **258** (212.2 mg, 1 mmol) and *N*-methyl-1,3-propanediamine (104 μL , 1 mmol). Purified by flash chromatography (eluting in 96:3:1 CH₂Cl₂:MeOH:NEt₃) to isolate **288** as an orange oil (190.2 mg, 98%).

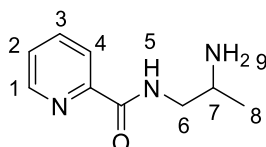
δ_{H} (400 MHz, CDCl₃): 8.55 (1 H, d, J 4.7, H-1), 8.39 (1 H, br s, H-5), 8.20 (1 H, d, J 7.8, H-4), 7.85 (1 H, td, J 7.8, 1.7, H-3), 7.42 (1 H, ddd, J 7.8, 4.7, 1.7, H-2), 3.58 (2 H, app. q, H-6), 3.29 (2 H, br s, H-9), 2.79 (2 H, t, J 6.8, H-8), 2.51 (3 H, s, H-10), 1.90 (2 H, quin., J 6.8, H-7).

δ_{C} (100 MHz, CDCl₃): 164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.2, 49.1, 37.5, 35.9, 29.1.

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

HRMS (m/z - ESI): Found: 194.1296 ($M+H$)⁺ C₁₀H₁₆N₃O Requires: 194.1288.

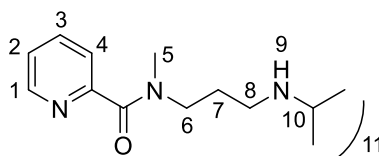
***N*-(2-aminopropyl)picolinamide (289)**



Prepared according to general procedure IV using **258** (106.1 mg, 1 mmol) and 1,2-diaminopropane (100 μL , 1.2 mmol). Purified by flash chromatography (eluting in 96:3:1 CH₂Cl₂:MeOH:NEt₃) to isolate **289** as an orange oil (190.2 mg, 98%).

δ_{H} (400 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).
δ_{C} (100 MHz, CDCl_3):	164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.3, 47.4, 46.9, 21.8.
ν_{max} (neat)/ cm^{-1} :	3302, 3058, 2971, 2931, 1656 (C=O), 1589, 1569, 1522, 1464, 1434, 1381, 1289, 1145, 1089, 997, 821, 748, 691, 620.
HRMS (m/z - ESI):	Found: 180.1136 ($\text{M}+\text{H}$) $^+$ $\text{C}_9\text{H}_{14}\text{N}_3\text{O}$ Requires: 180.1131.

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



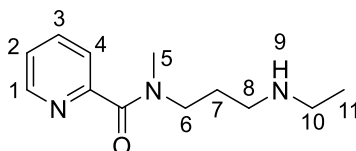
Prepared according to general procedure IV using **258** (212.2 mg, 1 mmol) and **164** (157.9 mg, 1.1 mmol). Purified by flash chromatography (eluting in 96:3:1 CH_2Cl_2 :MeOH: NEt_3) to isolate **290** as an orange oil (215.5 mg, 92%).

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

δ_{H} (400 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).
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δ_{C} (100 MHz, CDCl_3):	Rotamer (a). 169.1 (C=O), 154.8 (q), 148.3, 137.0, 124.3, 123.7, 48.8, 45.8, 44.3, 33.4, 27.5, 22.9. Rotamer (b). 168.9 (C=O), 154.7 (q), 148.1, 136.9, 124.2, 123.4, 48.9, 48.6, 44.2, 36.9, 29.0, 22.8.
ν_{max} (neat)/ cm^{-1} :	3413, 2964, 1624 (C=O), 1588, 1566, 1496, 1452, 1426, 1404, 1382, 1315, 1174, 1086, 751, 711, 674, 651, 618, 569.
HRMS (m/z - ESI):	Found: 236.1757 ($\text{M}+\text{H}$) $^+$ $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}$ Requires: 236.1757.

***N*-(3-(isopropylamino)propyl)-*N*-methylpicolinamide (291)**



Prepared according to general procedure IV using **258** (212.2 mg, 1 mmol) and **120** (130.4 mg, 1.1 mmol). Purified by flash chromatography (eluting in gradient from 100:1:1 to 90:10:1 CH_2Cl_2 :MeOH: NEt_3) to isolate **291** as a pale yellow oil (208.4 mg, 94%).

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

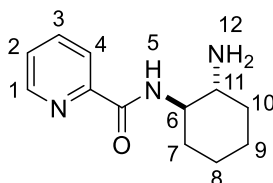
δ_{H} (400 MHz, CDCl_3):	Rotamer (a). 8.53-8.47 (1 H, m, H-1), 7.75-7.68 (1 H, m, H-4), 7.57-7.49 (1 H, m, H-3), 7.29-7.23 (1 H, m, H-2), 3.57 (2 H, t, J 7.0, H-6), 3.04 (3 H, s, H-5), 2.69-2.56 (4 H, m, H-8, H-10), 1.87-1.78 (2 H, m, H-7), 1.51 (1 H, br s, H-9), 1.05 (3 H, t, J 7.1, H-11). Rotamer (b). 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).
δ_{C} (100 MHz, CDCl_3):	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.

Rotamer (b). 168.8 (C=O), 154.6 (q), 148.1, 136.9, 124.2, 123.3, 46.5, 45.7, 44.0, 33.3, 27.3, 15.2.

$\nu_{\max}$ (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)⁺ C₁₂H₂₀N₃O Requires: 222.1601.

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



Prepared according to general procedure IV using **258** (160.0 mg, 0.5 mmol) and (1*R*,2*R*)-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 CH₂Cl₂:MeOH:NEt₃) to isolate **292** as an orange oil (169.1 mg, 77%).

δ_{H} (400 MHz, CDCl₃): 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).

δ_{C} (100 MHz, CDCl₃): 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.

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

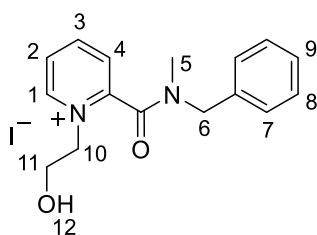
HRMS (*m/z* - ESI): Found: 220.1445 (M+H)⁺ C₁₂H₁₈N₃O Requires: 220.1444.

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 μ L, 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%).

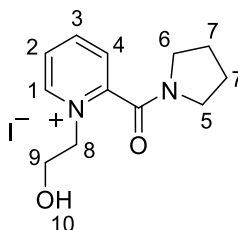
*A non-degenerate mix of isomers is observed in the ¹H and ¹³C NMR spectra of this compound. The NMR spectra of this compound are recorded at 60°C for more defined resonance signals.

δ_H (600 MHz, DMSO-*d*₆): 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).

δ_{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), 148.3, 147.2, 135.5 (q), 129.4, 128.4, 128.3, 127.9, 126.6, 61.4, 59.9, 54.2, 33.3.
ν_{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) ⁺ C ₁₆ H ₁₉ N ₂ O ₂ Requires: 271.1441.

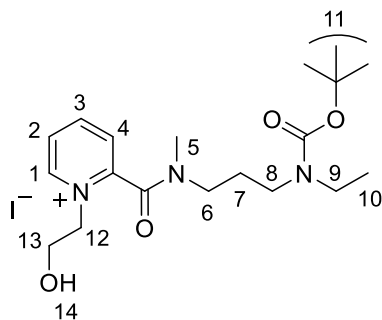
1-(2-Hydroxyethyl)-2-(pyrrolidine-1-carbonyl)pyridin-1-ium iodide (336)



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 μL , 1 mmol). Purified by flash chromatography (eluting in gradient from 100% CH₂Cl₂ to 5% MeOH in CH₂Cl₂) to isolate **336** as a pale-yellow oil (332.1 mg, 98%).

δ_{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).
δ_{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.
ν_{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.

2-((3-((*Tert*-butoxycarbonyl)(ethyl)amino)propyl)(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide (338**)**



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-*tert*-butyl dicarbonate (69.9 mg, 0.277 mmol) and CH₃CN (0.2 mL). The flask was sealed and heated to 120 °C until complete protection of **291** was detected (determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard). Upon complete Boc-protection of **291**, 2-iodoethanol (**234**, 22 μL, 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 *via* flash column chromatography (eluting in gradient from 100% CH₂Cl₂ to 5% MeOH in CH₂Cl₂) to isolate **338** as an orange oil (81.7 mg, 90%).

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

δ_H (400 MHz, DMSO-d₆) 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).

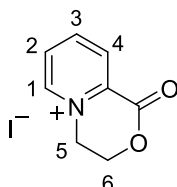
δ_C (100 MHz, DMSO-d₆): Major rotamer. 160.9 (C=O), 160.7 (C=O), 148.8 (q), 148.0, 147.1, 126.9, 126.3, 79.7 (q), 61.4, 60.1, 46.2, 43.8, 42.0, 37.1, 28.6, 25.7, 13.6.

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.

$\nu_{\max}$ (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)⁺ C₁₉H₃₂N₃O₄ Requires: 366.2387.

1-oxo-3,4-dihydro-1*H*-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 ¹H 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.

δ_{H} (600 MHz, DMSO-*d*₆): 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).

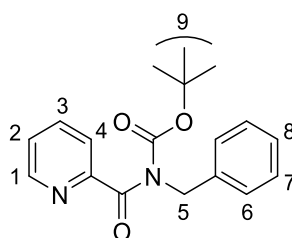
δ_{C} (100 MHz, DMSO-*d*₆): 157.1 (C=O), 147.8, 145.7, 139.2 (q), 131.3, 129.7, 65.7, 52.6.

$\nu_{\max}$ (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)⁺ C₈H₈NO₂ Requires: 150.0550.

Protection of secondary amides using di-*tert*-butyl dicarbonate

***Tert*-butyl benzyl(picolinoyl)carbamate (341)**



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%).

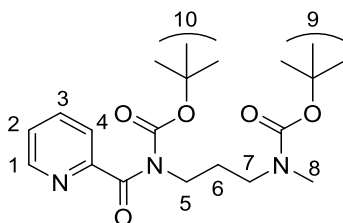
δ_{H} (400 MHz, CDCl₃): 8.61 (1 H, d, *J* 4.8, H-1), 7.83 (1 H, td, *J* 7.8, 1.6, H-4), 7.72 (1 H, app. d, H-3), 7.48 (2 H, app. d, H-7), 7.44-7.39 (1 H, m, H-2), 7.35 (2 H, app. t, H-6), 7.31-7.25 (1 H, m, H-8), 5.05 (2H, s, H-5), 1.17 (9 H, s, H-9).

δ_{C} (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.

ν_{max} (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%).

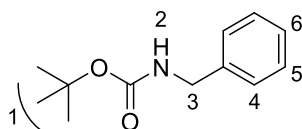
δ_{H} (400 MHz, CDCl_3):	8.58 (1 H, d, J 4.7, H-1), 7.82 (1 H, td, J 7.7, 1.6, H-4), 7.67 (1 H, d, J 7.8, H-3), 7.43-7.37 (1 H, m, H-2), 3.85 (2 H, t, J 7.5, H-5), 3.41-3.29 (2 H, m, H-7), 2.89 (3 H, s, H-8), 1.95 (2 H, quint., J 7.4, H-6), 1.47 (9 H, s, H-10), 1.20 (9 H, s, H-9).
δ_{C} (100 MHz, CDCl_3):	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.
ν_{max} (neat)/ 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 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{20}\text{H}_{31}\text{N}_3\text{NaO}_5$ 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_2O (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**)**



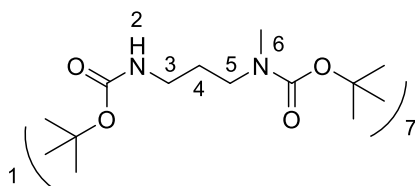
Prepared according to general procedure VI using *tert*-butyl benzyl(picolinoyl)carbamate (**341**, 110.0 mg, 0.352 mmol), NaBH₄ (28.5 mg, 0.704 mmol) and EtOH (2.8 mL) to isolate **344** as a colourless oil (65.5 mg, 90%).

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)⁺ C₁₂H₁₇N₃NaO₂ 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.

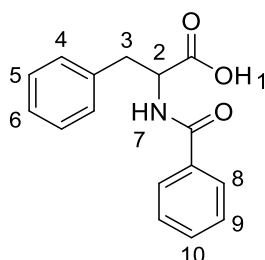
ν_{max} (neat)/cm⁻¹: 3357 (NH), 2976, 2931, 1679 (C=O), 1509, 1454, 1365, 1307, 1248, 1152, 1084, 872, 772, 640, 592.

HRMS (*m/z* - ESI): Found: 311.1953 (M+Na)⁺ C₁₄H₂₈N₂NaO₄ Requires: 311.1941.

4.3 Experimental data for Chapter 3

Azlactone synthesis

Benzoylphenylalanine (360)



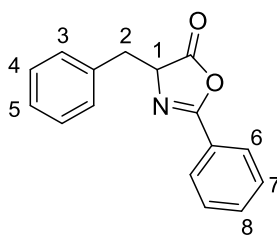
To a 50 mL round-bottomed flask equipped with a magnetic stirring bar DL-phenylalanine (**359**, 1.61 g, 9.7 mmol) was charged and dissolved in distilled H₂O (21 mL). NaOH (2 M, 19.4 mmol) was charged to the flask and the reaction mixture was cooled to 0 °C in a H₂O/ice bath. Benzoyl chloride (1.2 mL, 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

δ_{H} (400 MHz, CDCl₃): 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)

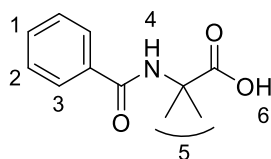


To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar, was charged benzoylphenylalanine (**360**, 1.81 g, 6.74 mmol) followed by CH₂Cl₂ (52 mL). DCC (1.42 g, 6.74 mmol) was added to the flask in one portion and the resulting suspension was stirred at room temperature overnight. 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% CH₂Cl₂ 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

δ_{H} (400 MHz, CDCl₃): 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**)



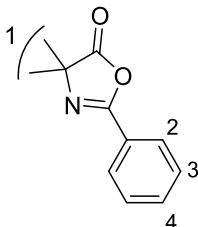
To a 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged, 2-methylalanine (**365**, 2.0 g, 19.4 mmol) and it was dissolved in distilled H₂O (40 mL). NaOH (2 M, 38.3 mmol) was charged to the flask and the reaction mixture was cooled to 0 °C in a H₂O/ice bath. Benzoyl chloride (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

δ_{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)



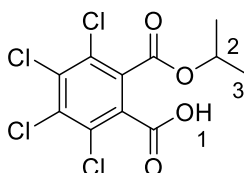
To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar, was charged 2-benzamido-2-methylpropanoic acid (**366**, 1.35 g, 6.51 mmol) followed by CH₂Cl₂ (80 mL). DCC (1.48 g, 7.16 mmol) was added to the flask in one-portion and the resulting suspension was stirred at room temperature 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)



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,

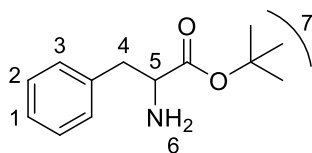
aqueous HCl (2 N, 35 mL) was charged to the flask and the reaction mixture was extracted into Et₂O (3 x 35 mL). The combined organic extracts were dried over MgSO₄ and the solvent concentrated under reduced pressure to yield **383** as a white solid (5.72 g, 94%). M.p. 143-145 °C (lit.,¹⁵⁶ M.p. 143-145 °C).

Spectral data for this compound were consistent with those in the literature.¹⁵⁶

δ_{H} (400 MHz, CDCl₃): 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 H₂O/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%).

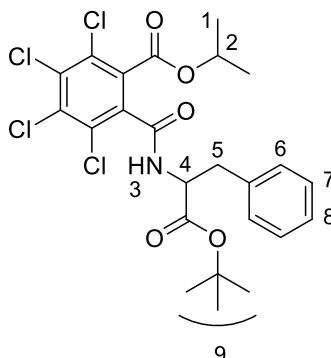
Spectral data for this compound were consistent with those in the literature.¹⁵⁶

δ_{H} (400 MHz, CDCl₃): 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)⁺ C₁₃H₂₀NO₂ Requires: 222.1416.

Isopropyl 2-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (387**)**

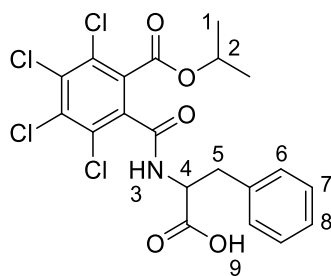


To a 250 mL oven-dried round-bottomed flask containing a magnetic stirring bar, 2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzoic acid (**383**, 10.7 g, 30.8 mmol) and *tert*-butyl phenylalaninate (**384**, 6.46 g, 29.2 mmol) were charged and the reaction vessel was flushed with argon and maintained under a protective argon atmosphere (using a septum and balloon). CH₂Cl₂ (103 mL) was charged to the flask *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 H₂O/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 *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

δ_{H} (400 MHz, CDCl₃): 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)

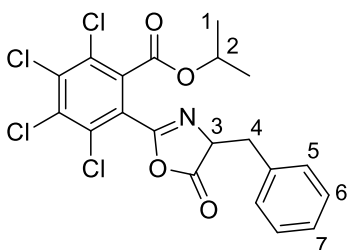


To a 25 mL oven-dried round-bottomed flask containing a magnetic stirrer, isopropyl 2-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**387**, 1.00 g, 1.83 mmol) was charged. The flask was flushed with argon and maintained under a protective argon atmosphere (using a septum and argon-filled balloon). CH₂Cl₂ (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 azeotrope 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). CH₂Cl₂ (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 CH₂Cl₂ 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

δ_{H} (400 MHz, CDCl₃): 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).

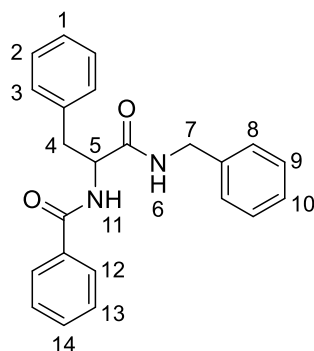
HRMS (*m/z* - APCI): Found: 473.9830 (M+H)⁺ C₂₀H₁₆Cl₄NO₄ Requires: 473.9828.

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 CH₂Cl₂ (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 ¹H 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 CH₂Cl₂. 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

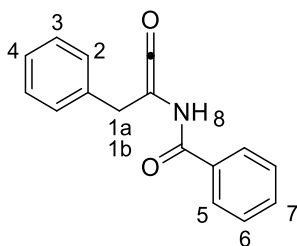
δ_{H} (600 MHz, DMSO- d_6): 8.64-8.58 (2 H, m, H-6, H-11), 7.82 (2 H, d, J 7.4, H-12), 7.51 (1 H, t, J 7.5, H-14), 7.44 (2 H, app. t, H-13), 7.35 (2 H, d, J 7.5, H-8), 7.31 (2 H, app. t, H-9), 7.28-7.21 (5 H, m, H-1, H-2, H-3), 7.17 (1 H, t, J 7.5, H-10), 4.78-4.72 (1 H, ddd, J 10.8, 6.5, 4.5, H-5), 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).

δ_{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.

ν_{max} (neat)/ cm^{-1} : 3230 (NH), 3029 (NH), 1660 (C=O), 1630 (C=O), 1535, 1455, 1327, 1289, 1185, 1026, 905, 873, 779, 616, 607, 588.

HRMS (m/z - ESI): Found: 381.1576 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{23}\text{H}_{22}\text{N}_2\text{NaO}_2$ Requires: 381.1573

***N*-(1-Oxo-3-phenyl-1H-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 ^1H 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.

δ_{H} (400 MHz, CDCl_3): 7.85-7.80 (2H, m, H-5), 7.59-7.52 (1H, m, H-7), 7.41 (2H, app. t, J 8.0, H-6), 7.23-7.13 (5H, m, H-2, H-3, H-4), 3.81 (1H, d, J 13.1, H-1a), 3.71 (1H, d, J 13.1, H-1b).

*Protic signal (H-8) is not visible in CDCl_3 .

δ_{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).

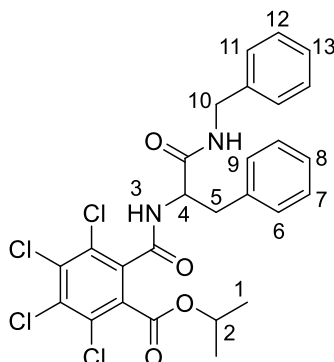
ν_{max} (neat)/ cm^{-1} : 2922 (NH), 1825 (C=O), 1732 (C=O), 1655, 1451, 1319, 1653, 975, 879, 788, 698.

HRMS (m/z - ESI): Found: 251.0937 (M) $^+$ $\text{C}_{16}\text{H}_{13}\text{NO}_2$ 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_2Cl_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 ^1H 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.

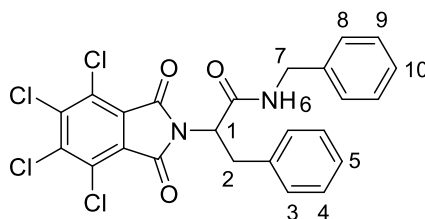
δ_{H} (600 MHz, CDCl₃): 7.33-7.23 (8 H, m, H-6, H-8, H-11, H-12, H-13), 7.21 (2 H, app. d, H-7), 6.70 (1 H, br s, H-3), 6.24 (1 H, d, *J* 7.9, H-9), 4.99 (1 H, sept., *J* 6.3, H-2), 4.93 (1 H, dd, *J* 6.2, 6.8, H-4), 4.44 (2 H, d, *J* 5.8, H-10), 3.39 (1 H, dd, *J* 14.0, 6.2, H-5a), 3.21 (1 H, dd, *J* 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).

δ_{C} (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.

ν_{max} (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-dioxisoindolin-2-yl)propenamide (393)



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 **393** as a white solid (19.8 mg, 15%). M.p. 225-228 °C.

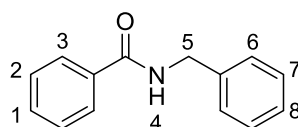
δ_{H} (600 MHz, CDCl₃): 7.35 (2 H, app. t, H-9), 7.30 (1 H, app. d, H-10), 7.26-7.22 (4 H, m, H-4, H-8), 7.19 (3 H, app. t, H-3, H-5), 6.13 (1 H, br s, H-6), 5.18 (1 H, dd, *J* 9.9, 6.9, H-1), 4.48 (2 H, d, *J* 5.6, H-7), 3.63-3.54 (2 H, m, H-2a, H-2b).

δ_{C} (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.

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)⁺ C₂₄H₁₇Cl₄N₂O₃ Requires: 520.9988

N-benzylbenzamide (394)

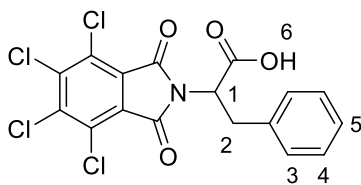


Prepared according to general procedure VIII. Purified via flash column chromatography eluting in gradient from 100% CH₂Cl₂ to 100:1 CH₂Cl₂:EtOAc to 100:2.5 CH₂Cl₂:EtOAc to 100:10 CH₂Cl₂:EtOAc to isolate **394** as a white solid (25.8 mg, 49%). M.p. 104-106 °C (lit.,²¹⁹ M.p. 104-106 °C).

Spectral data for this compound were consistent with those in the literature.²²⁰

δ_{H} (400 MHz, CDCl₃): 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-dioxoisindolin-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).

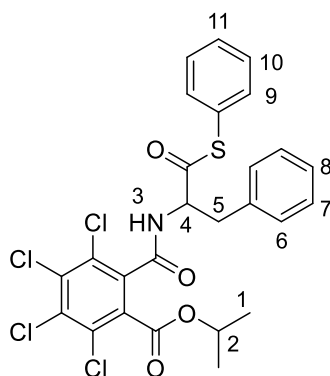
δ_{H} (400 MHz, CH₃OD): 7.26-7.08 (5 H, m, H-3, H-4, H-5), 5.07 (1 H, dd J 10.8, 3.6, H-1), 3.60 (1 H, dd, J , 13.7, 4.6, H-2a), 3.53 (1 H, app. t, H-2b).

* 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.

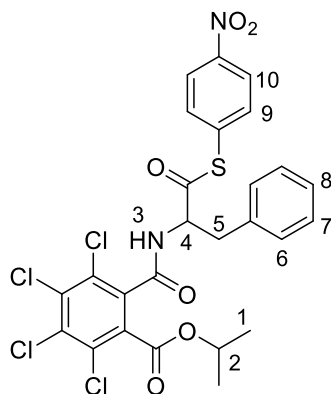
δ_{H} (400 MHz, CDCl_3): 7.46-7.38 (2 H, m, H-9), 7.38-7.31 (5 H, m, H-6, H-10, H-11), 7.30-7.24 (3 H, m, H-7, H-8), 6.38 (1 H, d, J 8.4, H-3), 5.30-5.16 (2 H, m, H-2, H-4), 3.29 (1 H, dd, J 13.7, 5.6, H-5a), 3.23 (1 H, dd, J 13.7, 6.8, H-5b), 1.34 (6 H, app. t, H-1).

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 ($\text{M}+\text{Na}^+$) $\text{C}_{26}\text{H}_{21}\text{Cl}_4\text{NNaO}_4\text{S}$ Requires: 605.9838.

Isopropyl 2,3,4,5-tetrachloro-6-(1-((4-nitrophenyl)thio)-1-oxo-3-phenylpropan-2-yl)carbamoylbenzoate (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, CDCl_3): 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, CDCl_3): 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 (NO_2), 1343 (NO_2), 1262, 1201, 1099, 1013, 934, 897, 849, 701, 657, 557.

HRMS (m/z - ESI): Found: 650.9683 ($\text{M}+\text{Na}^+$) $\text{C}_{26}\text{H}_{20}\text{Cl}_4\text{N}_2\text{NaO}_6\text{S}$ Requires: 650.9688.

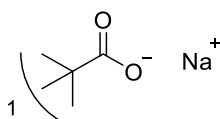
Synthesis of sodium salts for azlactone ring opening

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)



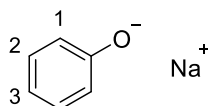
Prepared according to general procedure X using pivalic acid (**400**, 0.52 g, 5.1 mmol), NaH (0.21 g, 5.1 mmol) and THF (25.5 mL). Purified by trituration to isolate **398** as a white solid (0.47 g, 74%).

Spectral data for this compound were consistent with those in the literature.²²¹

δ_{H} (400 MHz, DMSO-*d*₆): 0.92 (9 H, s, H-1).

HRMS (*m/z* - ESI): Found: 101.0606 (M-Na)⁺ C₅H₉O₂ Requires: 101.0608.

Sodium phenolate (412)

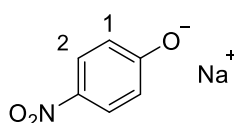


Prepared according to general procedure X using phenol (**411**, 0.10 g, 1.1 mmol), NaH (0.04 g, 1.1 mmol) and THF (5 mL). Purified by trituration to isolate **412** as a white solid (0.11 g, 89%). M.p. 58-60 °C (lit.,²²² M.p. 57-60 °C).

Spectral data for this compound were consistent with those in the literature.²²³

δ_{H} (400 MHz, DMSO- d_6): 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).

Sodium *p*-nitrophenolate (**414**)



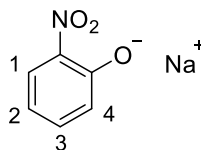
Prepared according to general procedure X using *p*-nitrophenol (**415**, 0.14 g, 1.0 mmol), NaH (0.04 g, 1.0 mmol) and THF (5 mL). Purified by trituration to isolate **414** as a red solid (0.13 g, 83%).

Spectral data for this compound were consistent with those in the literature.²²⁴

δ_{H} (400 MHz, DMSO- d_6): 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)⁺ C₆H₄NO₃ Requires: 138.0197.

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.

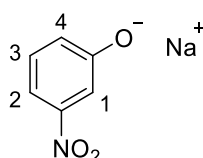
δ_{H} (400 MHz, DMSO- d_6): 7.61 (1 H, d, J 8.6, H-1), 6.93-6.86 (1 H, m, H-3), 6.31 (1 H, d, J 8.8, H-4), 5.85 (1 H, app. t, H-2).

δ_{C} (100 MHz, DMSO- d_6): 169.3 (q), 135.6 (q), 133.9, 128.3, 126.6, 107.6.

ν_{max} (neat)/ cm^{-1} : 3091, 1615, 1543 (NO_2), 1513, 1421, 1378, 1332 (NO_2), 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**)



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.

δ_{H} (400 MHz, DMSO-d_6): 6.82 (1 H, app t, H-1), 6.64 (1 H, app s, H-2), 6.60 (1 H, app d, J 7.6, H-3), 6.35 (1 H, app d, H-4).

δ_{C} (100 MHz, DMSO-d_6): 149.5 (q), 128.6 (q), 126.6, 111.5, 102.0.

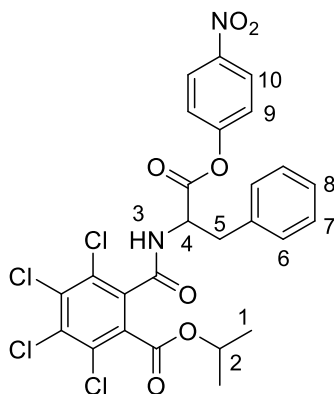
ν_{max} (neat)/ cm^{-1} : 3247, 1600, 1555, 1512 (NO_2), 1466, 1437, 1358 (NO_2), 1308, 1279, 1250, 1078, 991, 865, 736, 667.

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 *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 ^1H NMR spectroscopy (using *p*-iodoanisole as the internal standard) until 100% consumption of **381** was observed in the ^1H NMR spectrum of the reaction mixture. The reaction mixture was concentrated under reduced pressure and the residue purified *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 CH₂Cl₂:EtOAc) to isolate **417** as a white solid (8.3 mg, 14%). M.p. 122-125 °C.

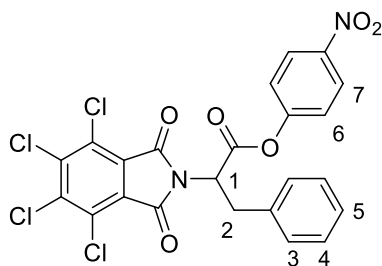
δ_{H} (600 MHz, CDCl₃): 8.28 (2 H, d, *J* 8.9, H-10), 7.38 (2 H, app. t, H-6), 7.36-7.31 (3 H, m, H-7, H-8), 7.18 (2 H, d, *J* 8.9, H-9), 6.47 (1 H, d, *J* 7.4, H-3), 5.30-5.21 (2 H, m, H-2, H-4), 3.43 (1 H, dd, *J* 14.1, 5.9, H-5a), 3.34 (1 H, dd, *J* 14.1, 6.9, H-5b), 1.36 (6 H, d, *J* 6.2, H-1).

δ_{C} (100 MHz, CDCl₃): 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.

ν_{max} (neat)/cm⁻¹: 3302 (NH), 2988, 1776 (C=O), 1733 (C=O), 1655 (C=O), 1525 (NO₂), 1491, 1349 (NO₂), 1290, 1202, 1165, 1127, 991, 887, 776, 704, 650.

HRMS (*m/z* - ESI): Found: 634.9911 (M+Na)⁺ C₂₆H₂₀Cl₄N₂NaO₇ 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.

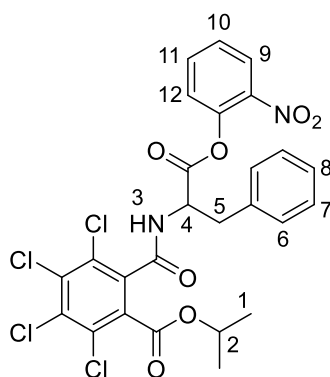
δ_{H} (600 MHz, CDCl₃): 8.31 (2 H, d, *J* 9.0, H-7), 7.32 (2 H, d, *J* 9.0, H-6), 7.30-7.27 (2 H, m, H-3), 7.23 (3 H, app. t, H-4, H-5), 5.45 (1 H, dd, *J* 11.1, 5.4, H-1), 3.74 (1 H, dd, *J*, 14.4, 5.4, H-2a), 3.59 (1 H, dd, *J* 14.4, 11.1, H-2b).

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.

HRMS (*m/z* - ESI): Found: 550.9384 (M-H)⁻ C₂₃H₁₁Cl₄N₂O₆ Requires: 550.9377.

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%).

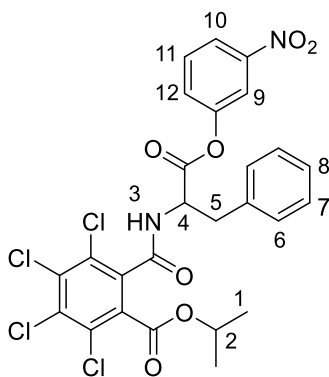
δ_{H} (400 MHz, CDCl_3): 8.11 (1 H, dd, J 8.2, 1.5, H-9), 7.66 (1 H, td, J 8.2, 1.5, H-10), 7.45 (1 H, app. t, H-11), 7.38-7.27 (5 H, m, H-6, H-7, H-8), 7.19 (1 H, dd, J 8.2, 1.5, H-12), 6.39 (1 H, d, J 7.4, H-3), 5.27 (1 H, td, J 7.4, 5.4, H-4), 5.15 (1 H, app. sept., H-2), 3.53 (1 H, dd, J 14.6, 5.4, H-5a), 3.34 (1 H, dd, J 14.6, 7.4, H-5b), 1.30 (6 H, app. t, H-1).

δ_{C} (100 MHz, CDCl_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_{max} (neat)/ cm^{-1} : 3295 (NH), 2926, 1774 (C=O), 1732 (C=O), 1655 (C=O), 1530 (NO_2), 1348 (NO_2), 1262, 1135, 1093, 931, 897, 734, 699, 590, 557.

HRMS (m/z - ESI): Found: 634.9923 ($\text{M}+\text{Na}^+$) $\text{C}_{26}\text{H}_{20}\text{Cl}_4\text{N}_2\text{NaO}_7$ Requires: 643.9917.

Isopropyl 2,3,4,5-tetrachloro-6-((1-(3-nitrophenoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (**448**)



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%).

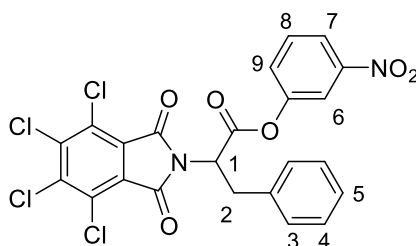
δ_{H} (400 MHz, CDCl_3): 8.15 (1 H, ddd, J 8.1, 2.1, 0.9, H-10), 7.86 (1 H, app. t, H-9), 7.58 (1 H, app. t, H-11), 7.44-7.32 (6 H, m, H-6, H-7, H-8, H-12), 6.47 (1 H, d, J 7.6, H-3), 5.33-5.22 (2 H, m, H-2, H-4), 3.45 (1 H, dd, J 14.0, 6.7, H-5a), 3.32 (1 H, dd, J 14.0, 7.6, H-5b), 1.38 (6 H, d, J 6.3, H-1).

δ_{C} (100 MHz, 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.

ν_{max} (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 ($\text{M}+\text{H}$) $^+$ $\text{C}_{26}\text{H}_{21}\text{Cl}_4\text{N}_2\text{O}_7$ 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 $^{\circ}\text{C}$.

δ_{H} (400 MHz, 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

H, dd, J 11.0, 5.2, H-1), 3.75 (1 H, dd, J 14.5, 5.2, H-2a), 3.60 (1 H, dd, J 14.5, 11.0, H-2b).

δ_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.

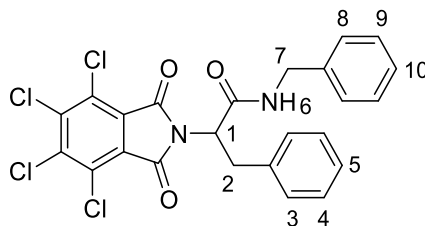
ν_{max} (neat)/ cm^{-1} : 3081, 2923, 2853, 1790 (C=O), 1772 (C=O), 1722 (C=O), 1533 (NO_2), 1457, 1351 (NO_2), 1278, 1197, 1003, 946, 801, 738, 628, 553.

HRMS (m/z - ESI): Found: 550.9373 (M-H)⁻ $C_{23}H_{11}Cl_4N_2O_6$ Requires: 550.9377.

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 ^1H NMR spectroscopy (using *p*-iodoanisole as the internal standard) until 100% conversion of azlactone **381** to the corresponding phenolic ester was observed in the ^1H 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 ^1H 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-dioxoisindolin-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 μ L, 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 $^{\circ}$ C.

CSP-HPLC analysis. Acquity UPC² step 3 – Trefoil CEL2 (2.5 μ m, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 $^{\circ}$ C, UV detection at 254 nm with PDA detector, retention times: 4.868 min (major enantiomer) and 5.494 min (minor enantiomer).

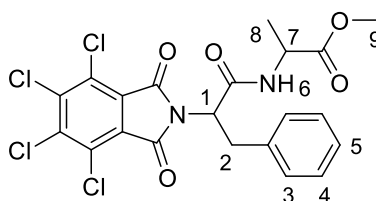
δ_{H} (600 MHz, CDCl₃): 7.35 (2 H, app. t, H-9), 7.30 (1 H, app. d, H-10), 7.26-7.22 (4 H, m, H-4, H-8), 7.19 (3 H, app. t, H-3, H-5), 6.13 (1 H, br s, H-6), 5.18 (1 H, dd, *J* 9.9, 6.9, H-1), 4.48 (2 H, d, *J* 5.6, H-7), 3.63-3.54 (2 H, m, H-2a, H-2b).

δ_{C} (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.

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)⁺ C₂₄H₁₇Cl₄N₂O₃ Requires: 520.9988

Methyl-(3-phenyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-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 μ L, 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.

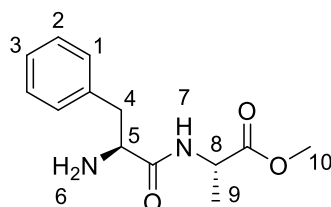
δ_{H} (600 MHz, CDCl₃): 7.27 (2 H, app. t, H-3), 7.22 (3 H, app. d, H-4, H-5), 6.59 (1 H, d, *J* 6.6, H-6), 5.18 (1 H, app. t, H-1), 4.61 (1 H, q, *J* 6.8, H-7), 3.78 (3 H, s, H-9), 5.81 (2 H, app. d, H-2), 1.43 (3 H, app. t, H-8).

δ_{C} (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.

ν_{max} (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 μ L, 0.177 mmol) was charged to the flask dropwise. The reaction was warmed to room temperature over 1 hour after which time 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

δ_{H} (400 MHz, CD_3OH): 7.30-7.24 (2 H, m, H-1), 7.24-7.16 (3 H, m, H-2, H-3), 4.40 (1 H, q, J 7.3, H-8), 3.67 (3 H, s, H-10), 3.61-3.53 (1 H, m, H-5), 3.04 (1 H, dd, J 13.6, 5.6, H-4a), 2.89-2.73 (1 H, m, H-4b), 0.96 (3 H, d, J 7.3, H-9).

* The protic signals H-6 and H-7 are not visible in CD_3OH .

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Cite this: DOI: 10.1039/c9cc06937b

Received 5th September 2019,
Accepted 15th October 2019

DOI: 10.1039/c9cc06937b

rsc.li/chemcomm

Highly chemoselective, sterically sensitive NHC-catalysed amine acylation with pyridil†

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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 bonds¹ continues to inspire chemists to develop new and unconventional methods for their synthesis.² We recently³ developed an N-heterocyclic carbene (NHC)-catalysed oxidative amidation of aldehydes^{4,5} which allows the coupling of benzaldehydes **1** with a range of primary and secondary amines **2** in the presence of precatalyst **3**, 1,2,4-triazole, stoichiometric DBU and phenazine (**4**) to produce amides **5** in good to excellent yields at ambient temperature. We could show that the reaction proceeded through symmetrical 1,2-diketones of general type **6** (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 **7**.

The steric congestion associated with **7**^{6,7} (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,⁸ the temporary masking of amine (Lewis)-basicity and nucleophilicity *via* a variety of methods⁹ usually remains a *sine qua non* in the synthesis of complex molecules.

While the selective acylation of primary over secondary amines in polyamines is often possible,¹⁰ and the exploitation of biomolecules to achieve high selectivity has been reported,^{11,12} 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.¹³

The state-of-the-art in this domain is the recent comprehensive study of the use of **9** as an acylating agent by Doyle *et al.* (Fig. 1B).¹⁴ The heterocycle could transfer a single benzoyl group with consistently (and uniformly) outstanding selectivity to a range of polyamines: for instance – diamine **8** could be transformed into the monobenzoyl-protected **10** in excellent yield; driven by the formation of an aromatic conjugate base of the leaving group **11**. While the selectivity possible is akin to that which one would expect from biocatalysis – the harsh acidic/basic conditions required to cleave *N*-benzoyl amides¹⁵ (no aroyl variants of **9** were reported) and the non-trivial synthesis of **9** from simple starting materials¹⁶ 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

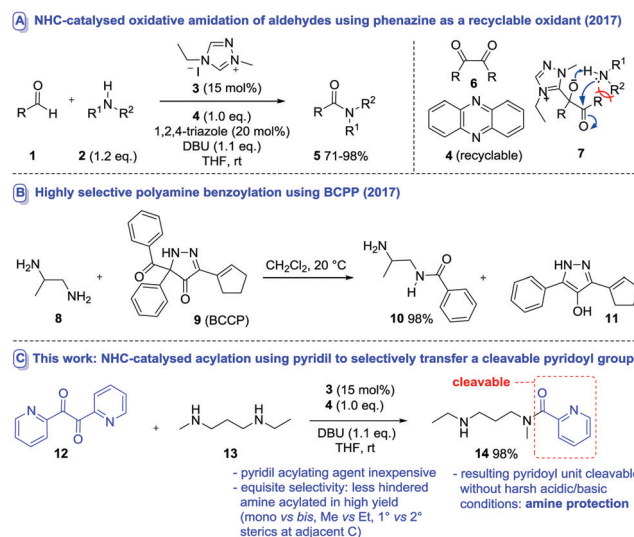


Fig. 1 NHC catalysed oxidative amidation of aldehydes, chemoselective amine acylation using a pyrazol-4-one and amine acylation using pyridil.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc06937b

(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**)¹⁷ to generate product amides **15–26** (Table 1). Simple primary benzyl-, allyl- and propargyl¹⁸ 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 amines 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

Table 2 Chemoselective acylation of diamines

Entry	Diamine	Product	Yield ^a (%)
1 ^b	29	30	94
2	31	32	98
3	8	33	98
4 ^b	34	35	77
5	36	37	94
6	13	38	98

^a Isolated yield. ^b 0.5 eq. of **12** utilised.

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.^{19–21} Under NHC catalysis the reaction formed the monoacyl product **35** in reduced yet appreciable yield; with the remainder bis-acylated material (entry 4).

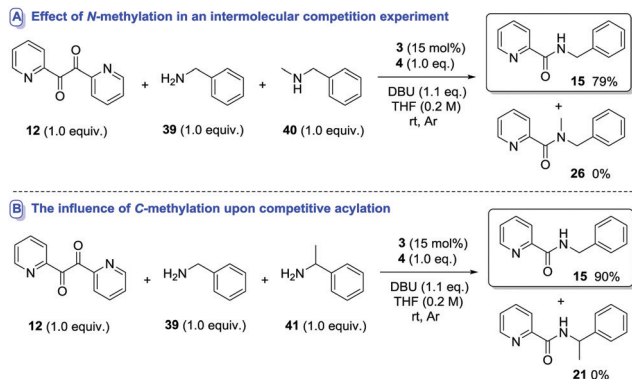
The methodology can also act upon steric variations between two different secondary amines. For instance, the preference for efficient reaction at the *N*-Me group associated with diamine **36** over its *N*-iPr counterpart is clear (entry 5). More strikingly, complete *N*-Me vs. *N*-Et selectivity is 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 monoacyl 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 1 Influence of amine structure on NHC-catalysed acylation by pyridil

15 , 91%	16 , 83%	17 , 99%	18 , 79%
19 , 93%	20 , 83%	21 , 81%	22 , 93%
23 , 94%	24 , 68%	25 , 65%	26 , 66%

Scheme 1 Influence of *N*- and *C*-substitution on competition experiments.

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 by the study could be deprotected in high yield without

requiring heating under strongly acidic or basic aqueous conditions (Scheme 2).

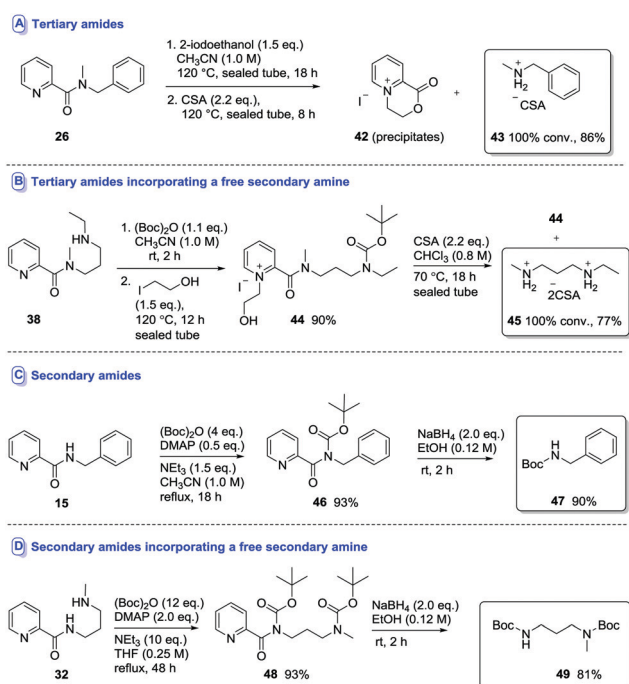
Tertiary amides can be deprotected in an *ad hoc*-designed one-pot procedure involving alkylation with iodoethanol followed by ring closure in the presence of dry camphorsulfonic acid (CSA) to generate the corresponding heterocyclic lactone **42** – which precipitates from solution and facilitates purification – and the deprotected salt **43** (Scheme 2A). Amides which are the product of chemoselective acylation and incorporate free amino groups on the pendant chain such as **38** can be first Boc-protected and then subjected to similar conditions to generate the double ammonium salt **45** via **44** (Scheme 2B).

Simple secondary amides (e.g. **15**) can be deprotected *via* initial carbamate formation to give **46**, followed by treatment with sodium borohydride²² to afford the Boc-protected **47** (Scheme 2C), whereas a similar strategy involving installation of two Boc-groups allows the cleavage of secondary amides incorporating a secondary amine such (e.g. formation of **49** from **32** via **48**, (Scheme 2D)).

In summary, the use of pyridil as an unconventional acylating agent for reaction with a range of primary and secondary amines in the presence of an N-heterocyclic carbene catalyst is reported. The system is able to easily discriminate between 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.



Scheme 2 Pyridoyl-amide cleavage.

Conflicts of interest

There are no conflicts to declare.

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