Synthesis of Medicinally Relevant Scaffolds *via* Earth Metal Catalysis

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Declaration

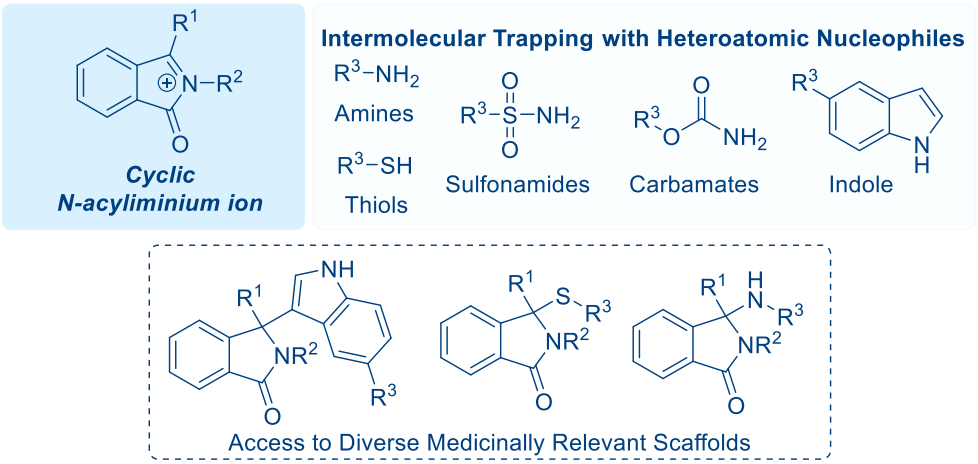
I declare that none of the work detailed herein has been submitted for any other award at Lancaster University or any other Institution.

I declare that, except where specifically indicated, all the work presented in this report is my own and I am the sole author of all parts. I understand that any evidence of plagiarism and/or the use of unacknowledged third part data will be dealt with as a very serious matter.

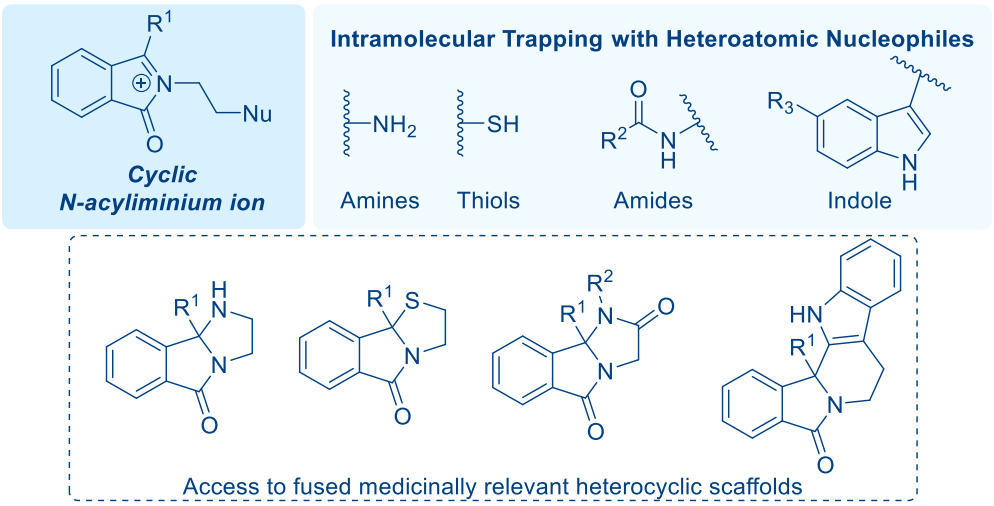
Abstract

Chapter 1 contains an overall introduction to this thesis, outlining the fundamentals of Lewis acid catalysis of the s-block elements with a particular focus on calcium. The application of calcium as a Lewis acid towards the catalytic generation of carbon, oxygen and limited nitrogen containing reactive intermediates is then described. The chapter then introduces *N*-acyliminium ions and describes the limited mild catalytic methods for their generation. The structure and reactivity of these highly electrophilic intermediates is presented followed by a conclusion describing how calcium(II) Lewis acids are ideal catalysts for catalytic generation of *N*-acyliminium ions.

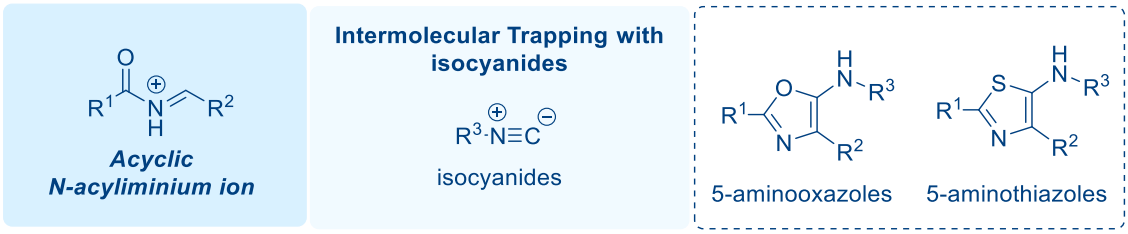
Chapter 2 focuses on the calcium catalysed generation of isoindolinone derived *N*-acyliminium ions and explores trapping these with a range of external heteroatomic nucleophiles. The reaction proves tolerant to carbon nucleophiles in the form of indole providing access to densely tetra-substituted motifs. Furthermore, heteroatomic nucleophiles including thiols also prove tolerant to the reaction providing access to γ-lactam scaffolds. Nitrogen nucleophiles are also tolerated with the *N*-benzyl substituted *N*-acyliminium ion being required to prevent any deprotonation.



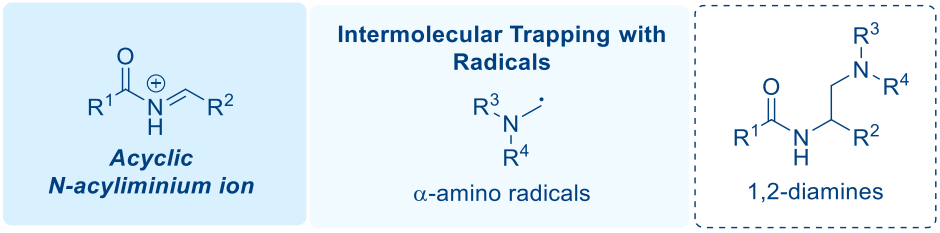
Chapter 3 focuses on the intramolecular trapping of isoindolinone derived *N*-acyliminium ions containing a tethered nucleophile which provides access to complex polycyclic scaffolds. The reaction proves tolerant to carbon, sulfur and nitrogen tethered nucleophiles forming the products in a rapid, high yielding dehydrative cyclisation strategy.



Chapters 4 builds on the seminal successes of the calcium catalysed generation of cyclic *N*-acyliminium ions and explores the catalytic generation of acyclic *N*-acyliminium ions and their reactivity towards isocyanides. This dehydrative/elimination-addition-cyclisation strategy provides modular access to highly substituted 5-aminooxazoles. The same strategy is then applied towards the synthesis of 5-aminothiazoles.

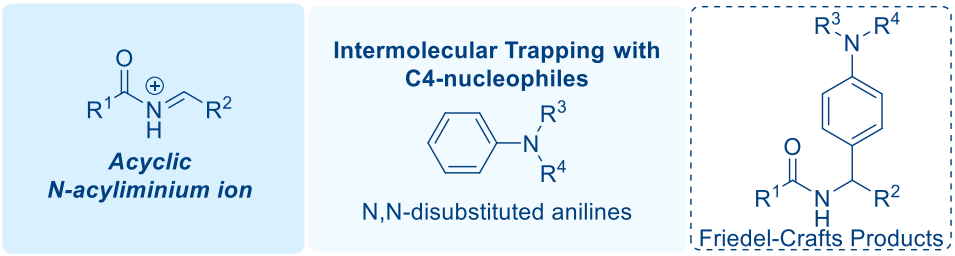


Chapter 5 studies the addition of radicals into the catalytically generated *N*-acyliminium ions, and aims to develop a synergistic calcium/photoredox catalysed coupling of *N*-acyliminium ions with α-amino radicals for access to 1,2-diamines. However, an aza-Friedel-Crafts side product forms as the major product. The addition of stoichiometric radicals is also studied which is found to reduce the *N*-acyliminium ion.

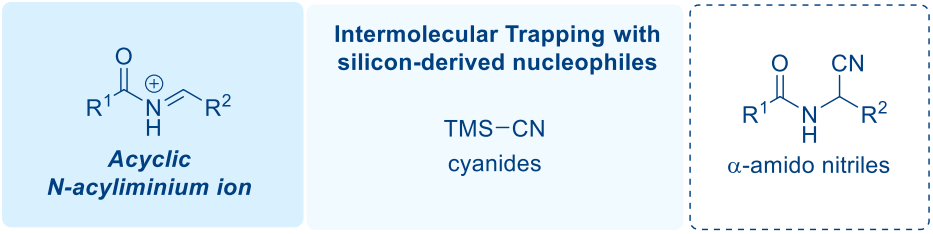


Chapter 6 explores the reactivity of the aza-Friedel-Crafts side product discovered in chapter 5 and optimises this reaction towards the synthesis of a range of functionalised

amides. The reactivity also proves successful towards isoindolinone derived *N*-acyliminium ions.



Chapter 7 studies the addition of trimethylsilyl cyanide into *N*-acyliminium ions to access highly versatile α-amido nitriles. Synthetic manipulation of α-amido nitriles into 1,2-diamine derivatives and α-amido esters is also presented.



Chapter 8 provides overall conclusions to the project and proposes areas of future work.

Chapter 9 contains the experimental details and characterisation of compounds synthesised within this thesis. An appendix will provide the complimentary spectra.

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Firstly, I would like to thank my supervisor Dr Mark McLaughlin for all his help and support both inside and outside of the lab throughout my PhD. Thank you for having that drive and motivation to constantly make me a better researcher. A special thank you to former post doc, Dr Tom Britten for his guidance, perseverance, and mentorship from day 1 and his significant contribution to the scientist that I am today.

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List of Abbreviations

Ac	acetyl
Aq	aqueous
Ar	unspecified aryl group
Bn	benzyl
Boc	*tert*-butylcarbonyl
Bz	benzoyl
DCM	dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ESI	electrospray ionisation
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HFIP	hexafluoroisopropanol
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
hr	hour
i	iso
IR	infrared
J	coupling constant
LUMO	lowest occupied molecular orbital
M	molar
Me	methyl

Min	minutes
mL	millilitre
mmol	millimole
m/z	mass/charge
NMR	nuclear magnetic resonance
PG	unspecified protecting group
Ph	phenyl
PIDA	(Diacetoxyiodo)benzene
ppm	parts per million
pr	propyl
Rf	retention factor
rt	room temperature
^{t}Bu	tert-butyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	4-toluensulfonyl (tosyl)
WERC	water exchange rate constant
δ	chemical shift
µ	micro
1,2-DCE	1,2-dichloroethane

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1. Chapter 1: Introduction

1.1. Lewis Acidity

1.1.1. Concepts

The concept of Lewis acidity was first introduced by G.N. Lewis in 1923.[1] Defined as an electron pair acceptor, this definition is more general than that proposed by Brønsted in the same year – a proton donor.

The fundamental interaction of a Lewis acid is with a Lewis base (an electron pair donor). This interaction results in the formation of a complex, in which electrons are shared between the two atoms, resulting in a dative or coordinate bond. A molecular orbital diagram (Figure 1) explains this interaction at a fundamental level whereby the lowest unoccupied molecular orbital (LUMO) of the Lewis acid and highest occupied molecular orbital (HOMO) of the Lewis base form a lower in energy bonding orbital.

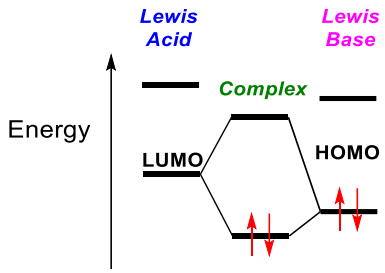


Figure 1. Molecular orbital depiction of a Lewis acid-base interaction.

The affinity and strength of a Lewis acid-base interaction was considered by Pearson in 1963.[2] He used the concept of hard and soft acids and bases (HSAB) to explain their affinity for each other, focussing particularly on interactions that are not explained by electronegativity. Hard acids are defined as small, highly charged electron acceptors whereas soft acids have a small positive charge with valence electrons that could easily be removed. Pearson formulated a table in which they were categorised into hard, soft and borderline Lewis acids (Table 1).

Table 1. Classification of Lewis acids according to Pearson.[2]

Hard	Soft	Borderline
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+, Cs^+	Fe^{2+}, CO^{2+}, Ni^{3+},
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Sn^{2+},	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+	Cu^{2+}, Zn^{2+}, Pb^{2+},
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	Tl^{3+}, $Tl(CH_3)_3$, BH_3	$B(CH_3)_3$, SO_2, NO^+
Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, Ir^{3+}	RS^+, RSe^+, RTe^+	
Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+}, Pu^{4+}	I^+, Br^+, HO^+, RO^+	
VO^{2+}, UO^{2+}, $(CH_3)_2Sn^{2+}$,	I_2, Br_2, ICN	
$Be(CH_3)_2$, BF_3, BCl_3, $B(OR)_3$	Trinitrobenzene	
$Al(CH_3)_3$, $Ga(CH_3)_3$, $In(CH_3)_3$	Chloranil, quinones,	
RPO_2^+, $ROPO_2^+$,	Tetracyanomethylene	
RSO_2^+, $ROSO_2^+$, SO_3	O, Cl, Br, I, R_3C^+	
I^{7+}, I^{5+}, Cl^{7+}	M^0 (metals)	
RaC^+, RCO^+, CO_2, NC^+	Bulk Metals	
HX		

1.1.2. Types of Lewis Acid

A Lewis acid is defined as any species with an inherent ability to accept electron pairs. Given the wide range of chemical entities that this definition can be applied to, Lewis acidic behaviour can be divided into six categories (Figure 2).

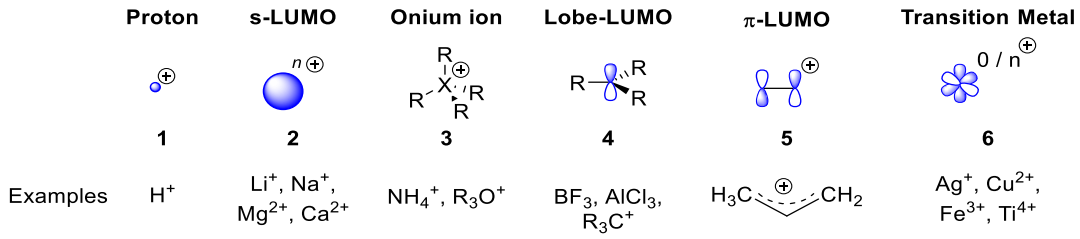


Figure 2. Classification of Lewis acids.

Perhaps the simplest type of Lewis acid is the proton **1**, which can accept electrons into its vacant 1s-LUMO orbital. Similarly, s-LUMO type Lewis acids **2** have shell like LUMOs,

derived from their s-orbitals accepting electrons into their vacant respective 2s, 3s, 4s orbitals. The Lewis acidity of onium ions **3** arises from an electron-deficient electronegative heteroatom (X) saturated with Lewis acidic ligands (R) which can be used to transfer an R group ligand upon reaction with a Lewis base/nucleophile. Lobe-LUMO Lewis acids **4** are defined as having a vacant p-orbital which can accept electrons from a Lewis base. π-LUMO Lewis acid species **5** contain a delocalised cation within a π-system and can accept electrons into their π-orbital. Transition metals **6** can also react as Lewis acids, accepting electrons into their partially filled d-orbitals. The focus within this thesis is on s-LUMO type Lewis acids **2**, in particular calcium based Lewis acids.

1.2. Calcium as a Lewis Acid

The development of new methods to catalyse powerful organic transformations in a more sustainable approach is of ever-increasing importance to the synthetic community with chemists continually looking for ways to adopt the twelve principles of green chemistry into their methodology.[3] Calcium, being the 5th most abundant element within the Earth's crust,[4] is therefore an ideal candidate for use in catalysing sustainable organic transformations.

The position of calcium within the periodic table results in the formation of highly stable Ca^{2+} complexes. The electropositive character together with the polarisation of the metal-base bonding system provides a high degree of charge separation. This provides extremely nucleophilic sources of base traditionally resulting in calcium acting merely as a counter cation for strong bases, with its strong Lewis acidic ability often ignored. This reactivity can be compared with group 1 and group 13 compounds (Figure 3). Lithium compounds display highly nucleophilic and basic properties. Aluminium species contain a highly reactive Lewis acidic Aluminium centre. Calcium compounds are ambiphilic and display characteristics of both group 1 and group 13 species. They contain high nucleophilic and strong basic properties through the anionic bound R group residues, comparable to that of the Group 1 compounds, whilst the calcium centre itself has Lewis acidic properties comparable to that of Group 13 compounds.

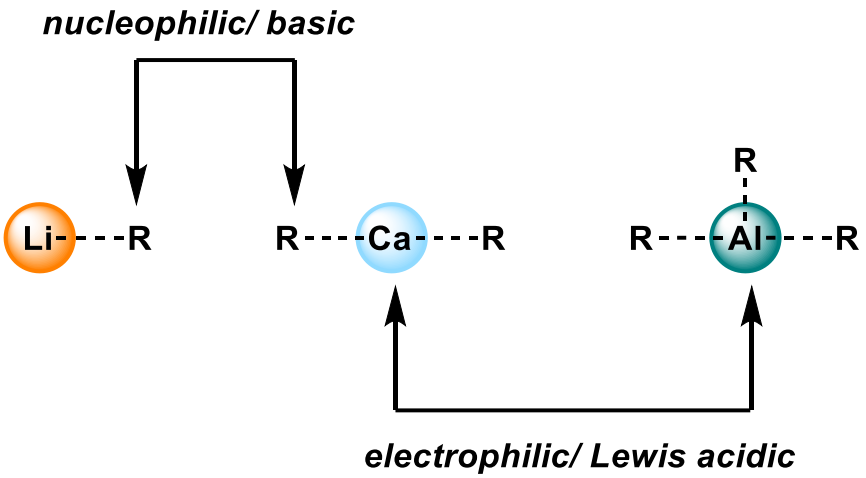


Figure 3. Ambiphilic nature of calcium complexes compared with group 1 and 13 compounds.

Furthermore, with a redox potential of E^0 = -2.87 V, calcium can be considered inert with respect to redox processes.[5] While this may appear a limitation, it precludes the possibility of any side reactions taking place therefore allowing a range of substrates to be used.

1.2.1. Effect of Counter Anions

To fully exploit the use of calcium as a Lewis acid, the choice of counter anion needs to be carefully considered. This is because the strength of Lewis acidity can be directly correlated to the strength of the interaction between the cationic centre and counter anions. For example, the strong σ-interactions in $CaCl_2$ result in the formation of strong covalent bonds, giving rise to a fully filled 2s LUMO orbital which subsequently results in poor Lewis acidity.

As it is not possible to formally have a cationic centre, a weaker interaction between cation and anion results in a more masked cation. The use of non-basic and weakly coordinating anions has shown the most promise.[6] Weakly coordinating ions must have a low overall charge and have a high degree of delocalisation.[6] This ensures no individual atom has a high concentration of charge, resulting in the point charge at the binding site remaining low.

The first examples of weakly coordinating anions were reported in the 1920's and concerned the perchlorate (ClO_4^-) salts of Li^+, Na^+ and K^+. Since then, other weakly

coordinating anions have been developed including perfluorinated phosphates (PF_6^-), antimonates (SbF_6^-), triflates (TfO^-) and triflimides (Tf_2N^-).[7, 8] The use of these weakly coorindating anions with calcium can be exploited to generate calcium complexes with low nucleophilicity/basicity and high Lewis acidity (Figure 4).

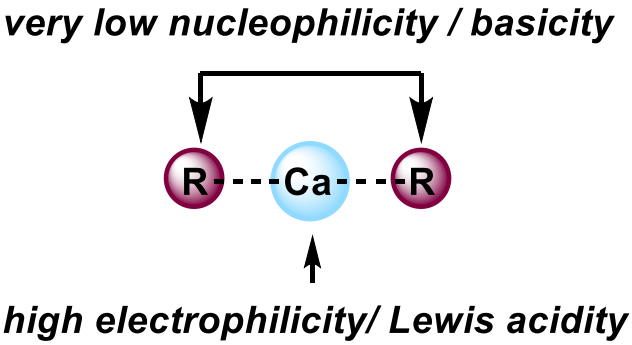


Figure 4. Tuning the calcium catalyst using weakly coordinating anions.

In addition to enhancing the Lewis acidity, weakly coordinating anions also improve the solubility in solvents with lower dielectric constants.[6] This allows the transformations to take place in less coordinating solvents which would otherwise inhibit the catalyst through coordination.

1.2.2. Effect of Solvent

It is unsurprising that solvents with strong Lewis basic atoms such as DMF, DMSO, MeCN and THF should be avoided. If the interaction between solvent and cation is stronger than that of the interaction between cation and weakly coordinating anion, catalytic poisoning will occur, significantly reducing activity. Therefore, non-coordinating solvents, particularly aromatic, aliphatic and chlorinated hydrocarbons should be used.

1.2.3. Water Tolerance

A distinct advantage of using calcium over traditional Lewis acids is its tolerance to water. Many traditional Lewis acids such as $AlCl_3$ and $TiCl_4$ decompose to their respective hydroxides or oxides in trace amounts of water resulting in loss of reactivity and therefore are typically not used catalytically.[8-10]

Decomposition of Lewis acids in the presence of water always proceeds by coordination of the water molecule to the Lewis acid (Figure 5). This enhances the polarisation of one

of the O-H bonds and is essentially turned into an acid, with the metal hydroxide forming the conjugate base. The Brønsted acidity of this interaction can be directly related to the strength of the interaction between the metal and oxygen atom. Hence, the stronger the interaction, the stronger the acidity of the complex.

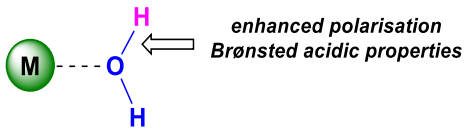


Figure 5. General depiction of the coordination of a water molecule to a Lewis acid

The hydrolysis constant, pK_h, is used to quantify this interaction, and the value is a good indicator of how susceptible Lewis acids are towards hydrolysis.[11] The pK_h value can be viewed in relation to pK_w = 14 as it is simply the value for water with the metal salt dissolved in it (Table 2).

Table 2. pK_h values and water exchange rate constants (WERC) for a range of metal ions

	Li^+	Na^+	Mg^{2+}	Ca^{2+}	Ni^{2+}	Sc^{3+}	Al^{3+}
pK_h	13.64	14.18	11.44	12.85	9.89	4.30	1.14
WERC ($M^{-1}s^{-1}$)	4.7×10^7	1.9×10^8	5.3×10^5	5.0×10^7	2.7×10^4	4.8×10^7	1.6×10^0

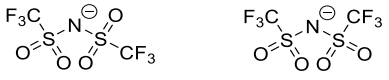
To maintain strong catalytic activity, a saturated metal centre must be able to exchange freely with inner sphere ligands and compete with the water molecules to access the substrate. This requires the exchange of inner sphere ligands to be fast. The rate of exchange of water molecules can be measured and has been quantified and termed the water exchange rate constant (WERC).[11] To date, the only study on this reactivity in organic synthesis was carried out by Kobayashi and co-workers studying the ability of a range of metal chlorides, perchlorates and triflates to catalyse an aldol reaction.[8, 9] The authors concluded that there was a WERC threshold value of 3.2×10^6 $M^{-1}s^{-1}$, whereby a value lower than this resulted in poor catalytic activity regardless of their Lewis acidity. Added to this, they also proposed that a pK_h value below 4 results in either decomposition or acid catalysed side reactions.

1.2.4. A Competing Brønsted Acid Catalysed Pathway

The high water tolerability of calcium precludes the need to carry out reactions under anhydrous conditions. Added to this, many calcium catalysed reactions produce water as a by-product. Therefore, it is plausible to suggest protons either generated or simply present in the reaction mixture could affect the reaction. Protons can also catalyse reactions in the same way that cationic Lewis acids can, offering the possibility of a second (or even primary) Brønsted acid catalysed pathway. This is particularly relevant to $Ca(NTf)_2/n Bu_4NPF_6$ which has been employed in a range of transformations.[12] There is a potential alternative Brønsted acid catalysed pathway employing a displaced NTf_2^- anion which could easily be protonated, forming the Brønsted superacid triflimide. The use of triflimide ($HNTf_2$) to catalyse a range of transformations has been well explored.[13] To avert this possibility, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), a proton sponge, is often added as part of the reaction optimisation.[14] However, in some cases DTBMP does not inhibit the reaction fully and therefore a dual catalytic pathway cannot be ruled out whereby the Lewis and Brønsted acid work in cooperation providing a rapid and efficient transformation.[15] As little is known about the true, active $Ca(NTf)_2/n Bu_4NPF_6$ catalytic species, a DTBMP control reaction should be an essential part of optimisation.

1.2.5. Calcium(II) bistriflimide as a Lewis Acid

The triflimidate ion ($^-NTf_2$) is a highly delocalised ion which can be used as a metal counter ion with partial negative charges on the oxygen atoms. In its anionic form, it can exist in either a *transoid* or *cisoid* conformation (Figure 6). The *transoid* conformation **7** has been shown to be slightly favoured and is usually observed when there is a weak cation/anion interaction. Whereas the *cisoid* conformation **8** is usually observed when chelated to a metal centre.[16, 17]



7 ***transoid*** **8** ***cisoid***

Figure 6. Conformations of the triflimidate anion.

Metal triflimidate salts are highly positively charged at the metal centre with a partial negative charge existing on the oxygen atoms.[7] The crystal structure of $Ca(NTf)_2$ has been determined to be an 8-coordinate complex, displaying the triflimidate anion coordination through η^2-oxygen interactions (Figure 7).[18] The conformation of the CF_3 groups exists in a *syn* relationship, which is typical of the other main group metal triflimidates.

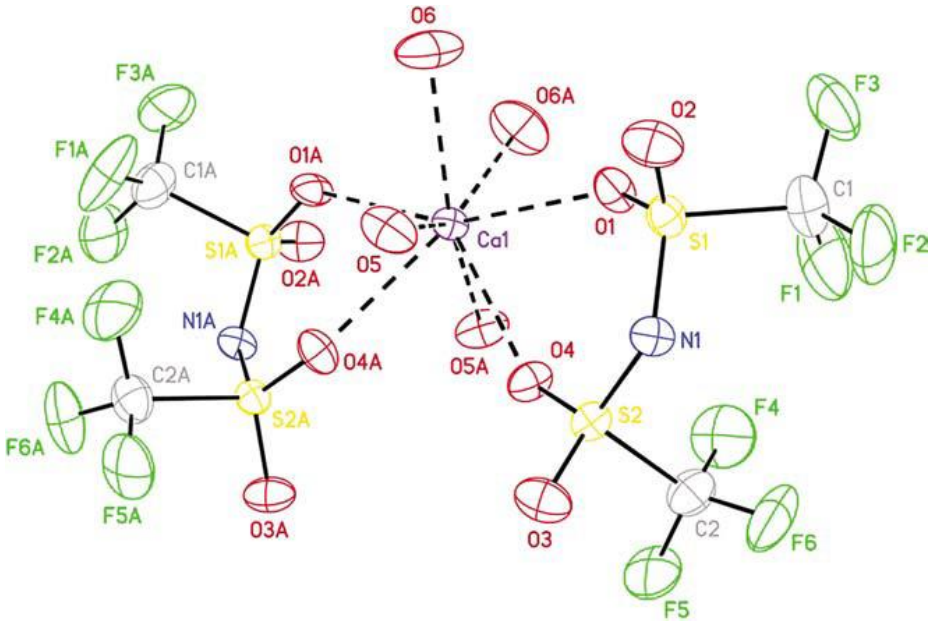
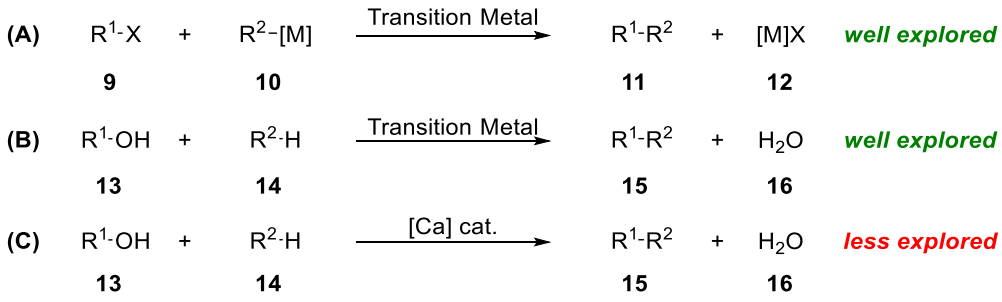


Figure 7. Crystal structure of $[Ca(H_2O)_4(NTf_2)_2]$ determined by DesMarteau (scheme extracted from paper)[18]

1.3. Calcium Catalysed Transformations using $Ca(NTf_2)_2$

The formation of carbon-carbon and carbon-heteroatom bonds is a highly desirable transformation in organic synthesis. Traditionally, transition metals have been used to catalyse this transformation *via* a cross-coupling reaction between an electrophile **9** and nucleophile **10** (Scheme 1A).[19] More recently, the reaction of alcohols **13** in the presence of a transition metal has been proven successful in a more atom-economical and environmentally benign approach to achieve carbon-carbon and carbon-heteroatom bond formation producing water as the sole by-product (Scheme 1B).[20] However, a distinct disadvantage of this transformation is that the use of transition metals is still required and many require harsh reaction conditions. It is the use of calcium, in

particular $Ca(NTf_2)_2$, as a Lewis acid catalyst to mediate this transformation that has been of considerable interest in recent years and has offered the potential to carry out these transformations under milder and more sustainable conditions, without the need for use of precious transition metals (Scheme 1C).

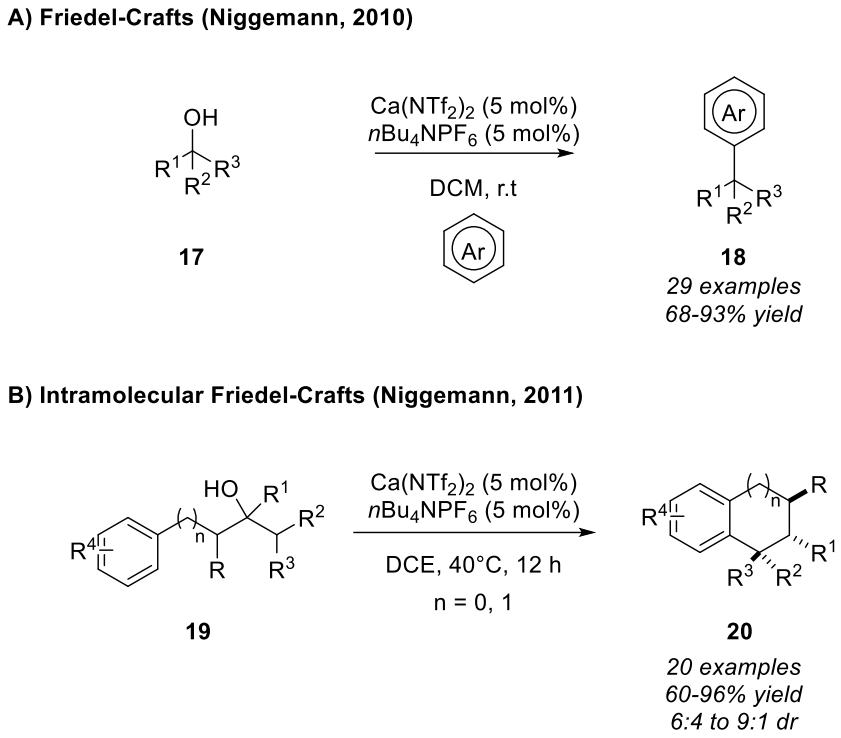


Scheme 1. Methods of carbon-carbon and carbon-heteroatom bond formation.

1.3.1. Generation of Carbocations

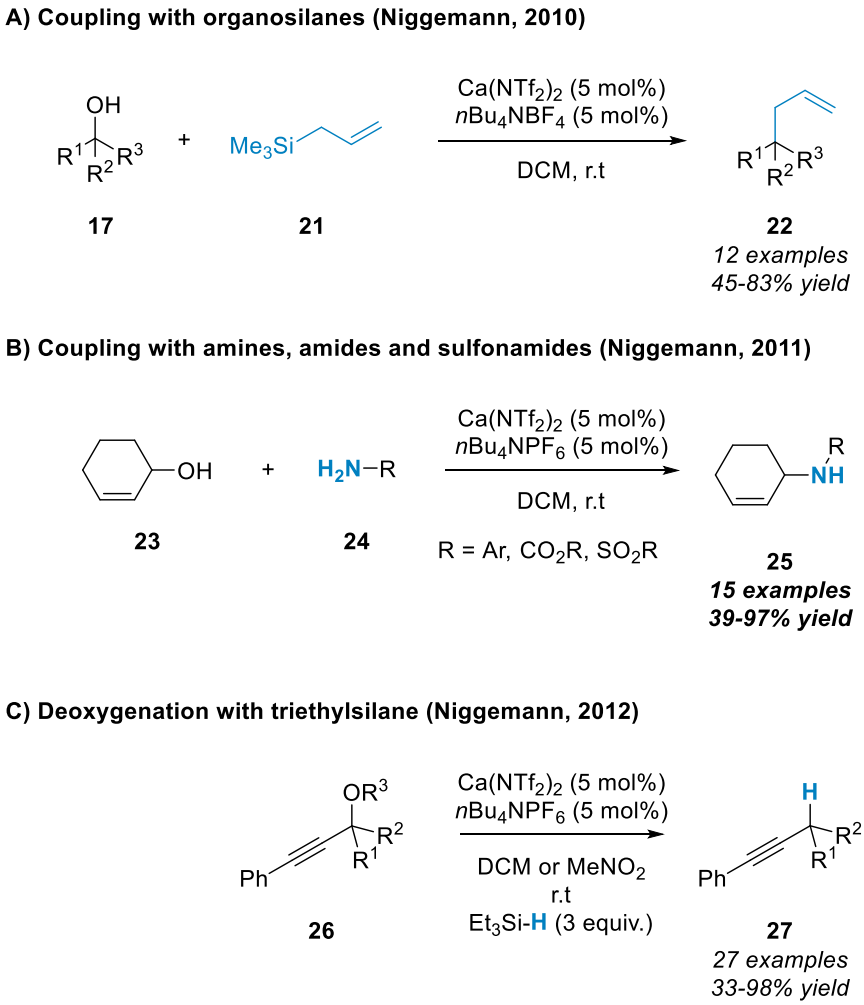
The use of $Ca(NTf_2)_2$ as a Lewis acid catalyst was first reported in 1995, however further development was hindered due to its poor solubility and subsequent ability to catalyse a Diels-Alder reaction.[21] In 2006, the lack of reactivity of $Bi(OTf)_3$ towards a hydroamination was shown to be overcome by the addition of a NH_4PF_6 or KPF_6 additive promoting anion metathesis resulting in an enhanced Lewis acidic bismuth catalyst.[22]

Merging these two concepts together, Niggemann reported the first calcium catalysed dehydrative Friedel-Crafts alkylation using a $Ca(NTf_2)_2$/$n$$Bu_4NPF_6$ catalyst system (Scheme 2A).[23] Aryl, allyl and propargyl alcohols **17** could be dehydrated under the optimised conditions and were subjected to a range or electron-donating arenes along with thiophenes, furans and pyrroles. The presence of the additive, $n$$Bu_4NPF_6$ was proven essential for the reaction to proceed, pointing towards the formation of a $Ca(NTf_2)(PF_6)$ active catalytic species, comparable to that postulated by Shibasaki.[22] This work was extended by the same group, towards an intramolecular alkylation for the synthesis of tetralins and indanes **20** with high regio- and diastereoselectivity (Scheme 2B).[24]



Scheme 2. Calcium catalysed Friedel-Crafts alkylation (A) and intramolecular Friedel-Crafts (B)

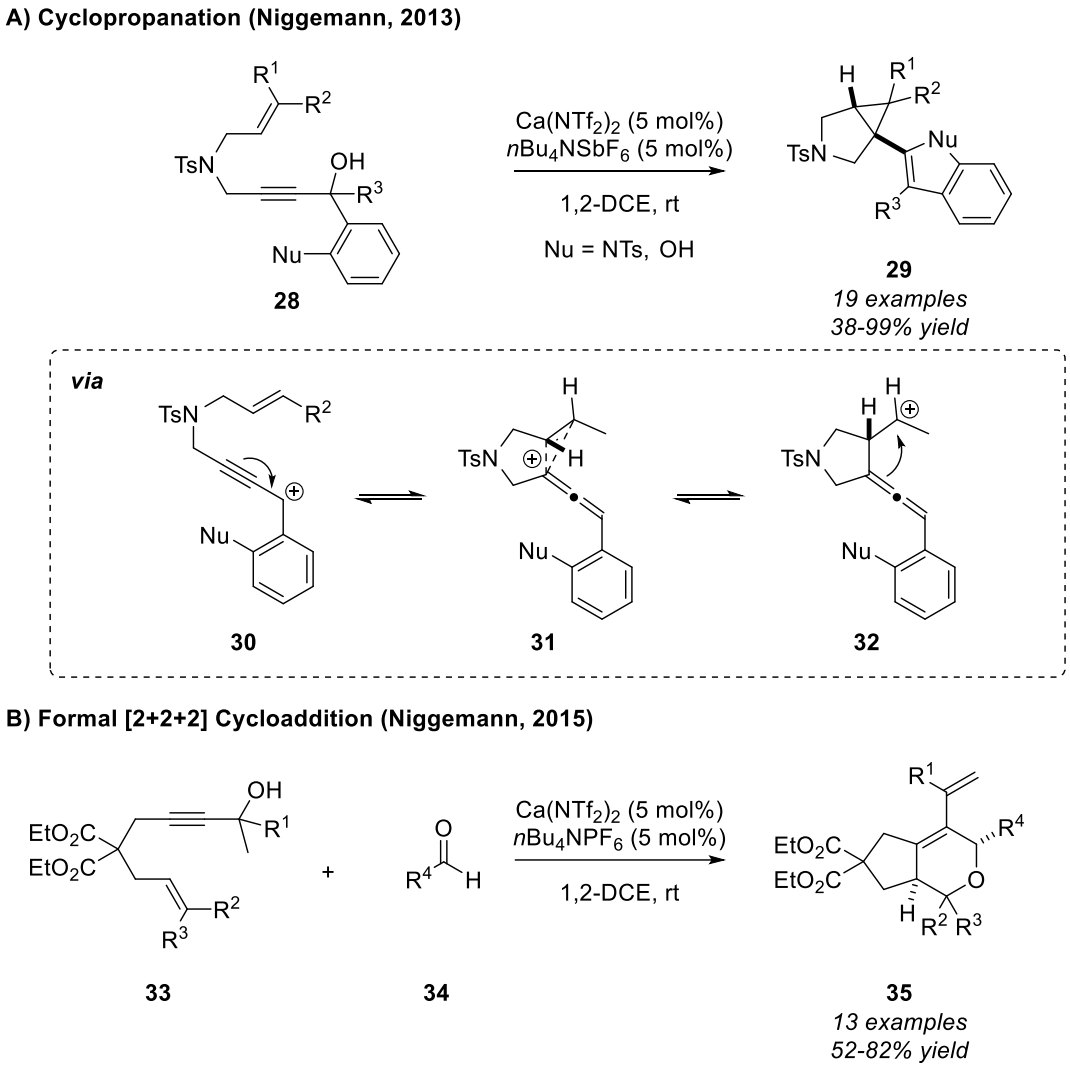
This seminal discovery was then exploited further by the same group in which the range of nucleophiles that could trap the catalytically generated carbocation were studied. Allyl **21** and vinyl silanes could be successfully coupled with secondary, tertiary and propargylic alcohols **17** affording a range of allylated and vinylated scaffolds **22** in moderate to excellent yields (Scheme 3A).[25] Furthermore electron-deficient amines,[26] carbamates and sulfonamides **24** have also been shown to be tolerant to access cyclic allyl amine derivatives **25** upon reaction with cyclic allylic alcohol **23** (Scheme 3b)**.**[26] Dehydrative reductions of propargylic alcohols **26** using silanes has also proven successful to access functionalised propargylic scaffolds **27** (Scheme 3c).[27]



Scheme 3. Direct coupling of alcohols with organosilanes (A),[25] amines, amides, sulfonamides (B)[26] and triethylsilane (C).[27]

Building on these initial studies, the Niggemann group then further explored whether this dehydration strategy could be applied towards more complex cascade type cyclisations. In 2013, they reported a cycloisomerisation reaction of **28** resulting in highly substituted cyclopropanes **29** (Scheme 4A).[28] The reaction proves tolerant to NTs and phenol substituted aromatics which results in the formation of an indole or benzofuran being formed as part of the cyclisation. DFT analysis suggests the reaction proceeds *via* an isomerisation of the propargylic cation **30** followed by an intramolecular prins cyclisation **31-32**. The high diastereoselectivity arises from a lack of energy minima thereby limiting the amount of bond rotation, with the stereochemical outcome of the reaction being set upon the formation of minima **32**. The same authors then explored this isomerisation step further in 2015 and reported a [2+2+2] cycloaddition of **33**,

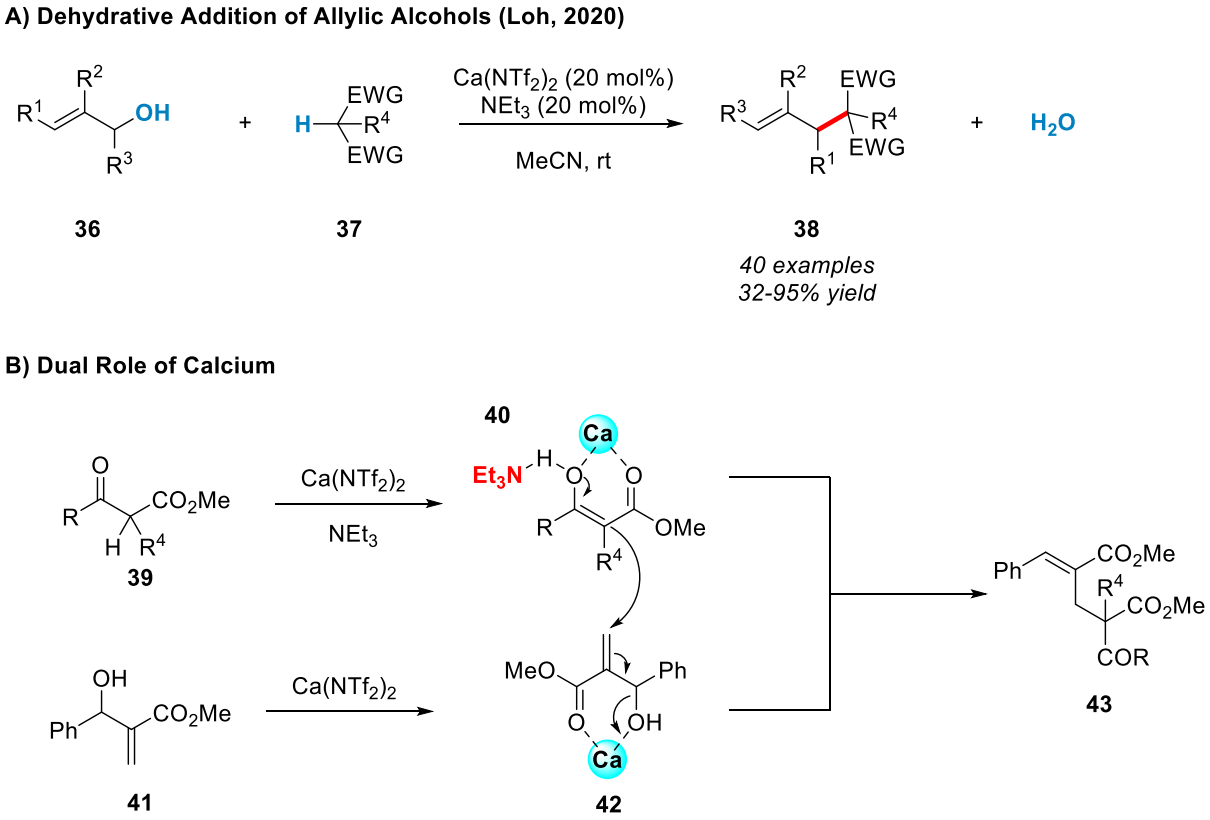
proposing the reaction proceeds *via* the same isomerisation step (Scheme 4B).[29] These reactions demonstrate how calcium catalysis is continually evolving and can be used to catalyse transformations that would otherwise require the use of π-acidic transition metals to activate propargylic substrates.[30]



Scheme 4. Applications of calcium catalysed isomerisation of propargylic cations.

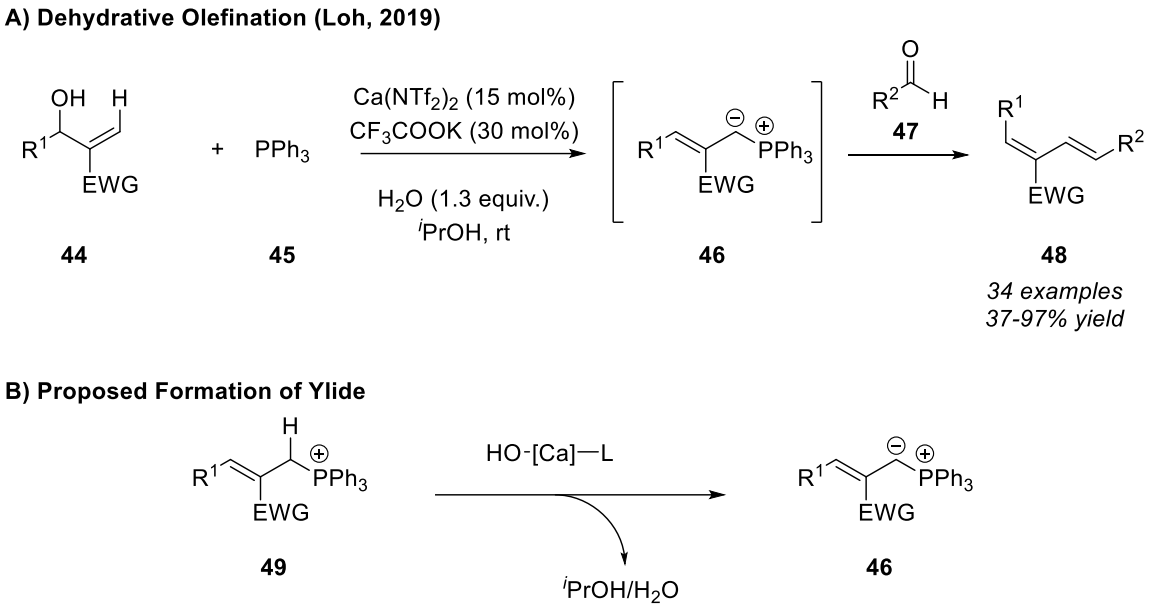
The Loh group have capitalised on the versatile and mild nature of catalytic dehydration using calcium and developed a Tsuji-Trost type allylic alkylation from allylic alcohols **36** and 1,3-dicarbonyl compounds **37** (Scheme 5A)**.**[31] The motivation behind this was again to provide a transition metal free alternative to the Tsuji-Trost reaction which traditionally requires a palladium catalyst.[32] The reaction proved tolerant to a range of Morita-Bayliss-Hillman derived alcohols along with both cyclic and acyclic β-keto esters. The authors propose a dual activation model in which both the β-keto ester **39** and MBH-

derived alcohol **41** are activated by the calcium catalyst **40, 42** with the amine stabilising the enol tautomer **40** (Scheme 5B).



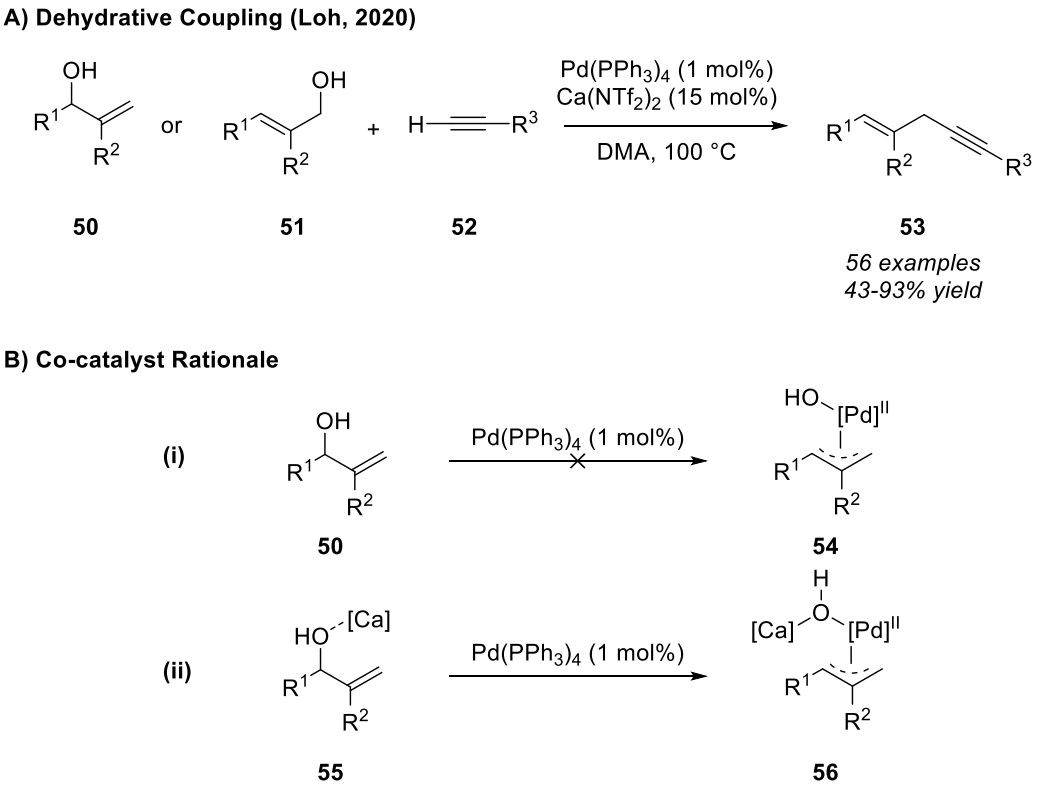
Scheme 5. Calcium catalysed dehydrative allylic alkylation (A) with a bi-functional role of calcium proposed (B).[31]

The same group have also studied the dehydration of similar Morita-Bayliss-Hillman alcohols **44** to access phosphorus ylides **46** which were subjected to a range of aldehydes in-situ to access 1,3-dienes **48** *via* a Wittig olefination (Scheme 6A).[33] Traditionally, in order to achieve this type of reactivity, stoichiometric quantities of base are typically required, however, the authors report how the resulting coordinated hydroxyl anion can undergo a proton transfer/deprotonation to generate the phosphorus ylid **49** and water by-product (Scheme 6B). They postulate this is facilitated by the ^{i}PrOH protic solvent that the reaction is carried out in.



Scheme 6. Calcium catalysed dehydrative olefination *via* allylic phosphorus ylides.

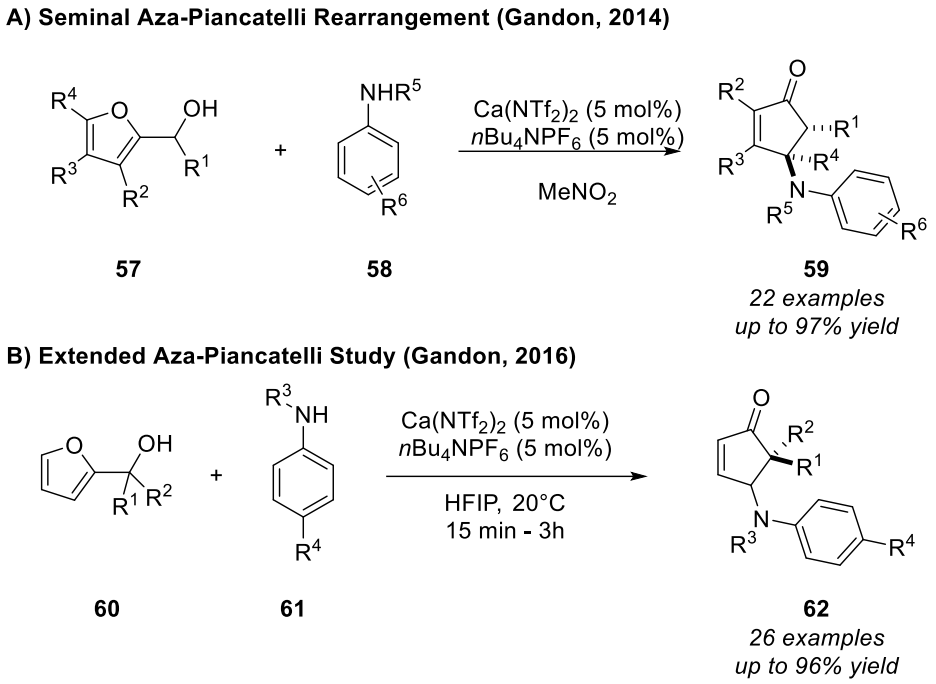
Furthermore, the Loh group have reported a dehydrative cross coupling of allylic alcohols **50,51** with alkynes **52** to afford 1,4-enynes **53** (Scheme 7A).[34] The authors propose a calcium-palladium co-catalyst system whereby oxidative addition of the allylic alcohol to generate palladium-π-allyl species **54** cannot proceed without the assistance of $Ca(NTf_2)_2$ in which the in-situ generated hydroxide ion from **55**, deprotonates the alkyne which ultimately results in the formation of product **56** (Scheme 7B). This report further supports how $Ca(NTf_2)_2$ is a mild and versatile catalyst as it can now be used in conjugation with transition metal redox processes.



Scheme 7.Calcium catalysed dehydrative coupling of allylic alcohols with enynes.

1.3.2. Generation of Oxocarbenium Ions

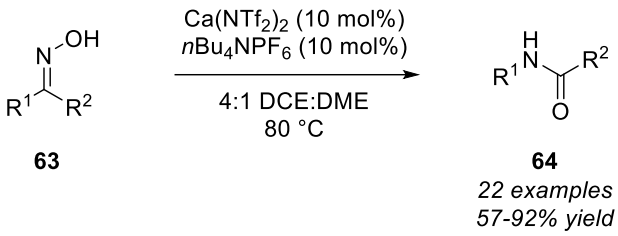
The use of calcium to catalytically generate reactive intermediates is not just limited to the formation of carbocations. The extension of calcium catalysis towards the catalytic dehydrative generation of oxygen containing reactive intermediates was pioneered by Gandon and Lebeouf. In 2014, they reported a calcium catalysed Aza-Piancatelli reaction of 2-furylcarbinols **57** with secondary anilines **58** (Scheme 8A).[35] Utilising 5 mol% catalyst, the reaction proved tolerant to a range of electron-deficient anilines and furan substitution patterns. This study was extended towards more wide-ranging substrates after finding that carrying out the reaction in HFIP improved both reaction rate and yield (Scheme 8B).[36]



Scheme 8. First calcium catalysed Aza-Piancatelli reaction (A),[35] followed up with an in-depth study of the calcium catalysed Aza-Piancatelli reaction with a wider functional group tolerance enhanced by Lewis acidic HFIP (B).[36]

1.3.3. Generation of Nitrilium Ions

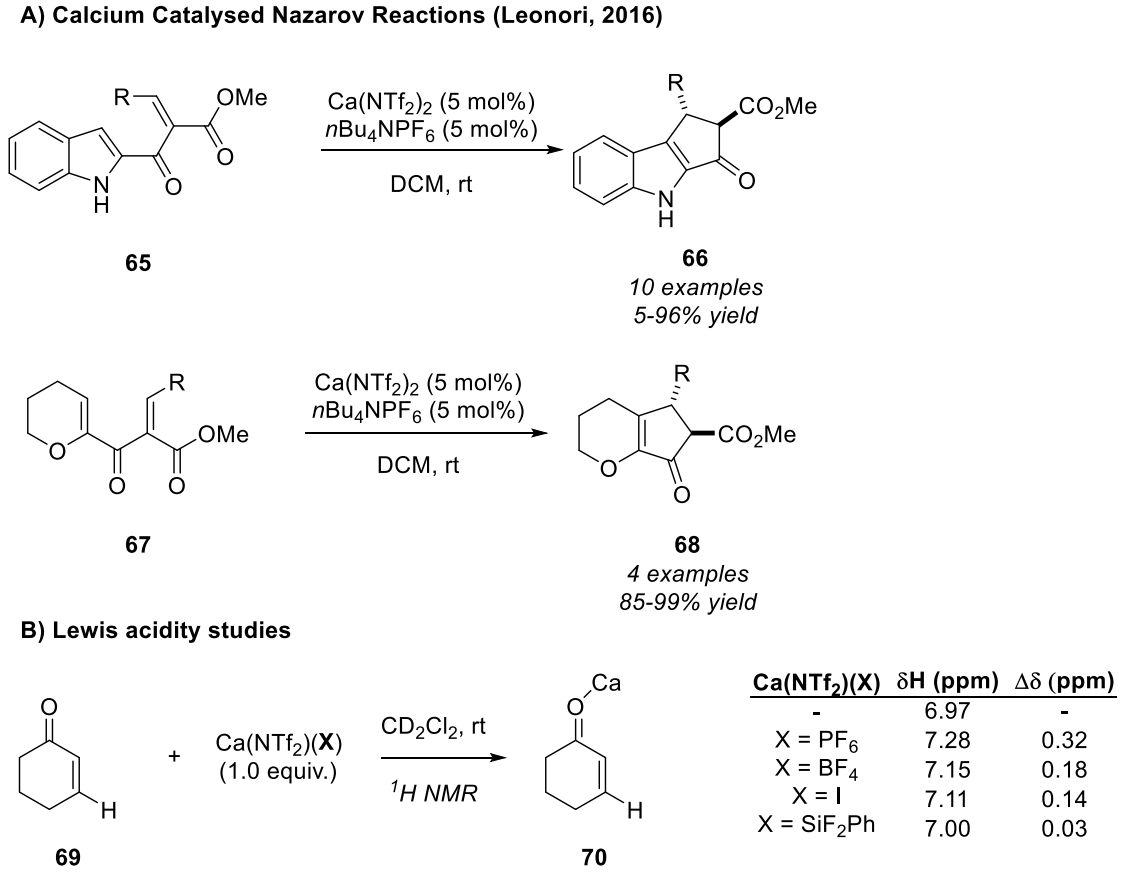
Furthermore, nitrogen containing reactive intermediates in the form of nitrilium ions have also been catalytically generated by calcium containing Lewis acids. A calcium catalysed Beckmann rearrangement was reported by McLaughlin in 2018 to afford a range of amides **64** (Scheme 9).[37] The use of calcium is particularly advantageous offering a milder, more tolerant alternative to strong acids and high temperatures traditionally employed and demonstrated how calcium can be utilised for the catalytic generation of nitrogen containing reactive intermediates.



Scheme 9. Calcium catalysed Beckmann rearrangement reported by McLaughlin.[37]

1.3.4. Further Applications

In addition to dehydrations, $Ca(NTf_2)_2$ has been shown to be a versatile catalyst towards a range of other transformations. In 2014, Leonori reported a calcium catalysed Nazarov cyclisation of **65** and **67** which is undeterred by electronics and heterocycles (Scheme 10).[38] A range of mechanistic studies were also carried out to understand the role and strength of calcium as a Lewis acid and the influence of the weakly coordinating anions. The authors reported a change in chemical shift of the β-proton of **69** when subjected to $Ca(NTf_2)_2$ with differing weakly coordinating anions. The hexafluorophosphate anion was found to result in the largest change in chemical shift suggesting $Ca(NTf_2)(PF_6)$ to be the strongest Lewis acid.



$Ca(NTf_2)(X)$	δH (ppm)	Δδ (ppm)
-	6.97	-
X = PF_6	7.28	0.32
X = BF_4	7.15	0.18
X = I	7.11	0.14
X = SiF_2Ph	7.00	0.03

Scheme 10. Calcium catalysed Nazarov cyclisation (A) with Lewis acidity studies showing the effect of the weakly coordination anion on Lewis acid strength (B).[38]

1.3.5. Mechanistic Studies

There are currently two distinct accepted mechanisms for the $Ca(NTf_2)_2$/$n$$Bu_4NPF_6$ catalysed transformations described above; a classical Lewis acid mode of activation and a HFIP-calcium mediated activation.

The more classical mode of activation proceeds *via* combination of $Ca(NTf_2)_2$ **71** and $n$$Bu_4NPF_6$ **72** in an aprotic solvent, usually 1,2-DCE or DCM. This is thought to generate a more Lewis acidic calcium species **73** and $n$$Bu_4NTf_2$ **74** (Figure 8). Early mechanistic studies by the Niggemann group studied this by ^{19}F NMR (Figure 9).[26] Additive **72** alone displayed a doublet which is characteristic of the PF_6^- anion. Upon generating a 1:1 mixture of $Ca(NTf_2)_2$ and $n$$Bu_4NPF_6$, the signal for the additive disappeared and instead a singlet at -79 ppm was observed, which corresponds to $n$$Bu_4NTf_2$. The formation of $n$$Bu_4NTf_2$ is also thought to improve the overall solubility of the solute.

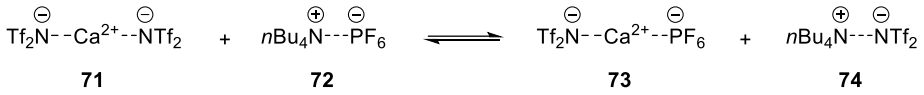


Figure 8. Generation of active catalystic species 73 *via* anion metathesis.

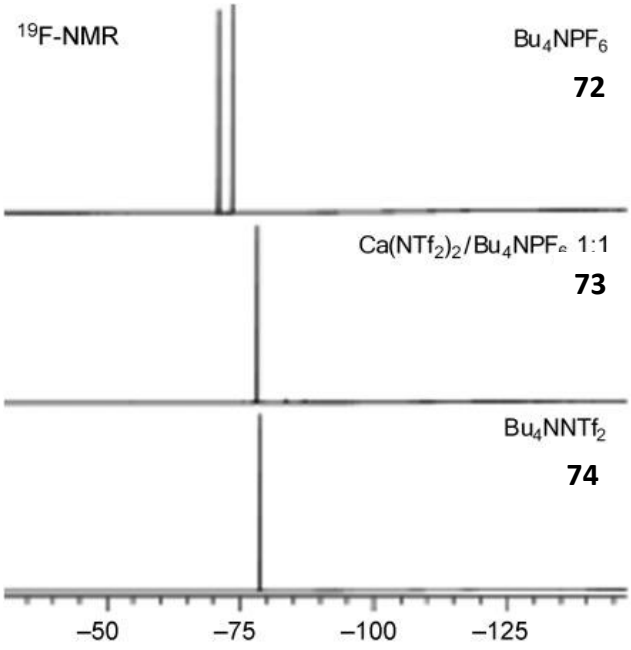


Figure 9. Stacked ^{19}F NMR spectra showing the anion methathesis between $Ca(NTf_2)_2$ and $n$$Bu_4NPF_6$ in $CDCl_3$. (extracted from manuscript without permission).[26]

The current accepted mechanism for a calcium catalysed dehydroxylation in a chlorinated solvent is *via* an auto-catalytic cycle (Figure 10). Following on from the seminal mechanistic studies outlined above, the active catalyst is believed to be **75** following the first catalytic turnover.[39] It seems unlikely for [$PF_6^-Ca^{2+}NTf_2^-$]to exist solely in solution when there are increasing amounts of water within the reaction medium as the reaction proceeds to completion. Coordination of alcohol **76** forms a hydrogen bridging network facilitated by the calcium centre giving rise to intermediate **77**. C-O cleavage results in the formation of cation **78** and forms a poorly soluble calcium hydroxide species **79** which displaces the PF_6^- weakly coordinating anion. The addition of the nucleophile **80** to the cation, generates a proton which slowly reacts with the calcium hydroxide species to regenerate the active catalyst and water by-product. The recycling of the catalyst under these conditions can be explained by two-factors. Firstly, the poor solubility of calcium hydroxides in chlorinated solvents enhances the hydroxyl group cleavage by shifting the equilibrium according to Le Chatelier's principle. And secondly, the high hydrolysis constant of calcium (pK_h = 12.85) allows for ease of protonation of the hydroxide species bound to the calcium centre. Both these factors facilitate catalytic turnover.

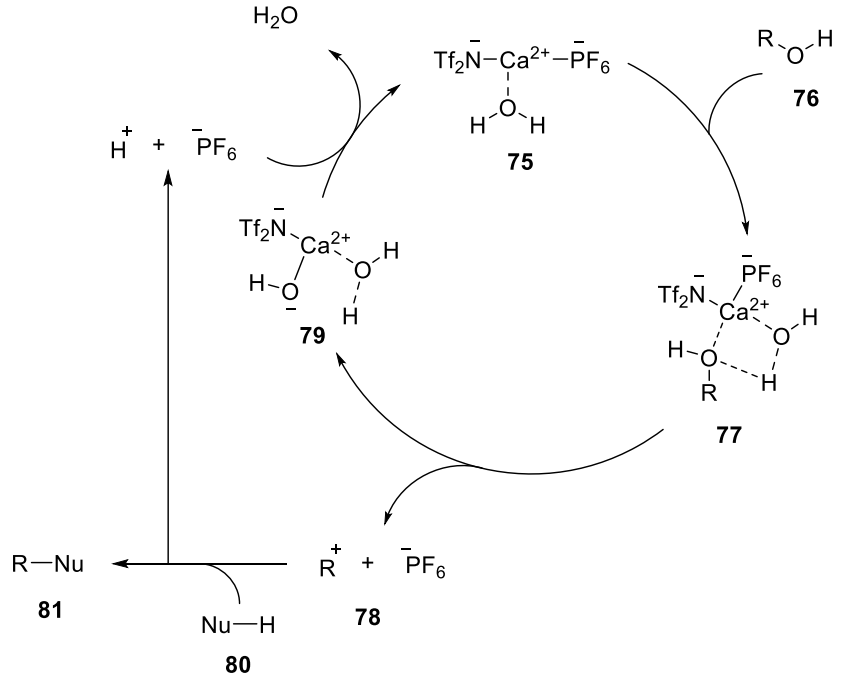
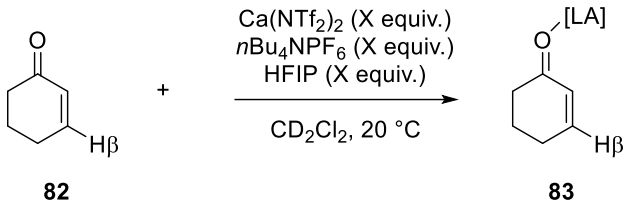


Figure 10. Proposed mechanism for the calcium catalysed dehydroxylation of alcohols in aprotic solvents.

The impact of the presence of HFIP on the outcome of the aza-Piancatelli cyclisation by Lebeouf prompted them to investigate the role of HFIP within the reaction[36] using Child's method (Figure 11).[40] The authors report that by adding a three-fold excess of HFIP results in a further downfield shift of the H_β proton of **83** and a further increase upon a 20-fold excess of HFIP which suggests that HFIP is acting as a Lewis acid itself. However, there is an even greater downfield shift when HFIP is combined with $Ca(NTf_2)_2$/$n$$Bu_4NPF_6$ suggesting a cooperative HFIP-calcium species.

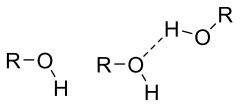


82 **83**

$Ca(NTf_2)_2$ [equiv]	nBu_4NPF_6 [equiv]	HFIP [equiv]	H_β [ppm]
0	0	0	6.97
1	1	0	7.28
0	0	3	7.14
0	0	20	7.30
1	1	20	7.76

Figure 11. HFIP acidity studies carried out by Lebeouf using Child's method.

This was further investigated using computational studies. The acidic hydrogen of HFIP was already shown to be a good electron pair acceptor and in particular when in a cluster.[41] The effect of hydrogen bonding on the LUMO energy of the monomer **84** and dimer of water, isopropanol and HFIP **85** was computed, clearly showing HFIP to have the lowest LUMO energy (Figure 12).



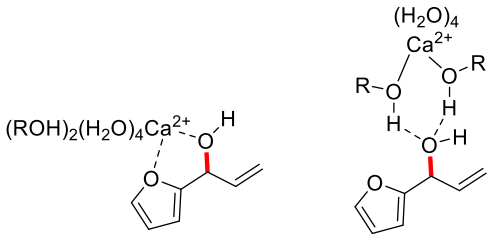
84 **85**

R = H	0.0838	0.0611
R = *i*Pr	0.0454	0.0366
R = $(F_3C)_2CH$	0.0383	0.0187

Figure 12. Effect of H-bonding on LUMO level (A.U) of monomer vs dimer.

This observation was then applied to the model substrate using calcium-HFIP dimers in both a chelate **86** and non-chelated manner **87**, with the bond length of the carbon-oxygen bond measured (Figure 13). There is a clear trend showing the superiority of the

calcium-HFIP species, with the dimer **87** having the most influence on the carbon-oxygen bond length. This suggests that there is indeed an interaction between calcium and HFIP given the authors report their reaction was sluggish without the presence of calcium.



	86	**87**
R = H	1.46	1.48
R = *i*Pr	1.46	1.47
R = $(F_3C)_2CH$	1.46	1.51

Figure 13. Computed C-OH bond lengths of calcium complexes with bond length measured in Å.[36]

In a later study, Lebeouf and Gandon modelled the free energy profile of an intermolecular hydroarylation of deactivated styrenes using a $Ca(NTf_2)_2$ and $n$$Bu_4NPF_6$ catalyst in HFIP (Figure 14A). Based on their previous studies, the authors compute adduct **93** as the active catalyst in which proton transfer to olefin **92** takes place through the proton from a coordinated HFIP ligand **93** (Figure 14B). This results in the formation of intermediate **94** and cation **95** in which the deprotonated HFIP ligand is stabilised by a hydrogen bond network from an additional HFIP ligand. Addition of the nucleophile **96** results in the formation of intermediate **99** in which rearomatisation following nucleophilic attack of the NTf_2 ligand deprotonating **97** to generate product **98** and adduct **91**. Regeneration of the active catalyst is believed to occur *via* an internal proton transfer from the NTf_2 to the alkoxide ligand.

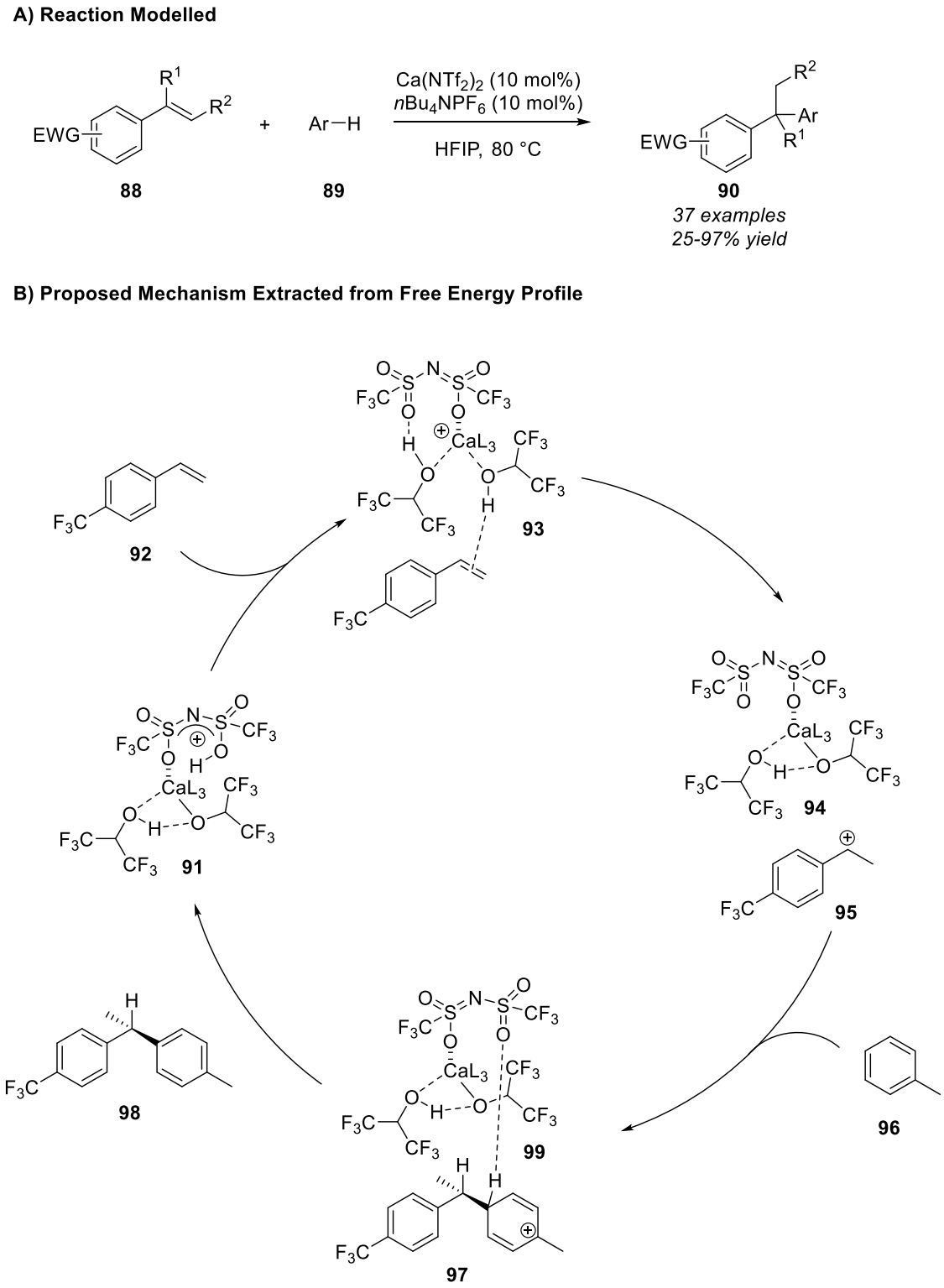
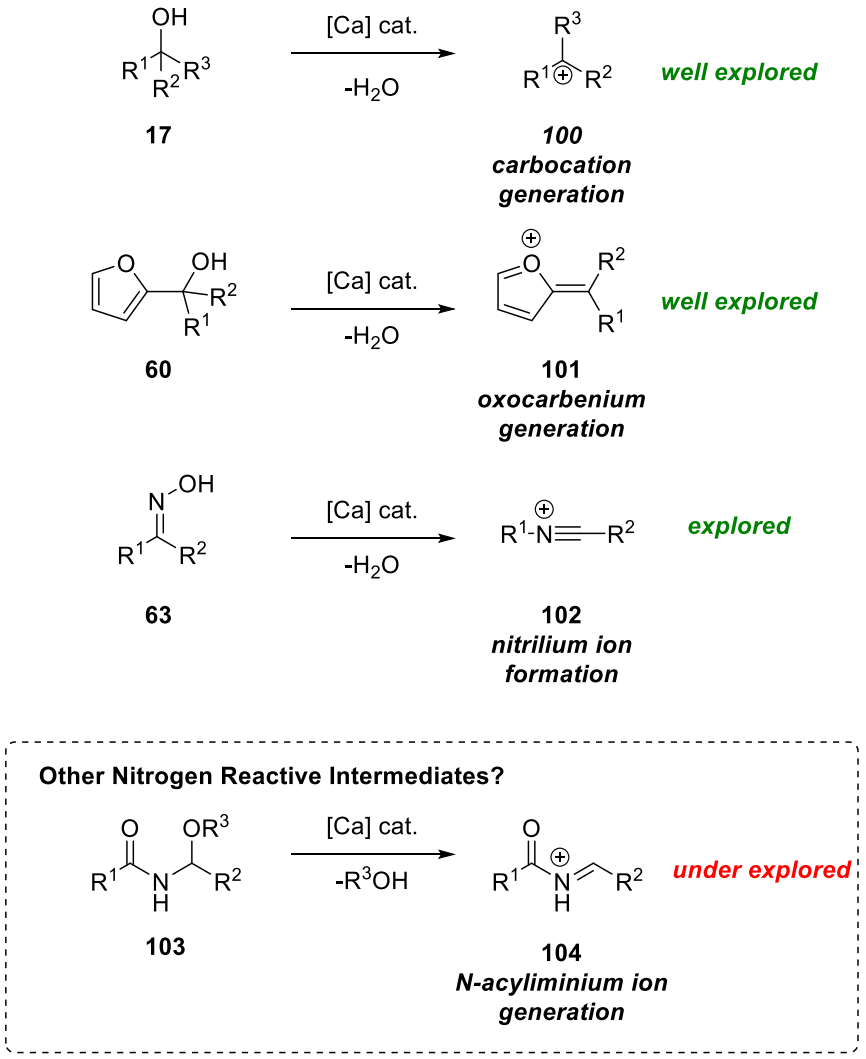


Figure 14. Calcium-HFIP catalysed intermolecular hydroarylation of styrenes (A) and the proposed mechanism extracted from the free energy profile (B). $L_3 = PF_6$ and further HFIP molecules.

The two mechanisms currently accepted by the scientific community display how the calcium catalyst can be tuned depending on the solvent the reaction is carried out in. It further demonstrates how the reaction conditions can be tuned to activate specific functional group by changing the solvent offering additional versatility of utilising calcium as a Lewis acid.

1.3.6. Summary and Outlook of Calcium Catalysis

The range of calcium catalysed transformations currently explored to date has been mostly limited to the generation of carbon reactive intermediates from **17**, utilising a dehydrative strategy to generate carbocations **100** (Scheme 11). Activation of pseudo-oxygen reactive intermediates from **60** to generate **101** has been explored by Lebeouf utilising an Aza-Piancatelli rearrangement. However, as a relatively new field, the full exploitation in using calcium as a mild and Earth abundant Lewis acid catalyst has not been fully investigated. Due to the high proficiency of calcium derived Lewis acids in dehydroxylation of alcohols, and effectiveness at catalysing the generation of nitrilium ions **102** from oximes **63**, the utilisation of this towards the activation of other nitrogen containing reactive intermediates, such as *N*-acyliminium ions **104**, is yet to be fully explored.



Scheme 11. Summary of calcium catalysed generation of carbon, oxygen and nitrogen containing reactive intermediates.

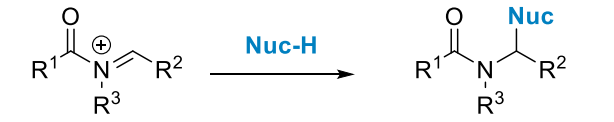
1.4. *N*-acyliminium Ions

Lewis acid mediated reactions offer access to valuable reactive intermediates and power many transformations that would not proceed without their presence. However, the presence of multiple Lewis basic heteroatoms within a molecule can often poison the Lewis acid thereby reducing the effectiveness and selectivity of it along with the subsequent desired transformation.

The synthesis and functionalisation of nitrogen containing compounds is extremely important in organic synthesis owing to the huge prevalence of nitrogen containing heterocycles in existing drugs.[42] A recent study has shown that 59% of FDA approved

pharmaceuticals contain a nitrogen heterocycle.[43] In order to access these vital compounds, and access novel derivatives, chemists must continually develop methods to access them in an efficient manner.

N-acyliminium ions **105** are highly versatile reactive intermediates that have been used in a range of transformations to access synthetically useful scaffolds (Figure 15).[44] Their electrophilic nature allows trapping with a range of carbon and heteroatom nucleophiles as a method to functionalise alpha to an amide **106** and offer a route to functionalise highly desirable nitrogen heterocycles. They are more electrophilic than their iminium ion counterparts due to the electron withdrawing nature of the acyl group, and therefore more reactive.[45]



105
N-acyliminium ion

106
α-functionalised amide

Figure 15. Structure of an *N*-acyliminium ion and trapping with a nucleohpile .

1.4.1. Formation of *N*-acyliminium Ions

Traditional methods to access *N*-acyliminium ions are through either the acylation of an imine **107** with an acyl chloride **108** or by the direct condensation of an amide **109** and aldehyde **47** (Figure 16). However, imine acylation requires precarious preformation of imine **107** and the direct condensation reaction is both reversible and can result in a large quantity of bis-amide by-product. Furthermore, these reactions are also typically required to be performed at high temperatures over prolonged reaction times, which limits functional group tolerance. This has resulted in a focus on the development of catalytic generation of these highly reactive intermediates.[46]

A mild and more controlled method of accessing *N*-acyliminium ions is by the release of a leaving group from the alpha position to the nitrogen **110**. Activated hydroxyl groups are generally the most widely used leaving groups, however, halogen, alkoxy, acetoxy, arylsulfonyl, carbamate and benzotriazolyl groups have also been used.[44]

Transition metals have also been shown to catalyse the formation of *N*-acyliminium ions by aerobic oxidation of amides **111**.[47] However, this requires the use of often non-sustainable transition metals along with exposure to oxidising conditions. A more contemporary approach to access *N*-acyliminium ions was reported by Masson in 2016, who reported a photoredox catalysed oxidative cleavage of α-amidosulfides **112**.[48] While a mechanistically interesting breakthrough, it does require access to the α-amidosulfide precursors.

Furthermore, the protonation of enamides **113** using Brønsted acids[49] along with electrochemical oxidation of amides **114**, known as the Shono oxidation, also provides access to *N*-acyliminium ions however this requires access to specialist equipment.[50]

It is the activation of a hydroxyl or alkoxy group however, that is of particular interest. When a hydroxy or alkoxy leaving group is used, a Brønsted or Lewis acid is typically employed to activate the leaving group by either protonation or coordination. Traditionally, stoichiometric quantities of Lewis acid have been used due to degradation of the catalyst in the presence of the water or alcohol by-products.

Brønsted acids used are usually either protic or formic acids such as TsOH, H_2SO_4 and TFA, however the use of Lewis acids has been much more widely explored. Lewis acids such as $BF_3.OEt_2$, $SnCl_4$, $FeCl_3$, $Sc(OTf)_3$, TMSOTf and $Ca(NTf_2)_2$[51-53] have all been utilised in the formation of *N*-acyliminium ions.

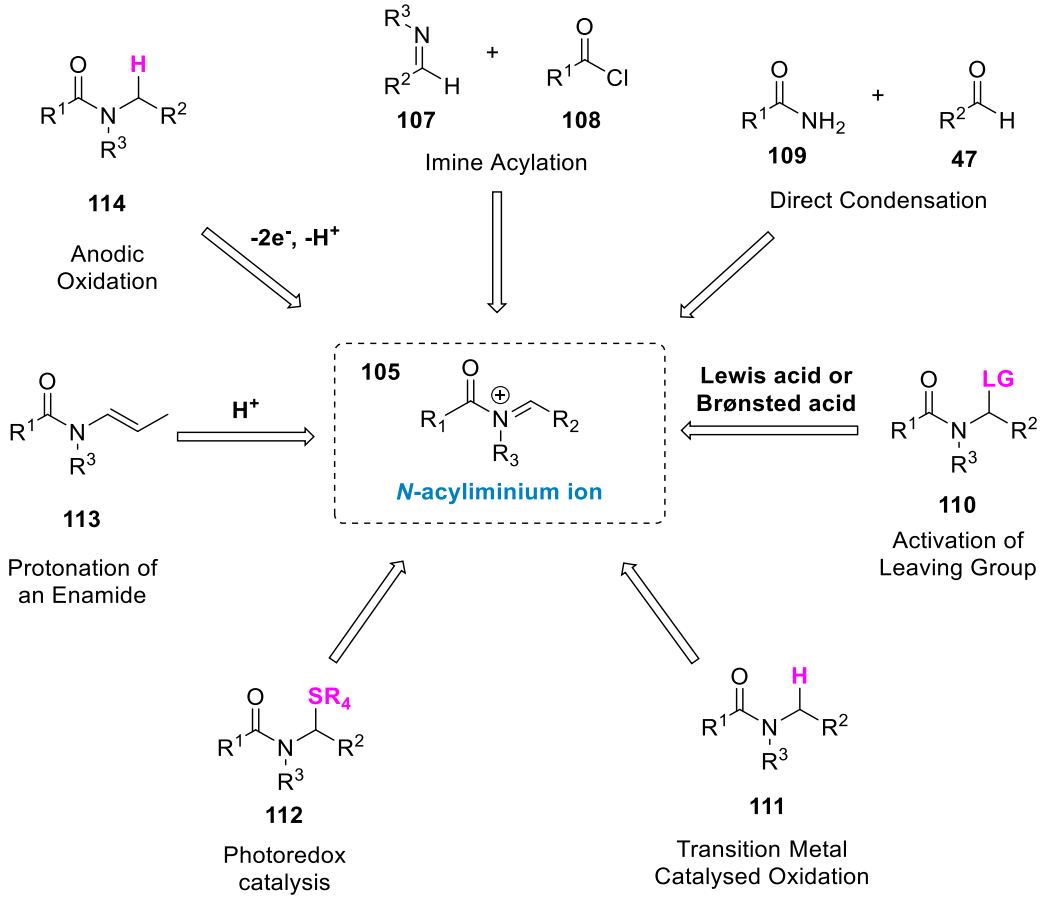
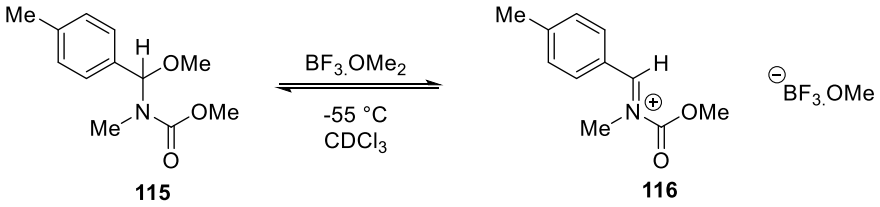


Figure 16. Methods for generation of *N*-acyliminium ions.

1.4.2. Structure and Reactivity of *N*-acyliminium Ions

N-acyliminium ions were first detected using NMR by Yamamoto.[54] Treating α-alkoxycarabamate **115** with $BF_3.OMe_2$ at -55 °C in $CDCl_3$ allowed for detection of *N*-acyliminium ion **116** (Scheme 12). Interestingly, there is an equilibrium between **115** and **116** which was proven by measuring the ratio of the α-protons using ^1H NMR. This equilibrium is affected by two factors: the equivalence of Lewis acid and the Lewis acid used. Increasing equivalence of Lewis acid results an increased formation of **116**.



Scheme 12. Detection of *N*-acyliminium ions by ^1H NMR.[54]

In 1975, Speckamp discovered that cyclic imides could successfully generate *N*-acyliminium ions[55] with these typically being the preferred choice of precursor.[56]

Eberlin made significant contributions to the understanding of the reactivity of *N*-acyliminium ions.[57] The reactivity of a range of *N*-alkyl **121** and *N*-acyliminium ions **122-127** towards allyltrimethylsilane was studied using gas-phase mass spectrometric experiments. The order of electrophilicity of the cyclic iminium ions is depicted below (Figure 17).

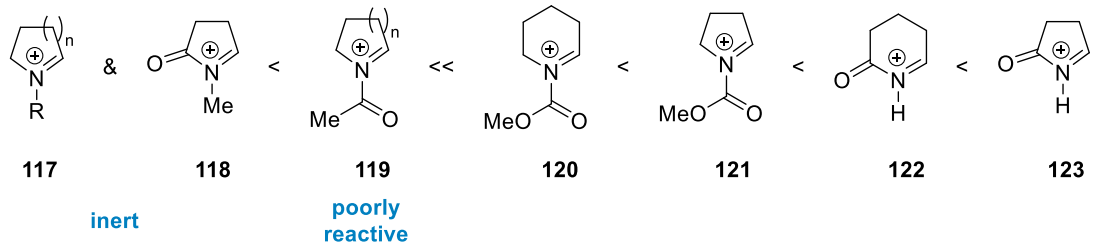


Figure 17. Order of reactivity of *N*-alkyl and *N*-acyl iminium ions towards allyltrimethylsilane in the gas phase (R = H, Me; n = 1, 2).[57]

The *N*-alkyliminium ions **117** and **118** were found to be inert towards allyltrimethylsilane. This was attributed to diminishing of the C2 charge due to delocalisation from the adjacent substituent on the nitrogen. *N*-acyliminium ions **119-121** in which the acyl group is on the outside of the ring were found to be slightly more electrophilic due to resonance interactions with the lone pair on the nitrogen resulting in an inductive effect. However, free rotation of the N-acyl bond, which has been calculated to be 10 kcal/mol, minimises the influence of this inductive resulting in decreased reactivity. The slight increase in reactivity of the N-alkoxyl carbonyl iminium ions can be explained by the more electron-withdrawing nature of the *N*-alkoxyl group which in turn strengthens the *N*-CO_2R bond and subsequently inhibits bond rotation.

Endocyclic *N*-acyliminium ions **122** and **123** are the most reactive due to being locked in a planar s-*trans* conformation and favours conjugation across the N-C=O bond. The *N*-Me acyliminium ion **118** however appears to provide enough stability which prevents said conjugation thereby marking it inert.

The LUMO energies of the *N*-acyliminium ions studied were calculated computationally (Figure 18). The findings were consistent with their displayed reactivity whereby the *N*-

alkyliminium ions were calculated to have the highest LUMO and the most reactive *N*-acyliminium ions **122** and **123** having the lowest energy LUMO.

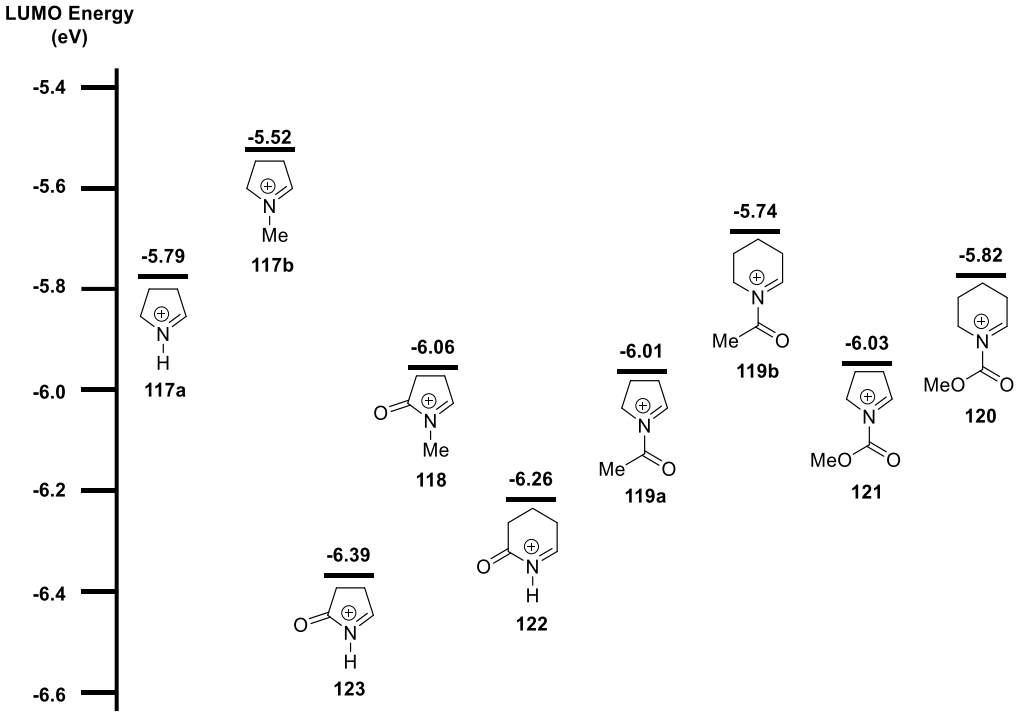
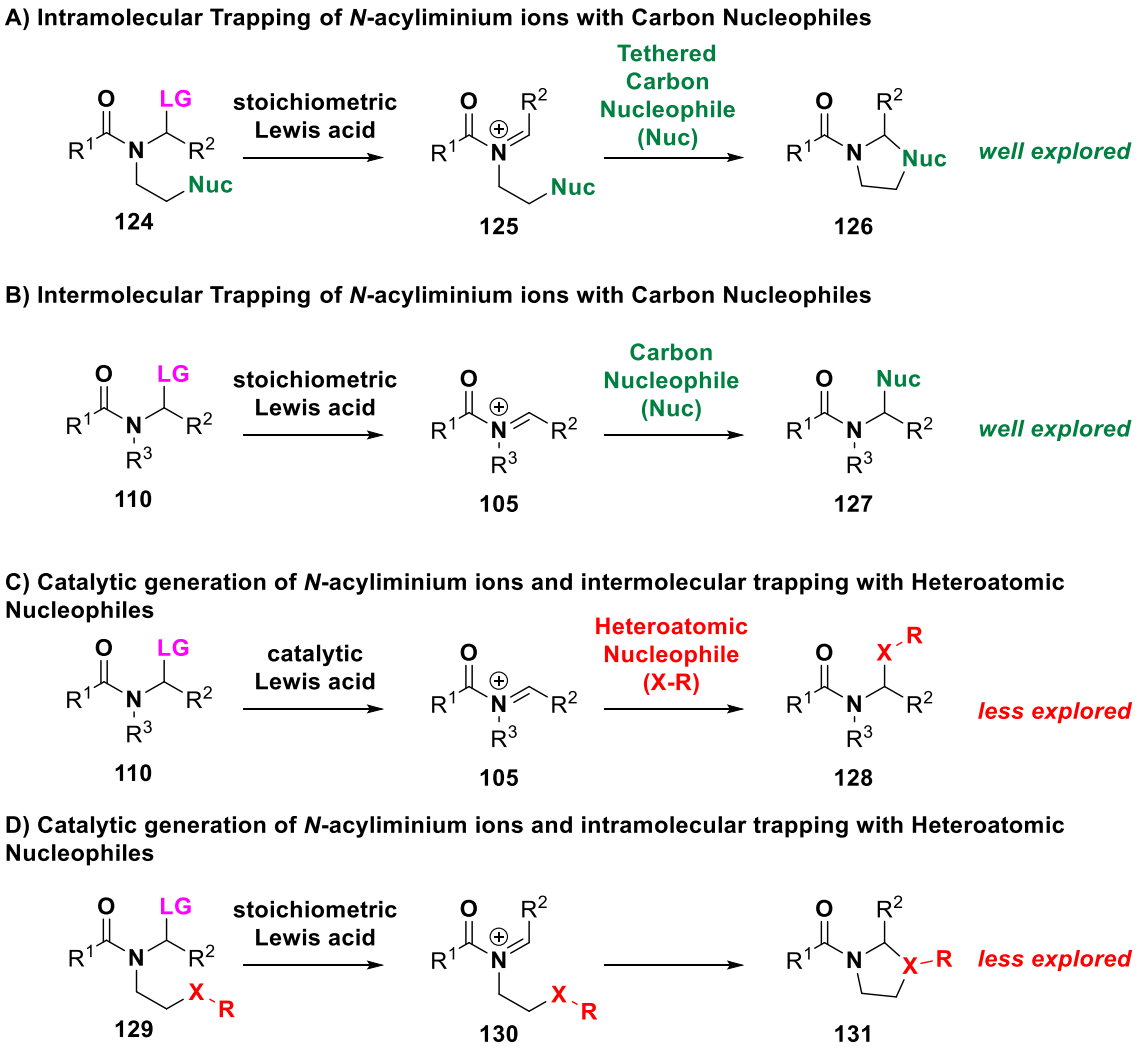


Figure 18. Calculated LUMO energies for cyclic *N*-alkyl- and *N*-acyliminium ions.[57]

The activation of *N*-acyliminium ions with a leaving group **124** or **110** and trapping with a range of nucleophiles has attracted significant interest in recent years.[44, 56, 58-60] They can be trapped either intramolecularly **125** or intermolecularly to give cyclic **126** or acyclic scaffolds **127** (Scheme 13A and B).[44, 56] Intramolecular trapping with carbon nucleophiles has been the most widely studied with the intra- and intermolecular trapping of heteroatomic nucleophiles often being overlooked, presumably due to catalyst poisoning. The trapping of catalytically generated *N*-acyliminium ions with the aforementioned heteroatomic based nucleophiles in both an inter- and intramolecular way, forming **128** and **131,** formulates the focus of this thesis (Scheme 13C and D). Specific examples of *N*-acyliminium generation and subsequent trapping will be discussed individually in each chapter.



Scheme 13. Summary of *N*-acyliminium ion chemistry.

The strength of the nucleophiles subjected to *N*-acyliminium ions must also be considered. Mayr and co-workers have devised a method of quantification for nucleophilicity and electrophilicity (Equation 1).[61] The second-order rate equation is derived from studying the rate of reaction (k_{20}) of a range of nucleophiles towards a range of reference electrophiles with a known electrophilicity (E). The nucleophilicity is characterised by two parameters s_N (slope) and N (nucleophilicity).

$$logk_{20} = s_N(N + E)$$

Equation 1. Mayr Nucleophilicity Equation.

The nucleophiles studied within this thesis cover a broad range of the Mayr scale, with allyl trimethylsilane being the weakest nucleophiles ($N = 1.68$)[62] that has been quantified

by Mayr. 5-bromoindoles (*N* = 4.38),[63] aniline (*N* = 12.64),[64] benzylamine (*N* = 14.29)[64] and isocyanides (*N* = 3.5-4.7)[65] have also been quantified and will be studied.

While the electrophilicity of *N*-acyliminium ions hasn't been quantified by Mayr, their iminium counterparts typically range from E= -8 to -12.[45] For commensurate reactivity, the sum of nucleophilicity and electrophilicity integers must be closer to zero. As such, the range of nucleophiles used within this thesis should display reactivity towards *N*-acyliminium ions.

1.5. Project Aims

Earth abundant Lewis acid catalysts have been significantly under explored within the literature. Their mild nature and effectiveness offer a distinct advantage over traditional Lewis acids, and in particular towards the formation of *N*-acyliminium ions.

Therefore, the underlying aim of this project is to answer the following questions:

1) How tolerant is calcium as a Lewis acid catalyst towards *N*-acyliminium ion formation? Can cyclic and acyclic *N*-acyliminium ions be generated?
2) What nucleophiles can be subjected towards the catalytically generated *N*-acyliminium ions? Can different strength nucleophiles be tolerated?
3) Can the *N*-acyliminium ions generated be trapped both intermolecularly and intramolecularly?

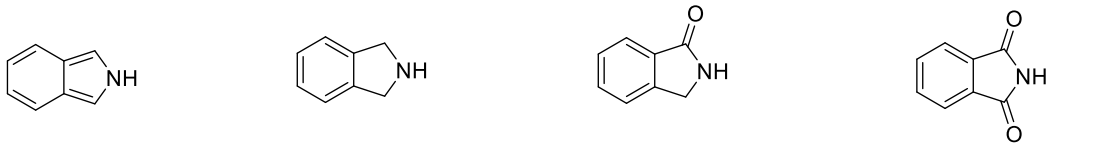
The successful development of this methodology would allow for a unified way to functionalise α to either a cyclic or acyclic amide without the need to use a precious transition metal or non-commercially available catalyst and without any requirement for access to specialised equipment or anhydrous conditions.

2. Chapter 2: Intermolecular Trapping of *N*-acyliminium Ions

2.1. Introduction

2.1.1. Isoindolinones

The isoindolinone ring is derived from the isoindole family which consists of a fused benzopyrrole ring **132** with the fully reduced member termed isoindolinone **133** (Figure 19). Partial and full oxidation of the 10π ring system results in the formation of isoindolinone **134** and phthalimide **135** which have been of interest to medicinal chemists.[66]



132
2*H*-isoindole

133
isoindoline
2,3-dihydro-1*H*-isoindole

134
isoindolinone
1,3-dihydro-2*H*-isoindole-1-one

135
phthalimide
1,3-dihydro-2*H*-isoindole-1,3-dione

Figure 19. Structural features of isoindolinone motif

2.1.2. Isoindolinones in Medicinal Chemistry

Isoindolinones are highly versatile motifs which feature in a range of natural products and pharmacologically relevant compounds.[66]

Arguably the most well-known isoindolinone is thalidomide **136**, which was used in the 1950s to treat morning sickness (Figure 20). Modification of thalidomide led to the development of lenalidomide **137**, which has been commissioned as a drug against multiple myeloma. In addition to their anti-cancer properties, Zopiclone **138** is an approved treatment for insomnia and Taliscanine **139** has potential for treatment of neurological disorders.[67] Furthermore, compounds such as A1 **140** have been shown to act as inhibitors of the MDM2-p53 protein interaction.[68]

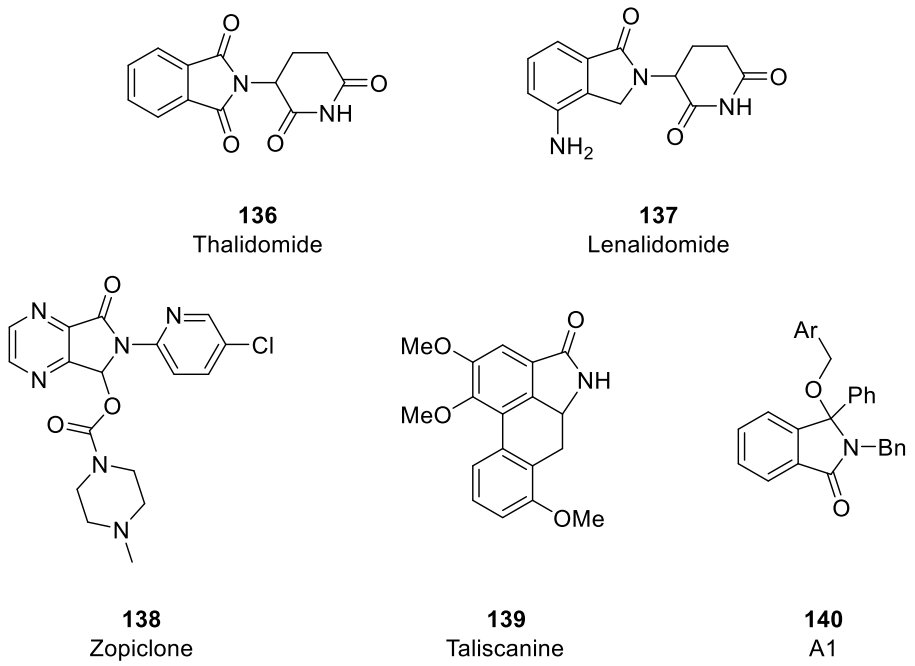


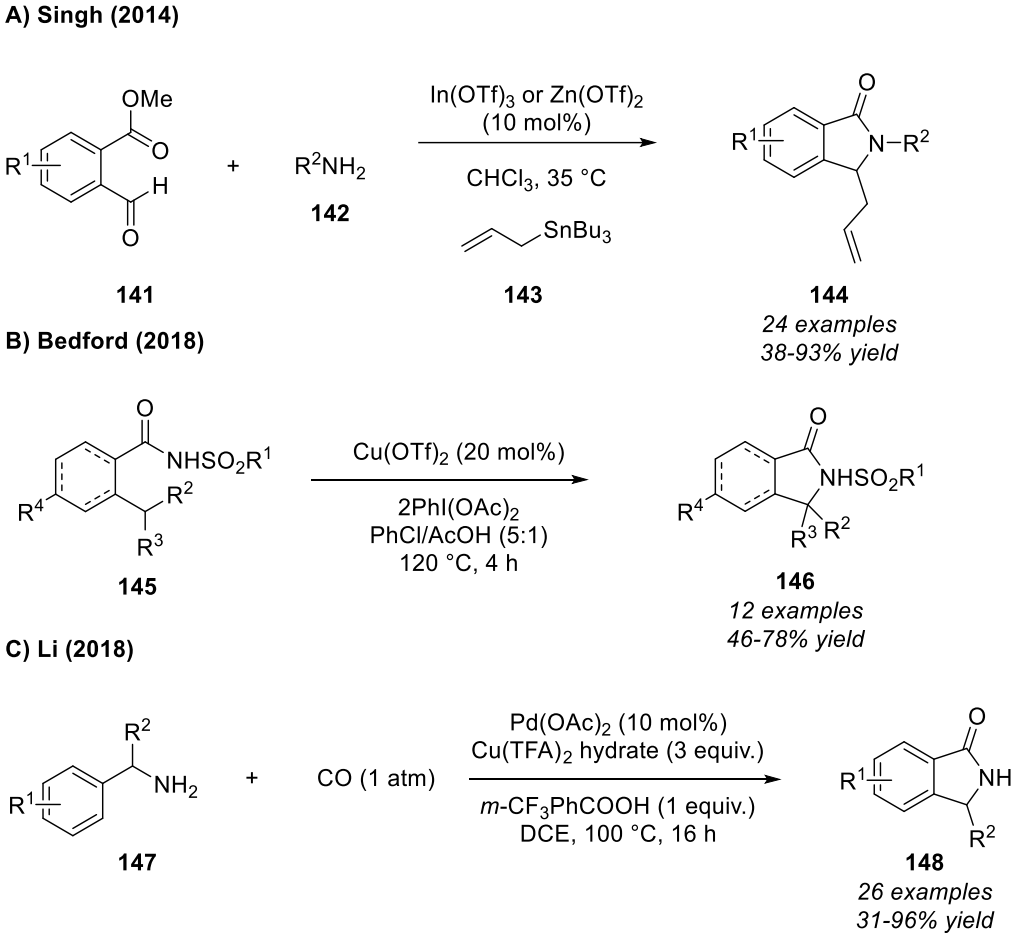
Figure 20. Medicinally relevant isoindolinones

The wide versatility of the isoindolinone and phthalimide core demonstrates the ever-needing desire to develop new methods to modify their structure and introduce functional handles with ease.

2.1.3. Synthesis of Isoindolinone Scaffold

Due to their pronounced biological activity, isoindolinone synthesis continually attracts the interest of synthetic chemists. Transition metals have been shown to be efficient catalysts to access isoindolinones in a single step (Scheme 14).[69] For example, in 2014, an $In(OTf)_3$ or $Zn(OTf)_2$ catalysed synthesis of branched allylated isoindolinones from 2-formyl benzoates **141**, amines **142**, and allylstannanes **143** was reported by Singh (Scheme 14A).[70] In 2018, Bedford reported a copper catalysed C-H sulfamidation reaction of *N*-tosyl amides **145** for access to 3-substituted isoindolinones **146** with the authors proposing the reaction proceeds *via* a radical pathway (Scheme 14B).[71] In the same year, Li reported a palladium catalysed C-H carbonylation reaction of benzylamines **147** to access 3-substituted isoindolinones **148** (Scheme 14C).[72] While these methods all provide access to isoindolinones in a single-step, they are synthesised from pre-functionalised starting materials and either use super-stoichiometric quantities of oxidant or require access to specialist equipment. Furthermore, they all

provide access to singly substituted C-3 isoindolinones. Crucially however, all these methods utilise transition metals, which synthetic chemists are continually trying to find alternatives for.

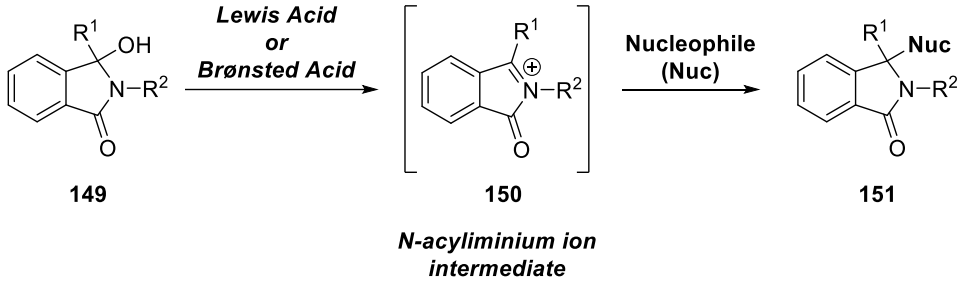


Scheme 14. Transition metal catalysed synthesis of isoindolinones.

2.1.4. Intermolecular Trapping of *N*-acyliminium ions; Functionalisation of Isoindolinones

As the examples outlined in Scheme 14 are concerned with the direct installation of the isoindolinone and require access to densely substituted starting materials, notwithstanding the requirement to use transition metals with various additives, alternative ways to access these scaffolds in a milder and more sustainable manner has been of significant interest.[73] In recent years, there have been increasing reports on the functionalisation of isoindolinones using 3-hydroxyisoindolinones **147** as precursors

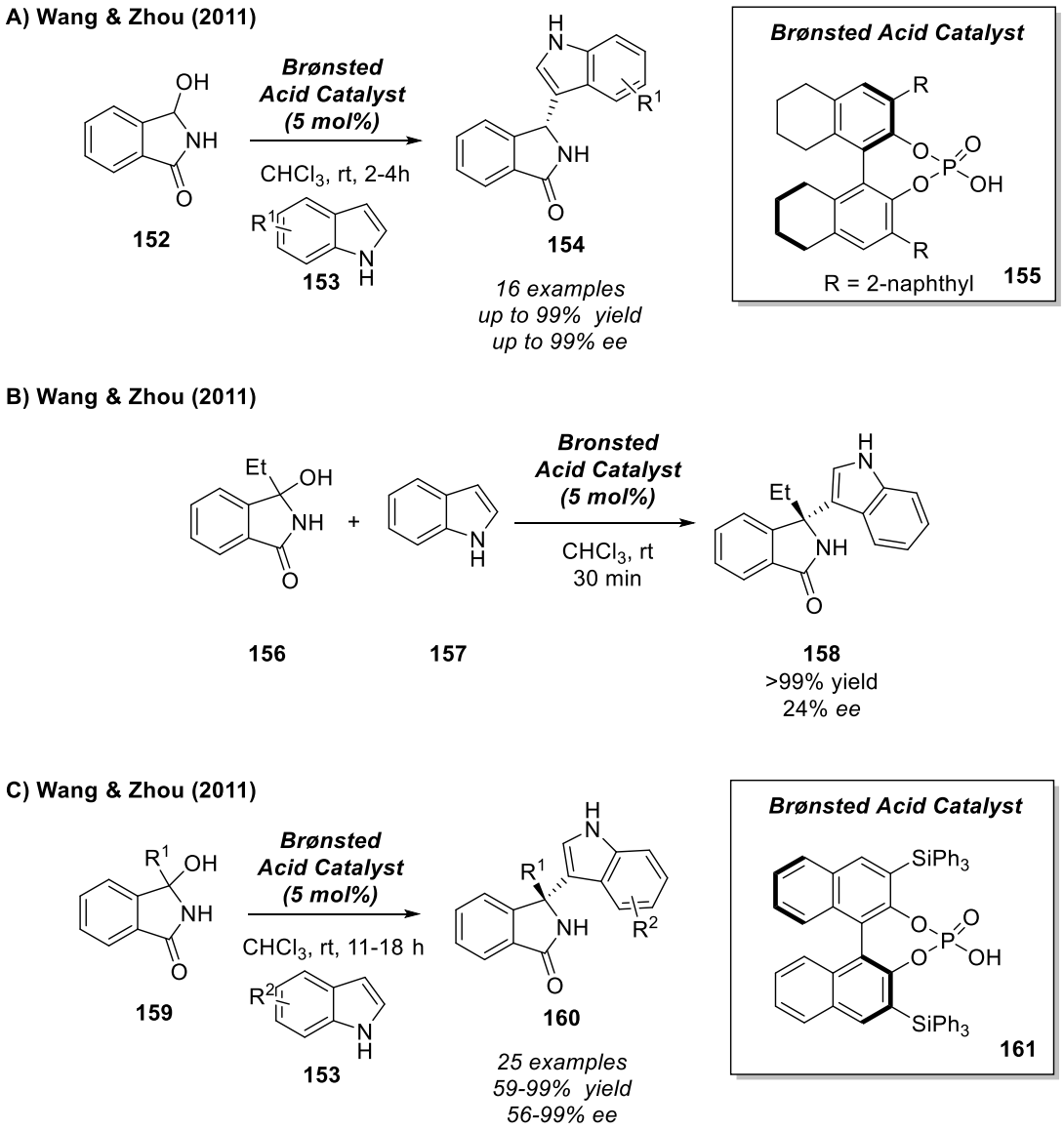
with the reaction proceeding *via* an *N*-acyliminium ion intermediate **148** (Scheme 15).[74] This route offers an alternative method to access 3-substituted or 3,3-disubstituted isoindolinones without the need for complex starting materials. The 3-hydroxyisoindolinone precursors **149** used here simply require activation with either a Brønsted or Lewis acid to generate an *N*-acyliminium ion **150** which allows for functionalisation in the presence of an external nucleophile demonstrating a more modular approach to access functionalised isoindolinones. The nucleophile employed here can be carbon, sulfur, nitrogen, or oxygen in nature, each of which will be discussed separately.



Scheme 15. General reactivity for the functionalisation of isoindolinones *via* an *N*-acyliminium ion intermediate.

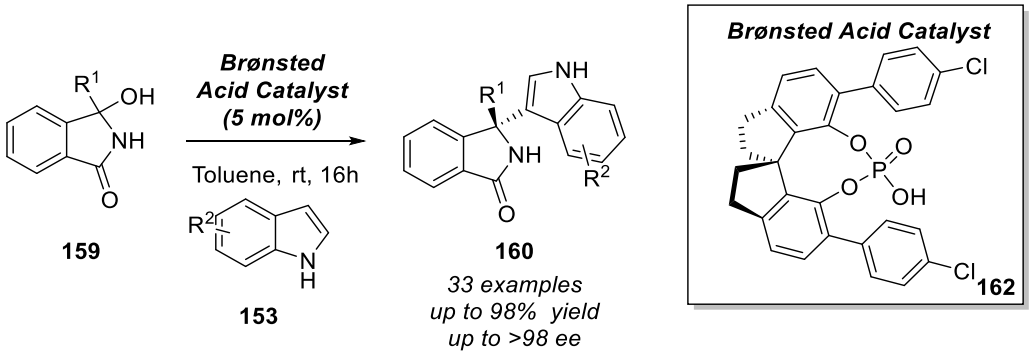
2.1.4.1. Carbon Nucleophiles

Due to the importance of C3-alkylated indoles in medicinal chemistry,[43] there has been much interest in the addition of indole derivatives to *N*-acyliminium ions. In 2011, Wang and Zhou first reported the chiral Friedel-Crafts alkylation of unsubstituted isoindolinones **152** with indole using Brønsted acid catalysis (Scheme 16A).[75] During this study the group extended this towards the synthesis of 3,3 disubstituted isoindolinones **158**, which resulted in a low 24% *ee* (Scheme 16B). Nonetheless, this was the first reported synthesis of these scaffolds. The same group then modified the catalyst to address the low enantioselectivity and reported a much more consistent method (Scheme 16C).[76]



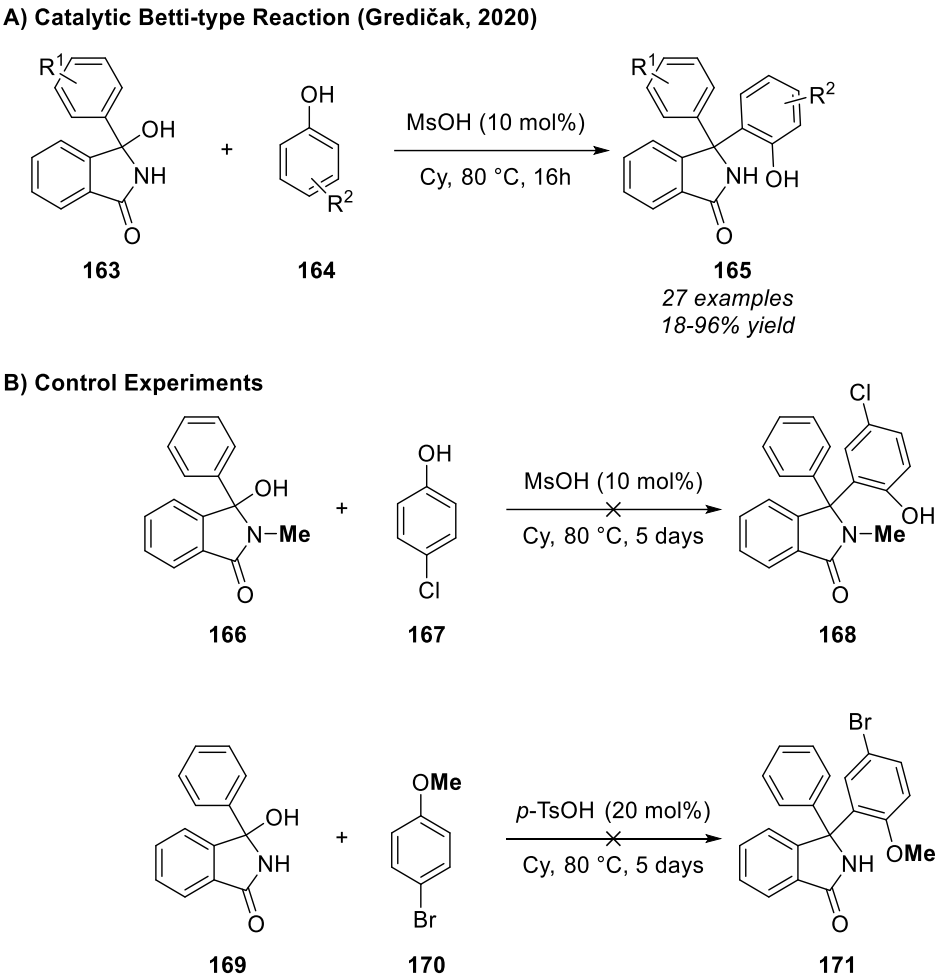
Scheme 16. Synthesis of indole substituted isoindolinones reported by Wang and Zhao.[75, 76]

Due to the moderate enantioselectivities observed by Wang and Zhou, Gredičak optimised an alternative reaction to obtain similar scaffolds **160** with the anticipation of improving the enantioselectivity (Scheme 17).[77] The substrate scope was more substantial than that by Wang, containing various heterocycles and indole substitution patterns.



Scheme 17. Synthesis of indole substituted isoindolinones developed by Gredičak.[77]

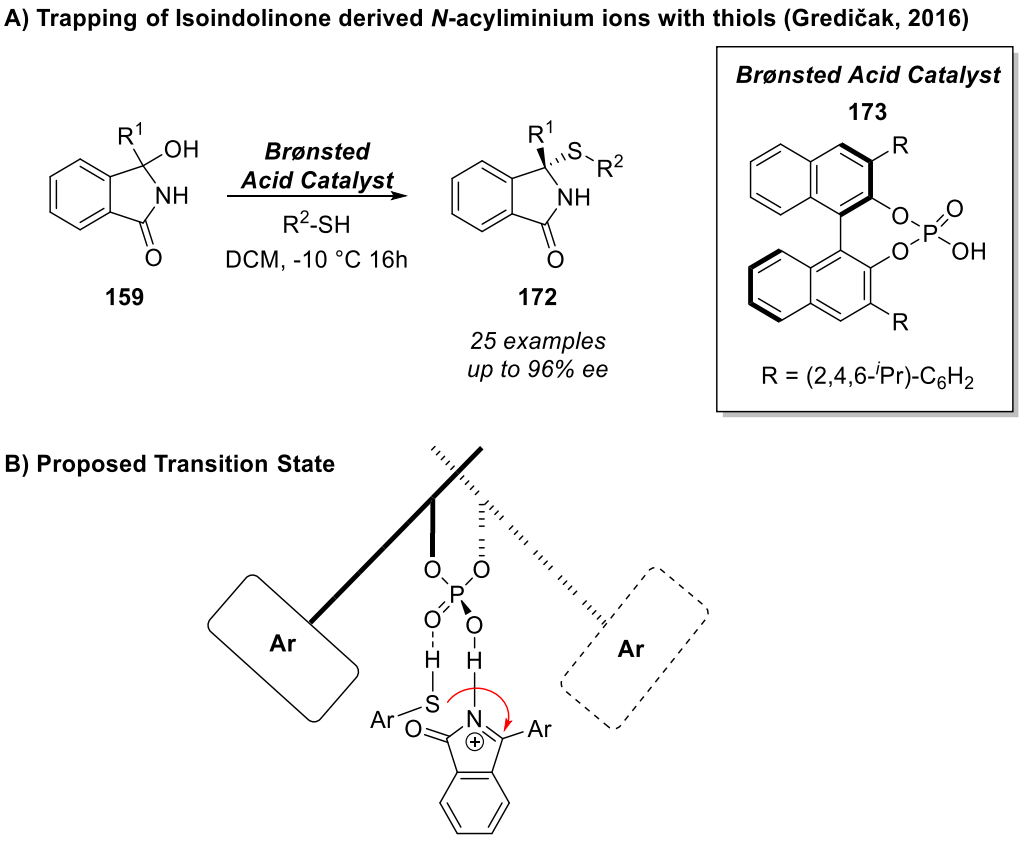
Utilising similar chemistry, Gredičak has reported a catalytic Betti type reaction, by trapping the *N*-acyliminium ion with a range of substituted phenols **164** using catalytic MsOH (Scheme 18A).[78] The authors found that the reaction did not proceed with ortho-substituted 3-aryl isoindolinones, attributed to increased steric hinderance and control experiments saw complete inhibition of the reaction when the NH or OH was substituted with a methyl group (Scheme 18B).



Scheme 18. Catalytic Betti-type reaction reported by Gredičak (A). Control experiments indicated the importance of both the OH and NH in order for the reaction to proceed (B).[78]

2.1.4.2. Sulfur Nucleophiles

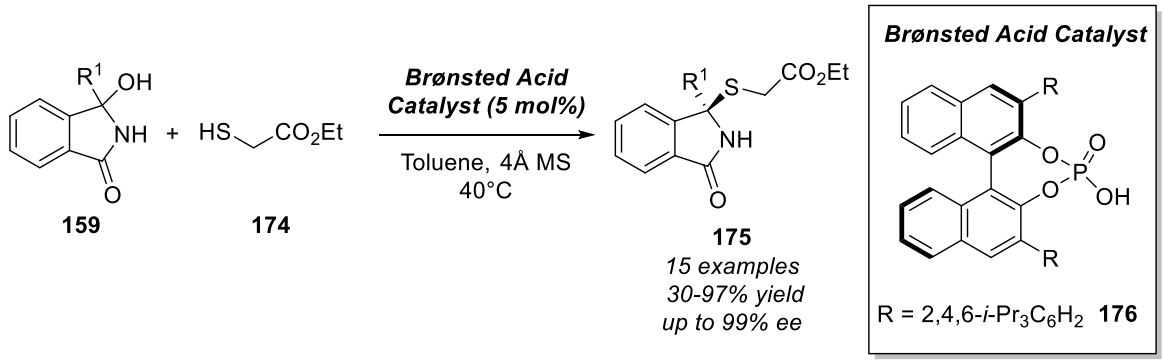
The synthesis of *N*(acyl),*S*-acetals **172** from 3-hydroxyisoindolinones **159** was first reported in 2016 by Gredičak (Scheme 19).[79] Using 10 mol% of chiral phosphoric acid catalyst **173**, the authors developed a substrate scope with a range of isoindolinones with various aromatic and aliphatic thiols. An application toward the synthesis of a HIV-I reverse transcriptase inhibitor was also provided showing the synthetic utility of the methodology.



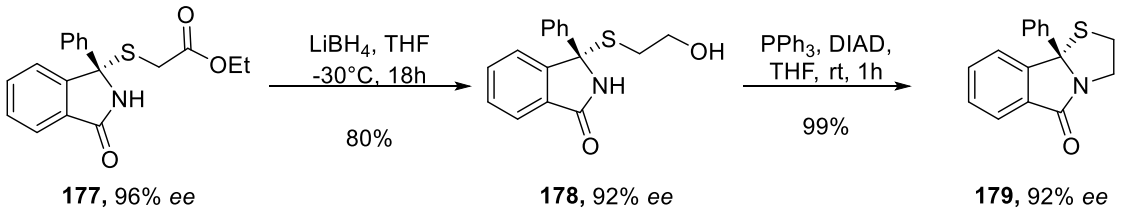
Scheme 19. Enantioselective synthesis of *N*(acyl),S-acetals using a chiral Brønsted acid.[79]

Singh and co-workers developed a similar protocol utilising phosphoric acid catalyst **176** for the addition of a range of thiols with a particular focus on ethyl thioglycolate **174** (Scheme 20).[80] The ester functional handle was chosen due to the ability to synthesise a library of HIV-1 reverse transcriptase inhibitors **179** by reduction of ester **177** followed by an intramolecular Mitsunobu cyclisation.

A) Trapping of Isoindolinone derived N-acyliminium ions with ethyl thioglycolate (Singh, 2017)



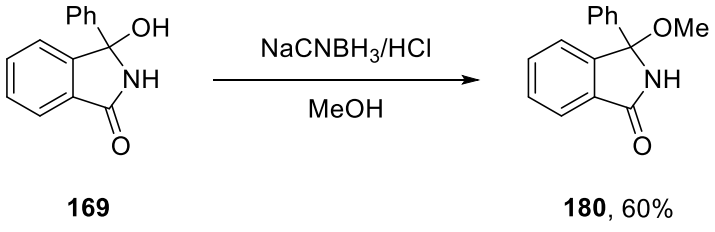
B) Application towards HIV-1 Reverse Transcriptase Inhibitors



Scheme 20. Synthesis of *N*(acyl),S-acetals using phosporic acid catalysis (A) and application to HIV-1 reverse transcriptase inhibitors (B).[80]

2.1.4.3. Oxygen Nucleophiles

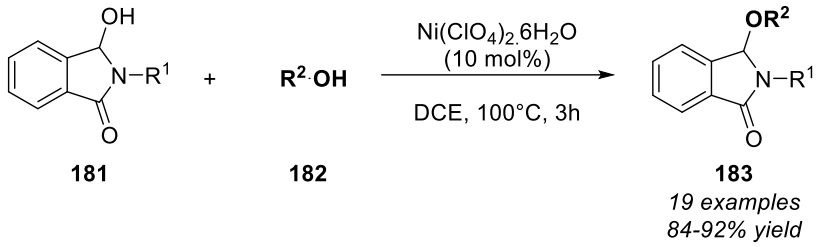
The synthesis of 3-alkoxy-substituted isoindolinones is reported sparingly within the literature. The first report was by Wang in 2002 whereby treatment of 3-hydroxyisoindolinone **169** with a HCl/$NaCNBH_3$ mixture in a protic solvent resulted in the formation of methoxy substituted isoindolinone **180** in a moderate yield (Scheme 21).[81]



Scheme 21. Synthesis of a 3-alkoxy-substituted isoindolinone.

More recently, Zhao and co-workers investigated a range of alcohols **182** in their broad study of trapping secondary isoindolinone **181** derived *N*-acyliminium ions with a range

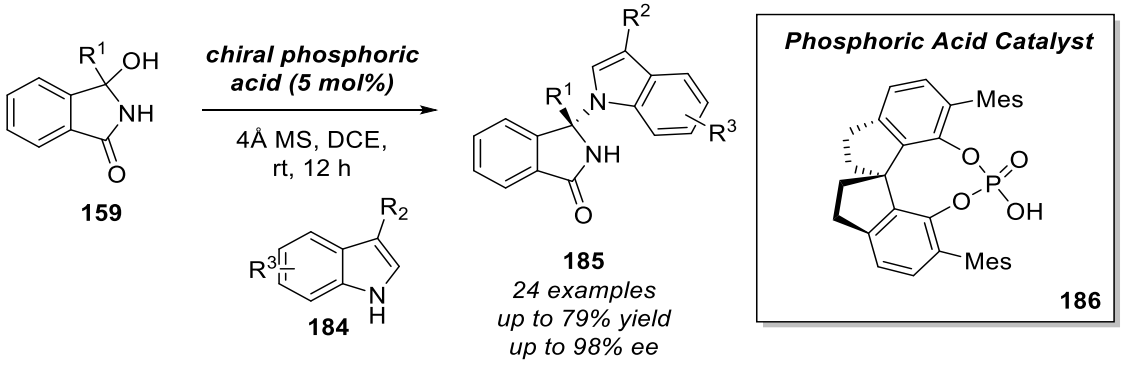
of different nucleophiles (Scheme 22).[82] This method provides access to a range of ethers **183** in good to excellent yields.



Scheme 22. Trapping of *N*-acyliminium ions with alcohols for the sythesis of 3-substituted alkoxy isoindoindolinones.[82]

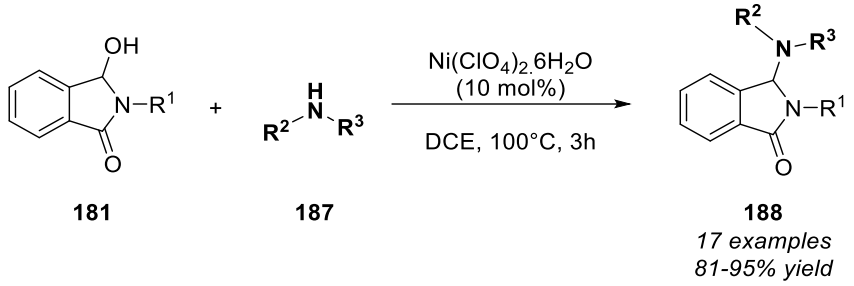
2.1.4.4. Nitrogen Nucleophiles

The functionalisation of isoindolinones employing nitrogen nucleophiles is far less explored with only a handful of examples present within the literature. Zeng and Zhong reported an enantioselective *N*-alkylation of indoles **184** into a 3-hydroxyisoindolinone **159** derived *N*-acyliminium ions using chiral phosphoric acid **186** (Scheme 23).[83] This allows access to tetrasubstituted chiral aminals **185** with excellent enantioselectivity.



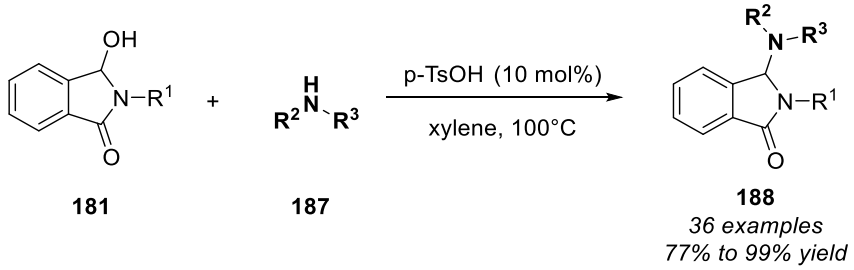
Scheme 23. *N*-alkylation of indoles for access to enantioenriched aminals.[83]

In 2019, Zhao reported the intermolecular trapping of *N*-acyliminium ions with primary and secondary amines **187** to access 3-aminoisoindolinones **188** (Scheme 24).[82] Using 10 mol% $Ni(ClO_4)_2.6H_2O$ as catalyst, heterocyclic amines were tolerated and generated a range of diverse scaffolds.



Scheme 24. Trapping of *N*-acyliminium ions with amines for the synthesis of 3-aminoisoindolinones.

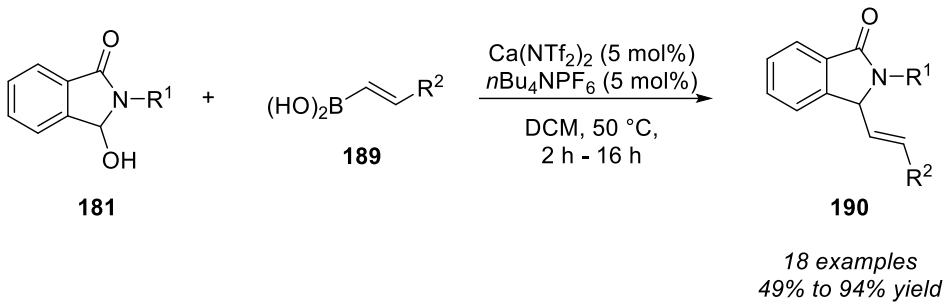
In 2022, Rao and co-workers reported a Brønsted acid catalysed variant, using catalytic quantities of p-TsOH (Scheme 25).[84] Much like Zhao's conditions, their reaction proved tolerant to both primary and secondary amines **187**, along with various heterocycles including morpholine, producing the desired products **188** in good to excellent yields.



Scheme 25. PTSA catalysed addition of amines to 3-hydroxyisoindolinones.[84]

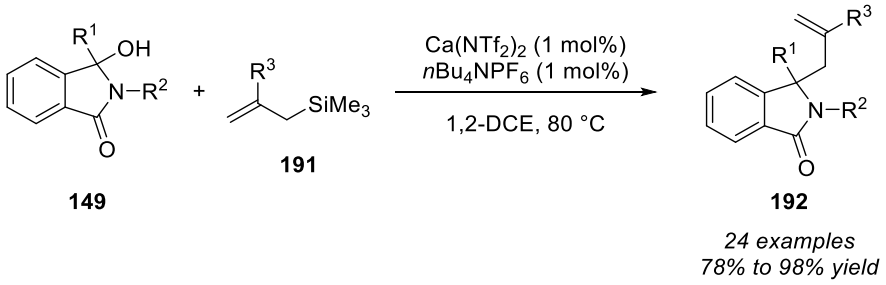
2.1.4.5. Functionalisation of Isoindolinones using Calcium as a Lewis Acid

The functionalisation of isoindolinones **181** using calcium was first reported by Leboeuf for the alkenylation of *N,O*-acetals using vinylboronic acids **189** (Scheme 26).[53] The substrate scope is developed from secondary hydroxyisoindolinones varying only R_1 and R_2. While the developed methodology provides access to high value scaffolds **190**, it is not without its limitations. The substrate scope is limited to secondary hydroxyisoindolinones, while the author's report no reaction being observed, when R_1 = H, losing access to a useful hydrogen bond donor.



Scheme 26. Calcium catalysed alkenylation of *N*-acyliminium ions with vinyl boronic acids.[53]

The McLaughlin group have previously reported the functionalisation of isoindolinones *via* a calcium catalysed Hosomi-Sakurai allylation (Scheme 27).[51] Employing allylsilanes **191** as nucleophiles, the reaction proceeds *via* an *N*-acyliminium ion with the sole by-product being innocuous TMSOH, observed by ^{1}H-NMR. Unlike previous reports, the reaction is tolerant to tertiary hydroxyisoindolinones ($R^1 \neq H$) **191** and does not require substitution at the nitrogen atom, providing access to highly substituted allylated isoindolinones **192**. Expanding upon this recent report forms the basis of this chapter.

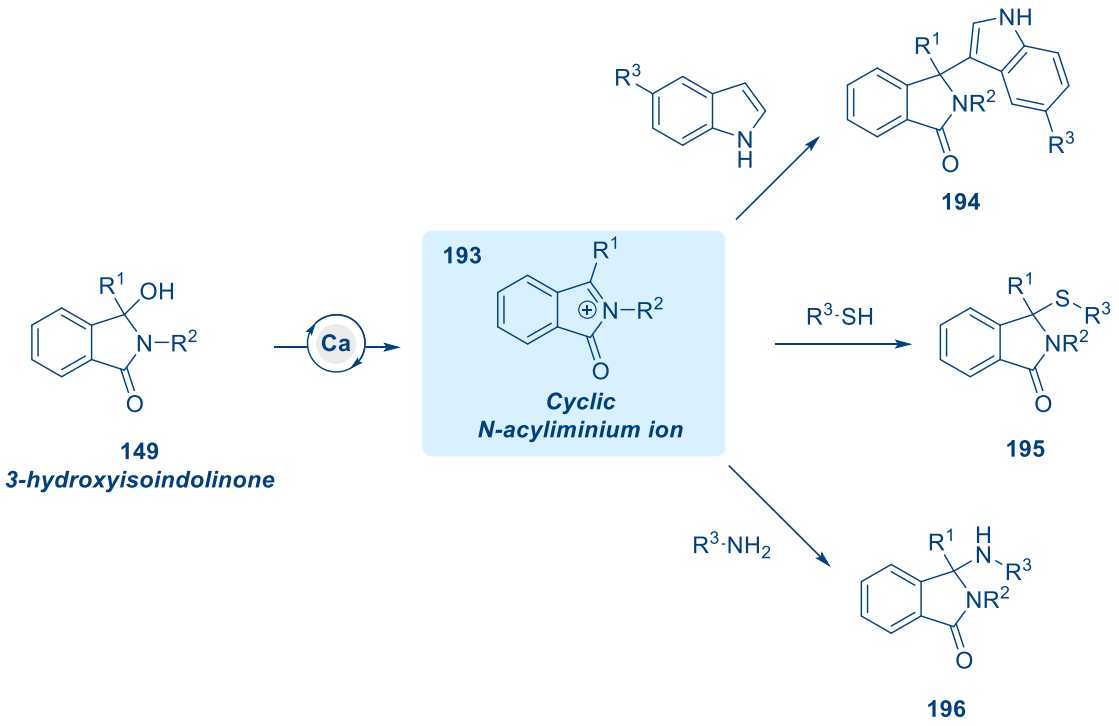


Scheme 27. Functionalisation of Isoindolinones *via* a calcium catalysed Hosomi-Sakurai allylation.[51]

Many of the methods discussed have several limitations. For example, many require the use of much harsher Brønsted acids which can somewhat limit functional group applicability. Furthermore, transition metal mediated approaches typically require super-stoichiometric amounts of additive. Thus, there is a need to develop milder, greener and more unified routes to such privileged scaffolds for the synthetic community without the need for complex reaction setups, anhydrous conditions or non-commercially available catalysts.

2.2. Aims

Following a communication from the group reporting the calcium catalysed allylation of isoindolinones using allyl silanes as nucleophiles,[51] the aim of this chapter is to provide a full investigation into the range of nucleophiles that can be employed to the catalytically generated *N*-acyliminium ion **193** (Scheme 28). In doing so, the aim is to develop a mild, universal, and efficient synthesis for rapid and convenient access to a range of densely substituted isoindolinones tolerant to traditional carbon and hetero-atomic nucleophiles **194-196**.



Scheme 28. Calcium catalysed functionalisation of isoindolinones; intermolecular trapping of *N*-acyliminium ions.

2.3. Results & Discussion

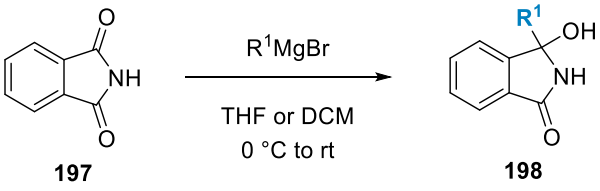
The work described in this section has been published.[52]

A. J. Basson and M. G. McLaughlin, *J. Org. Chem*. 2020, **85**, 5615

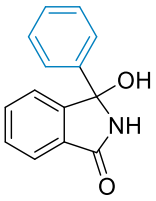
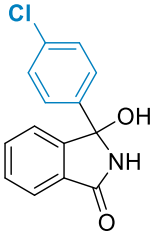
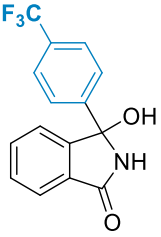
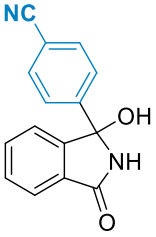
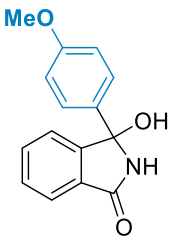
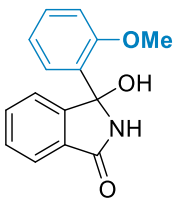
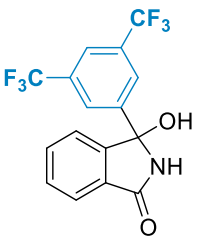
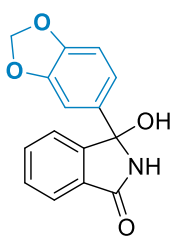
2.3.1. Preparation of Starting Materials

In order to access 3,3-disubstituted isoindolinones using the proposed methodology, access was first required to a library of 3-hydroxyisoindolinones. By utilising existing literature procedures[79, 85-87] a library of aryl-substituted 3-hydroxyisoindolinones **198** from phthalimide **197** and a Grignard reagent were able to be synthesised (Table 3). In addition to phenyl-substituted **198a**, halo-substituted **198b** and electron-deficient products **198c, 198d** were synthesised in useful yields. Electron-rich product **198e** was synthesised in moderate yield and various aryl-substitution patterns were also explored with *ortho*-substituted **198f** and *meta*-substituted products **198g** synthesised in good yields. Furthermore, heterocyclic acetal motif **198h** was also synthesised in moderate yield.

Table 3. Synthesis of 3-hydroxyisoindolinones by Grignard addition.

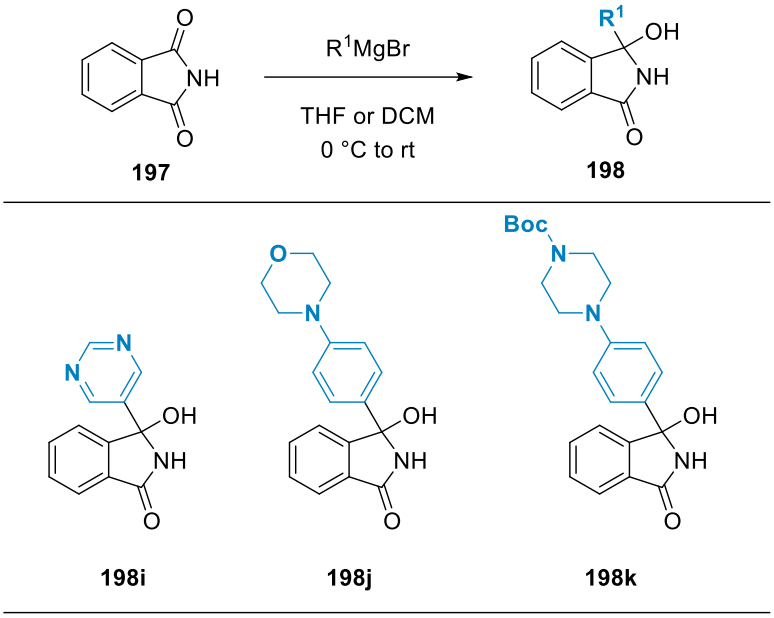


197 **198**

			
198a, 79%	**198b**, 64%	**198c**, 45%	**198d**, 15%
			
198e, 42%	**198f**, 80%	**198g**, 82%	**198h**, 53%

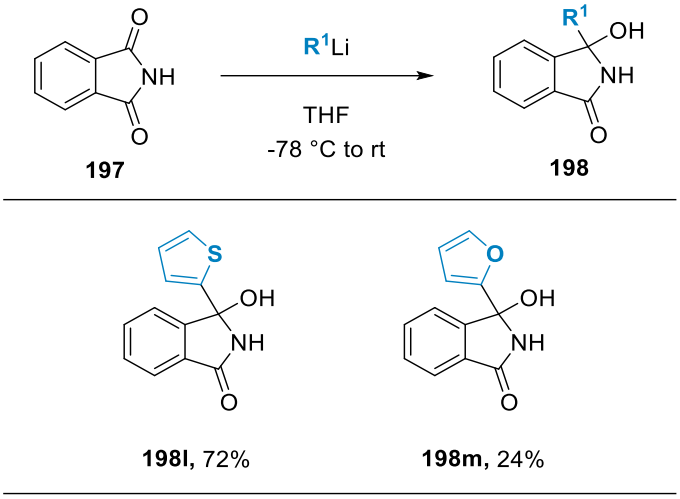
Introduction of more complex and traditionally difficult to access functionalities into the scaffolds was also studied, with a particular focus on nitrogen containing heterocycles (Table 4). However, when attempting synthesis of the pyrimidine moiety **198i**, a complex and inseparable mixture of products was obtained. This can be attributed to the 5-bromo-pyrimidine reacting with itself upon formation of the Grignard reagent. Furthermore, when attempting the synthesis of morpholine and piperazine derivatives **198j** and **198k**, unreacted aryl halide was re-isolated in both cases suggesting Grignard formation did not occur under these conditions.

Table 4. Unsuccessful substrates.



To expand the substrate scope further, thienyl-lithium could also be successfully added into phthalimide **197** affording thiophene-substituted 3-hydroxyisoindolinone **198l** in good yield (Table 5). Additionally, lithiation of furan and subsequent addition into phthalimide **197** also proved successful affording furan substituted 3-hydroxyisoindolinone **198m** in synthetically useful yield.

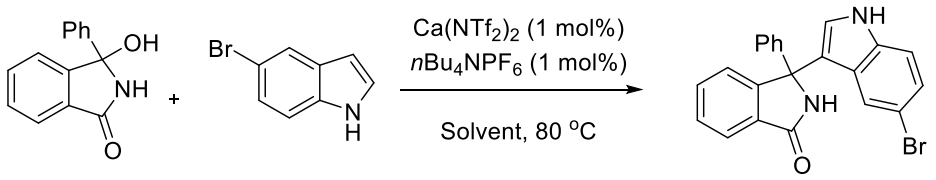
Table 5. Synthesis of thiophene and furan substituted isoindolinones.



2.3.2. Optimisation Studies

The development of a Lewis acid catalysed Friedel-Crafts alkylation of isoindolinones appears to have been overlooked by the synthetic community with previous reports focussing on Brønsted acid catalysed routes. Therefore, exploring other carbon nucleophiles beyond that of the previously reported allylation using allylsilanes was of interest.[51] 5-Substituted indoles were identified as a suitable carbon nucleophile. The investigation began by studying the addition of 5-bromoindole **199** to **198a** and subjecting this to previously optimised conditions (Table 6).[51] The reaction proceeded to completion in 30 mins forming product **200a** in excellent yield (entry 1). Screening a range of solvents saw no improvement in yield (entries 2-5). The reaction (entry 1) was then repeated without the presence of the additive which resulted in a significant decrease in yield (entry 6). Performing the reaction without the catalyst resulted in no reaction (entry 7). Utilising a calcium/HFIP Brønsted acid mediated pathway proved unsuccessful (entry 8) and a control experiment using Brønsted acid inhibitor 2,6-ditertbutylpyridine was performed with the reaction proceeding unhindered (entry 9) marking entry 1 as optimal conditions.

Table 6. Optimisation for the addition of indole.



198a **199** **200a**

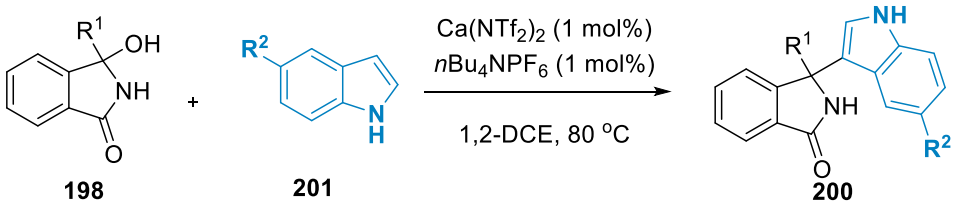
Entry	Catalyst	Additive	Solvent	Yield
1	**$Ca(NTf_2)_2$**	***n*Bu_4NPF_6**	**1,2-DCE**	**82%**
2	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	MeCN	66%
3	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	Toluene	n.r.
4	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	CH_2Cl_2	79%
5	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	THF	15%
6	$Ca(NTf_2)_2$	-	1,2-DCE	39%
7	-	*n*Bu_4NPF_6	DCE:DME	n.r.
8	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	HFIP	decomp.
9	$Ca(NTf_2)_2$	*n*Bu_4NPF_6	1,2-DCE	82% [a]

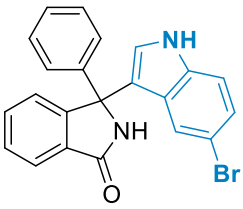
[a] 2,6-ditertbutylpyridine added

2.3.3. Carbon Nucleophiles

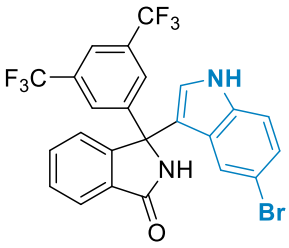
With optimised conditions in hand, the substrate scope was then completed on a range of 3-hydoxyisoindolinones (Table 7). As well as phenyl substituted **200a**, the reaction was tolerant to electron-withdrawing **200b**, electron-donating **200c** and heterocyclic isoindolinones **200d** and **200e**. To offer an alternative and complementary route for further functionalisation, 5-pinacolboronate indole was also studied as a coupling partner. Gratifyingly, the reaction was again tolerant to electron withdrawing **200g**, **200j**, electron donating **200h** and heterocyclic **200i** isoindolinones.

Table 7. Indole Substituted Isoindolinones.

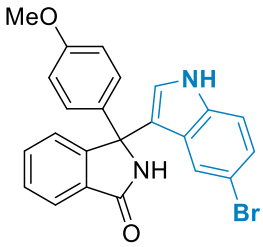




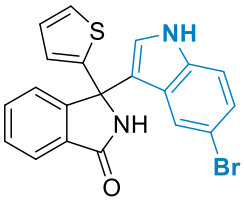
200a, 82%



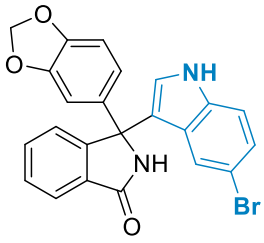
200b, 91%



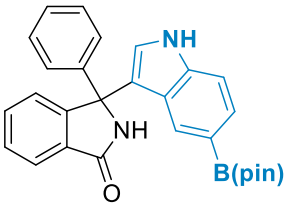
200c, 93%



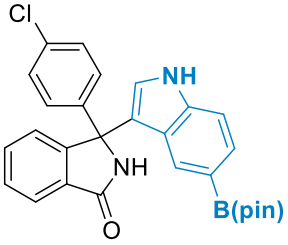
200d, 96%



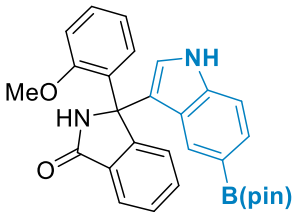
200e, 94%



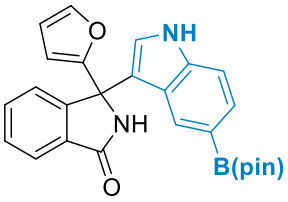
200f, 90%



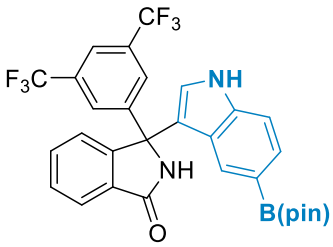
200g, 93%



200h, 98%



200i, 82%

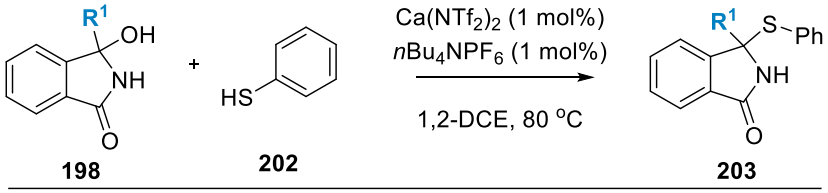


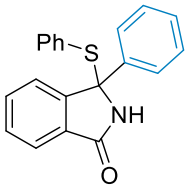
200j, 81%

2.3.4. Sulfur Nucleophiles

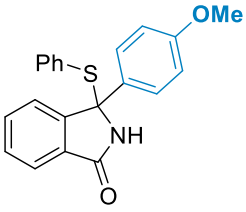
The tolerance of the reaction towards other coupling partners, in particular, sulfur containing fragments was then explored. Traditionally, more nucleophilic coupling partners bearing heteroatoms are prone to catalyst poisoning. However, the reaction with thiophenol proceeded well, going to completion in 15 minutes using the same conditions used for the indole derivatives. The substrate scope was then probed by first investigating reactivity of thiophenol **202** with a range of 3-hydroxyisoindolinones, producing a range of 3,3-disubtituted lactams **203** (Table 8). In addition to phenyl-substituted **203a**, the reaction was tolerant to a range of electronics with electron donating **203b** and electron-withdrawing substituents **203c-203e** working well, providing the desired products in excellent yields. Various substitution patterns on the phenyl ring were also well tolerated affording products **203f**, **203g.** Heterocyclic substrates also worked well, again in excellent yields, with thiophene **203h**, furan **203i** and fused acetal moiety **203j** synthesised.

Table 8. Thiophenol Substrate Scope.

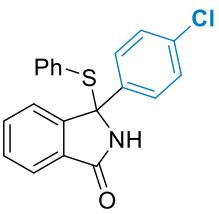




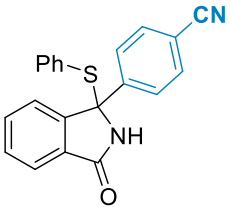
203a, 77%



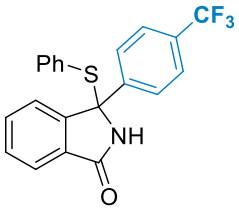
203b, 86%



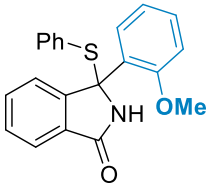
203c, 86%



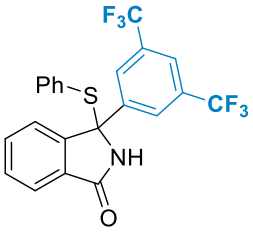
203d, 79%



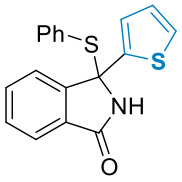
203e, 96%



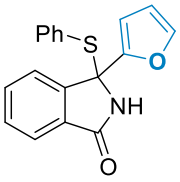
203f, 84%



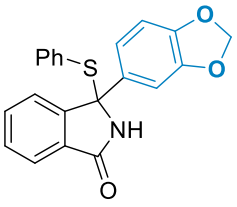
203g, 90%



203h, 86%



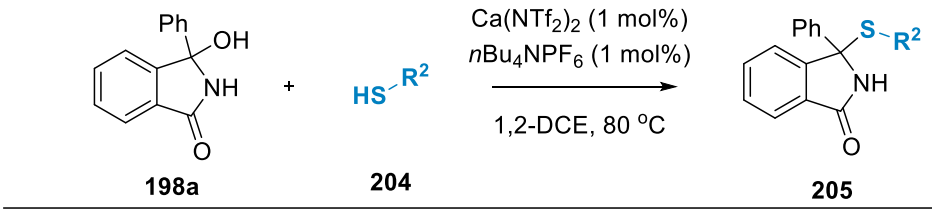
203i, 98%

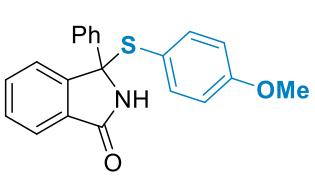


203j 91%

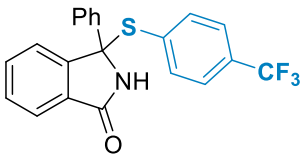
As all these examples used thiophenol as the coupling partner, tolerance toward other thiols was then explored (Table 9). The reaction was tolerant to a wide range of thiols, with electron donating **205a** and electron withdrawing **205b, 205c** thiols working well along with various substitution patterns on the aromatic ring of the thiol **205d**, **205e**. Furthermore, heterocyclic **205f**, **205g**, benzyl **205h** and alkyl thiols **205i**, **205j** were all also tolerated along with boronate esters **205k** providing scope for further functionalisation.

Table 9. Scope of Sulfur Nucleophiles.

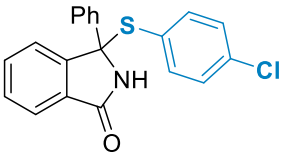




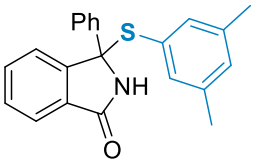
205a, 78%



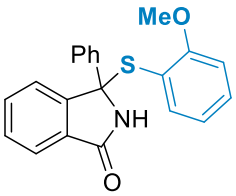
205b, 83%



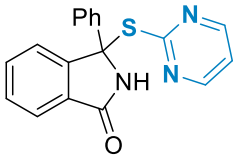
205c, 88%



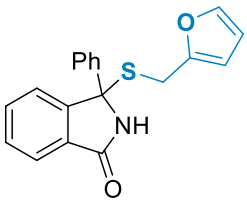
205d, 86%



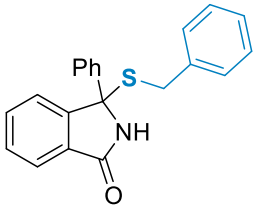
205e, 98%



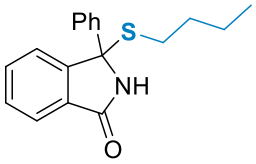
205f, 78%



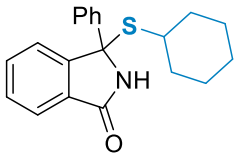
205g, 78%



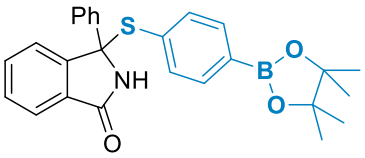
205h, 92%



205i, 91%



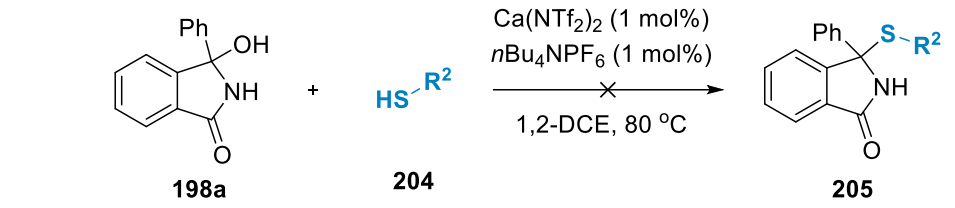
205j, 93%

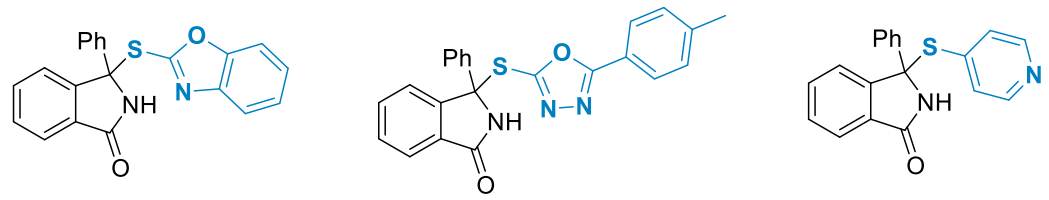


205k, 74%

The reactivity with thiols, however, was not without its limitations. When the optimised conditions were used with sulfur containing nitrogen heterocycles, a complex mixture was obtained in all cases **205l-205n**. (Table 10). This could be attributed to a decrease in the nucleophilicity of the thiols due to delocalisation of the lone pair of electrons of the sulfur into the aromatic ring.

Table 10. Unsuccessful Sulfur Nucleophiles.



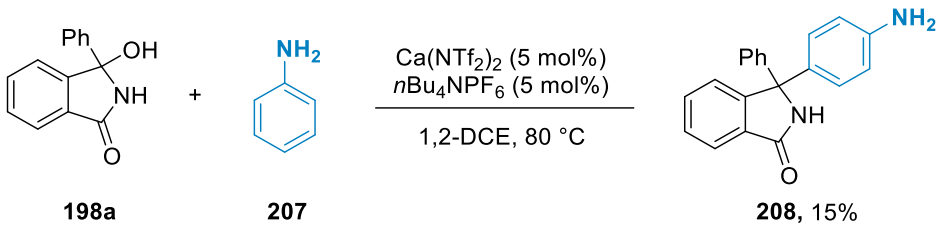


2.3.5. Nitrogen Nucleophiles

Attention was then turned to nitrogen nucleophiles and anticipated they would be much more troublesome due to their Lewis basic properties and could result in catalyst poisoning with Niggemann reporting coordination issues when using calcium with amines.[26] However, 3-aminoisoindolinones are significantly under explored within the literature and the aim was to explore if there was a reason for this, and if a robust method for their rapid synthesis could be achieved.

2.3.5.1. Amines

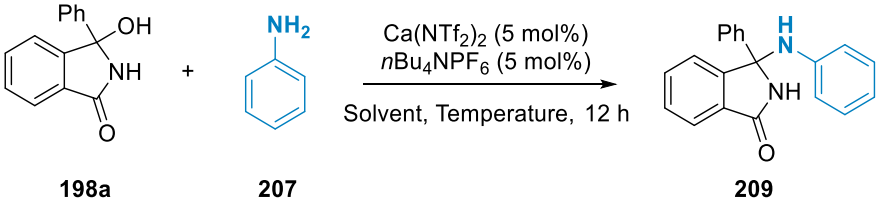
The reactivity of isoindolinone derived *N*-acyliminium ions towards amines was first explored. Preparation of tetrasubstituted 3-aminoisoindolinones is completely absent from the literature with no current methods available for their synthesis. When isoindolinone **198a** was subjected to the optimised conditions, with aniline **207** as the external nucleophile, **208** was isolated as the major product in 15% yield (Scheme 29). This observation was surprising given other groups who have attempted to add anilines to derivatives of **198a**, observed complex mixtures.[88, 89]



Scheme 29. Attempted synthesis of 3-aminoisoindolinone.

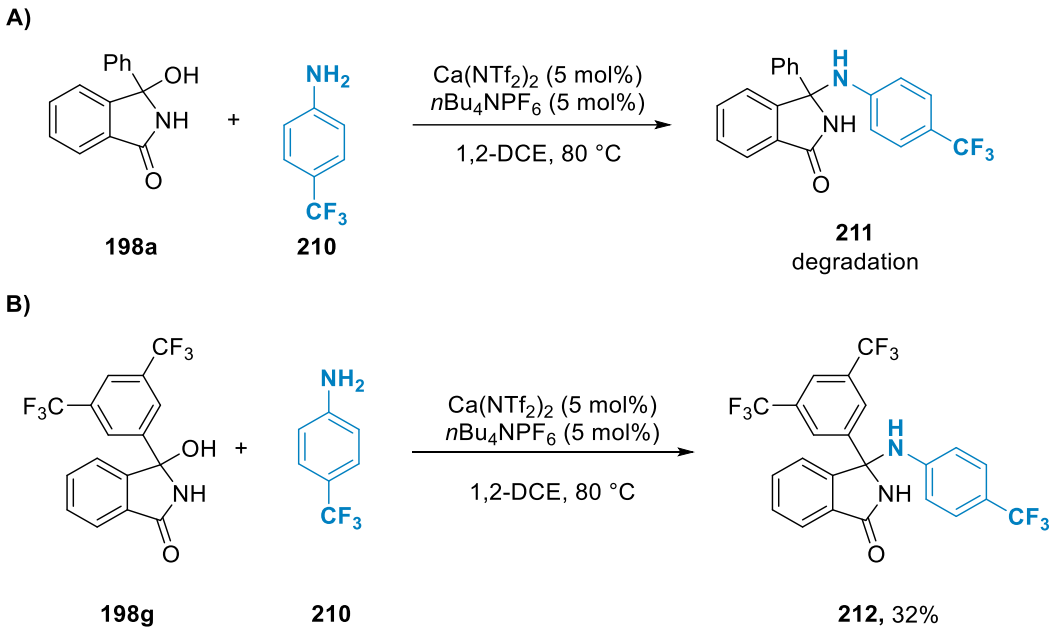
A range of solvent systems were then screened at various temperatures to see if the side reaction could be circumvented (Table 11). When lower temperatures were attempted, no reaction was observed, while HFIP and Toluene resulted in increased complexed mixtures at elevated temperatures. Addition rate of aniline was also studied, with lower temperature addition along with dropwise addition without success.

Table 11. Reaction conditions screened.



Entry	Temp	Solvent	Yield
1	25ºC	DCM	n.r
2	40°C	DCM	n.r
3	40°C	1,2-DCE	n.r
4	40°C	HFIP	n.r
5	80°C	HFIP	decomp.
6	80°C	Toluene	decomp.

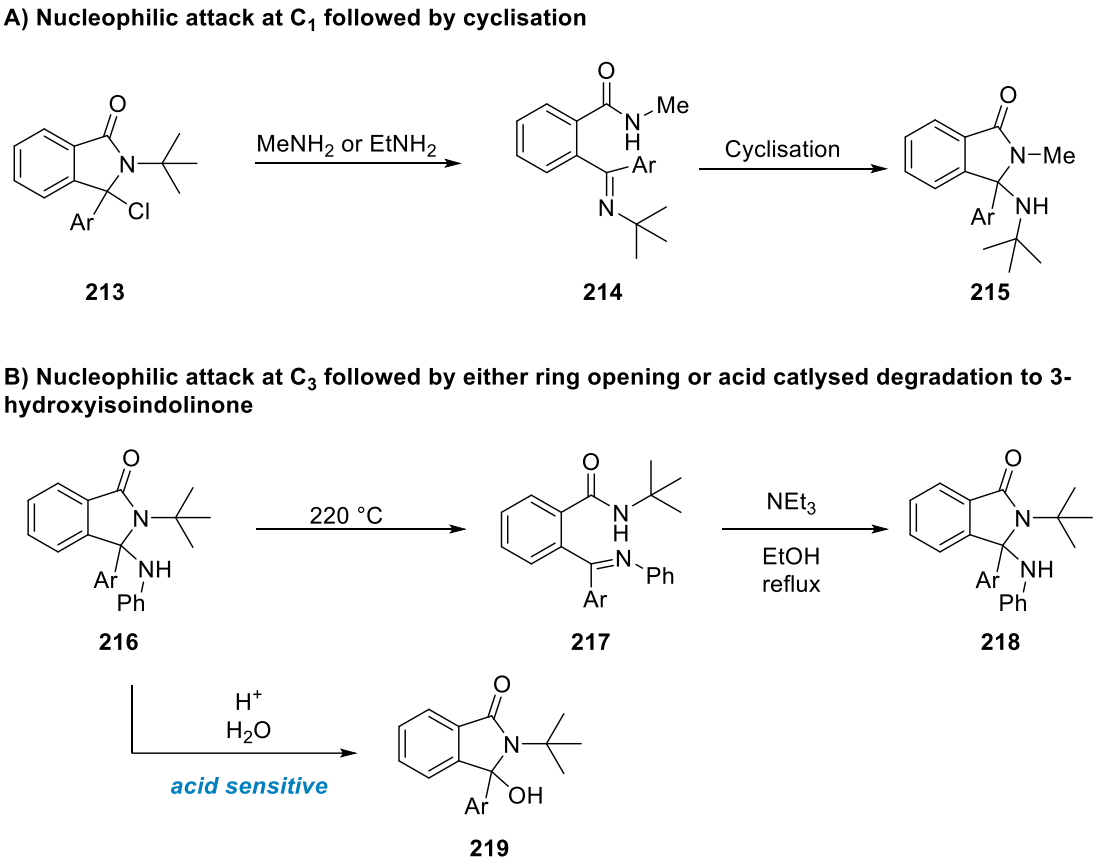
Given the formation of the Friedel-Crafts side-product could not be prevented from forming by adjusting the reaction conditions, it was then reasoned this could be prevented by using 4-substituted aniline derivatives, with 4-trifluoromethyl aniline **217** being chosen. The reaction proceeded to completion cleanly however upon isolation of product **211**, a rapid degradation profile was observed (Scheme 30A). Adjusting the electronics of the 3-hydroxyisoindolinone starting material to **198g** resulted in slightly increased stability allowing product **212** to be isolated in 32% yield (Scheme 30B). The differential stability can be attributed to the electron-withdrawing nature of the C-3 group strengthening the bond between the nitrogen of the aniline and the C3 carbon.



Scheme 30. Reaction of 3-hydroxylisoindolinones with electron-deficient anilines.

These results were interesting, as there is only one other study on 3-aminoisoinoldinones in the literature which observed a series of side reactions.[90] It was anticipated the milder conditions could avoid these side reactions and isomerisations which are outlined below and are inspired by the report by Valter in 1976 who experienced similar issues albeit using 3-chloroisoindolinone precursors.[90]

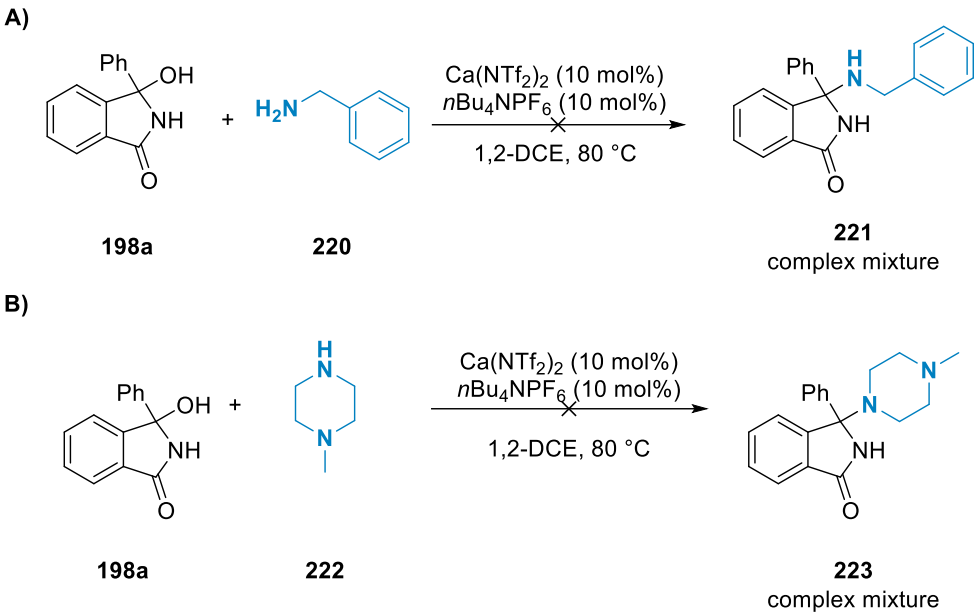
One potential side reaction is attack of the amine at the carbonyl position resulting in **214** followed by a cyclisation to **215** (Scheme 31A). Alternatively, attack of the iminium ion carbon resulted in product **216** which was found to be acid sensitive and again prone to ring opening to **217** under elevated temperatures followed by cyclisation to **218** (Scheme 31B). **216** was also prone to hydrolysis to form 3-hydroxyisoindolinone **219.** Given the clear sensitivity of these products, particularly with slight changes in their electronic properties, it is possible similar side reactions are taking place within the catalytic system.



Scheme 31. Nucleophilic attack of the amine at the C_1 position observed by Valter.[90]

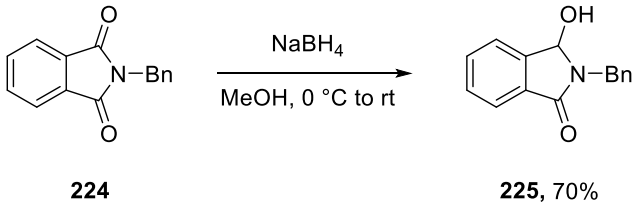
B) Nucleophilic attack at C_3 followed by degradation or ring opening observed by Valter.[90]

As the reactivity of aniline derived nucleophiles appeared to be incredibly capricious in terms of the electronics of the system, the use of more nucleophilic amines was then studied. Primary amine, benzyl amine **220** and secondary amine *N*-methyl-piperazine **222** were studied. In both cases, a complex mixture of products was obtained (Scheme 32). A possible reason for this could be due to the more basic amines deprotonating the *N*-acyliminium ion, forming an *N*-acylimine which could undergo then undergo decomposition.



Scheme 32. Reaction with benzylamine (A) and *N*-methyl-piperazine (B).

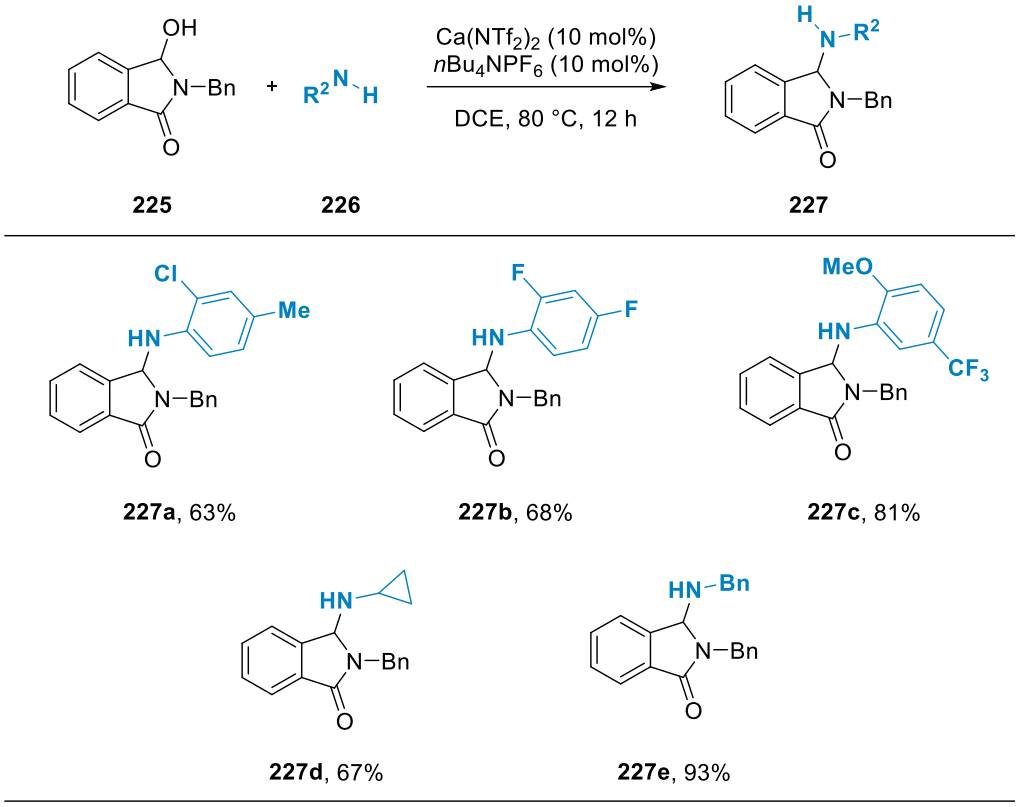
To prevent deprotonation occurring, *N*-benzyl-protected 3-hydroxyisoindolinone **225** was synthesised by partial reduction of *N*-benzyl-phthalimide **224** (Scheme 33).



Scheme 33. Synthesis of *N*-benzyl protecting 3-hydroxyisoindolinone.

This proved successful and subjecting **225** to the optimised conditions using 10 mol% catalyst afforded a range of 3-aminoisoindolinones from aniline derived amines with varying electronics **227a**-**227c**, cyclopropyl derivative **227d** and benzylamine derived product **227e** all in good yields (Table 12).

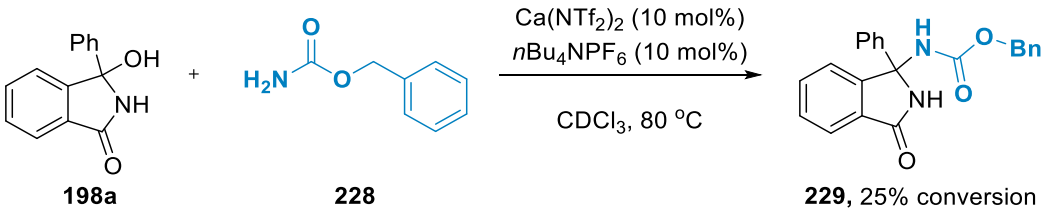
Table 12. 3-aminoisoindolinones.



2.3.5.2. Carbamates & Amides

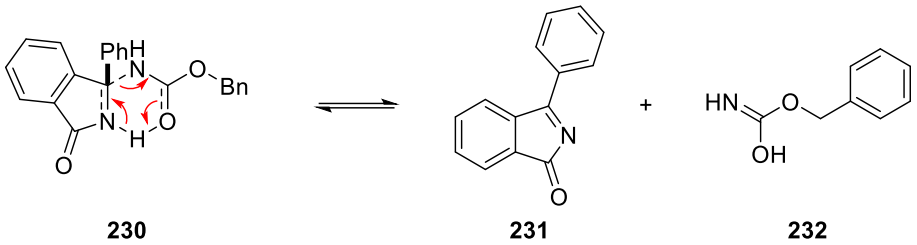
Due to the limited success and tolerance displayed by amines, attention was then turned to less nucleophilic nitrogen nucleophiles; amides and carbamates.

As with amines, benzyl carbamate **228** was first subjected to the same conditions used for the carbon and sulfur nucleophiles and a low isolated yield of 19% was obtained. The low yield was confirmed by an NMR experiment in which the reaction plateaued at 25% conversion confirming the sluggish nature of these reactions (Scheme 34). Leaving the reaction for longer periods of time resulted in the formation of side-products.



Scheme 34. NMR reaction with benzylcarbamate.

It was reasoned the product was potentially unstable due to the formation of a 6-membered ring transition state **230** which improves the leaving group ability of benzyl carbamate. (Figure 21).

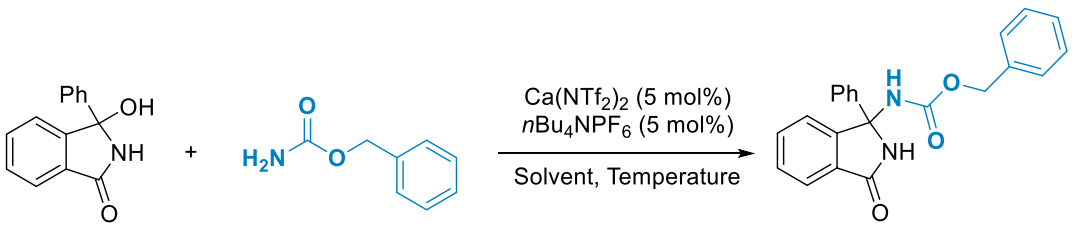


230 **231** **232**

Figure 21. Potential decomposition of the product.

A range of calcium tolerant solvents at varying temperatures were also screened, with little success (Table 13). Performing the reaction in toluene inhibited the reaction fully regardless of temperature (entry 1 and 2). Utilising the Brønsted acidity and stabilising ability of HFIP in an attempt that it would coordinate to the lone pairs on the carbamate, thereby minimising the decomposition of the product was also unsuccessful, with no reaction occurring at 40 °C (entry 3), while increasing the temperature to 60 °C and 80 °C respectively saw decomposition of the starting material **198a** (entry 4 and 5).

Table 13. Further attempts at optimisation.



198a **228** **229**

Entry	Temp	Solvent	Time	Yield
1	25ºC	Toluene	12	n.r
2	80°C	Toluene	12 h	n.r
3	40°C	HFIP	12 h	n.r
4	60°C	HFIP	12 h	decomp.
5	80°C	HFIP	12 h	decomp.
6	80°C	Toluene:HFIP (3:1)	12 h	n.r

To investigate the reaction further, ^{19}F NMR was used to study the change in chemical shift upon addition of benzyl carbamate in the hope of a noticeable shift of the CF_3 group of the triflimide (Figure 22). The ^{19}F NMR spectrum was first collected of the active

catalyst followed by recollection upon the addition of benzyl carbamate. There is a shift change of δ0.57 ppm suggesting the benzyl carbamate has some interaction with the catalyst with the catalyst potentially playing a role in the leaving group ability of benzyl carbamate and subsequent decomposition of the product.

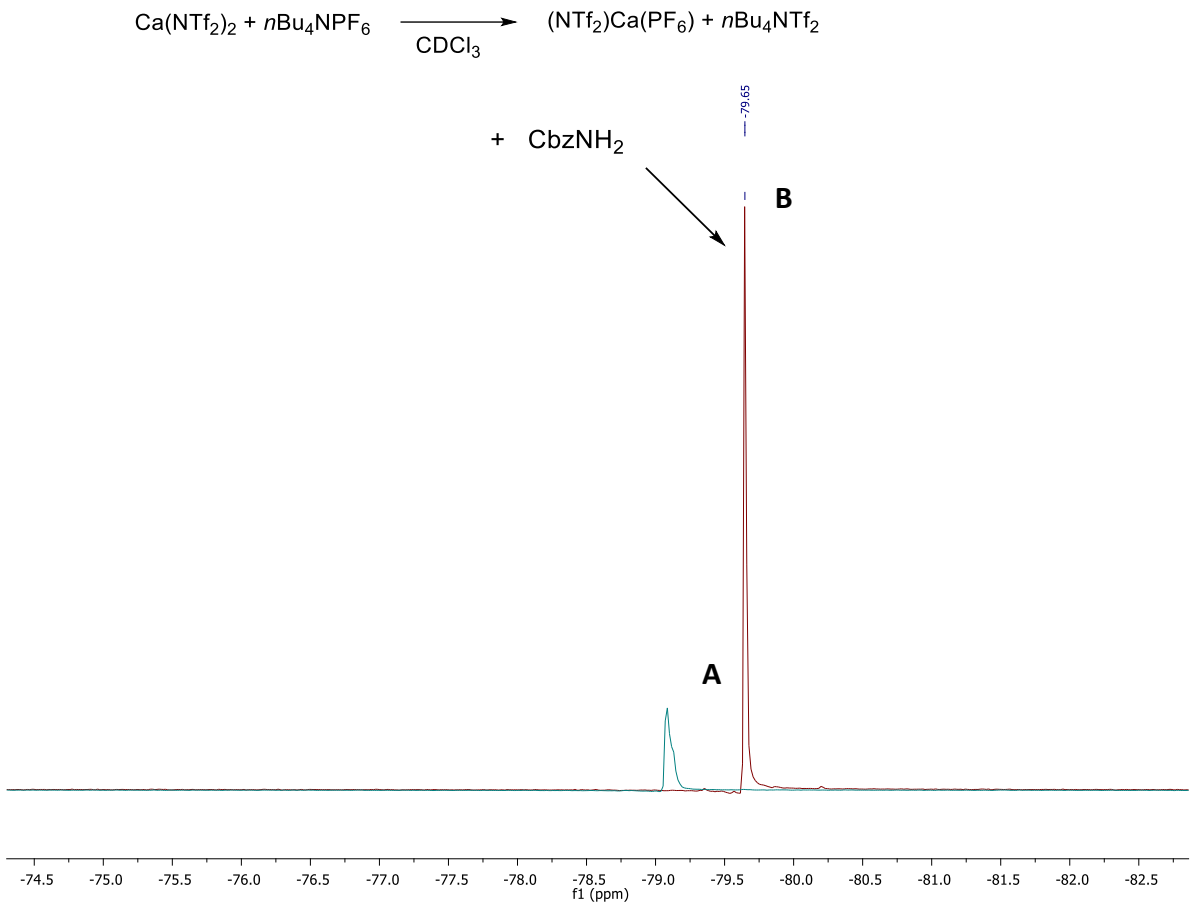
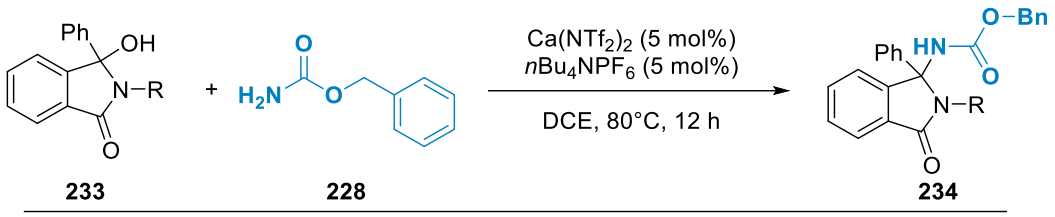
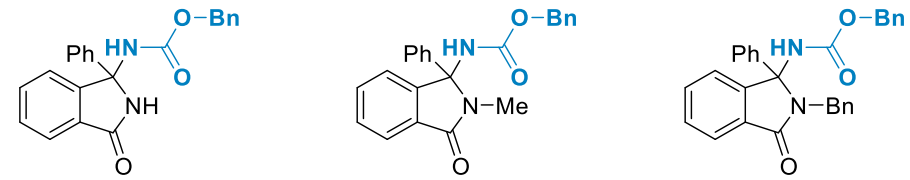


Figure 22. ^{19}F NMR spectrum of active catalyst (A) overlaid with spectrum upon addition of benzyl carbamate (B) reference using hexafluorobenzne (δ -173 ppm).

To prevent the formation of the 6-membered transition state, the reactivity of the *N*-H isoindolinone was compared with the *N*-Me and *N*-Bn substituted derivatives (Table 14). Firstly, increasing the catalyst loading saw an increase in yield of **234a**. This could be due to coordination of the catalyst to the carbonyl of the carbamate, preventing the oxygen lone pair hydrogen bonding with the N-H. When the *N*-Me and *N*-Bn isoindolinones were subjected to the reaction conditions, unreacted starting material was re-isolated in both cases **234b** and **234c**. This is consistent with the findings of Eberlin who showed *N*-substituted *N*-acyliminium ions to be much less reactive.[57]

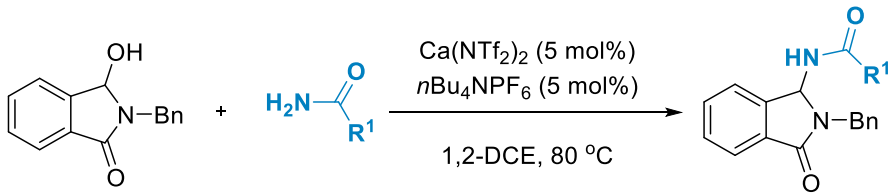
Table 14. Effect of isoindolinone *N*-substituion on reaction.

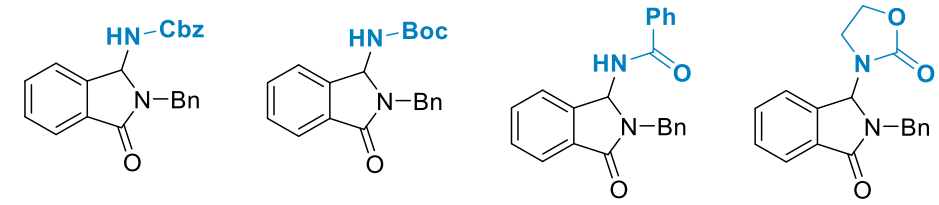




The reaction was then studied using *N*-Bn isoindolinone **225** which proved successful (Table 15). The substrate scope was probed providing access to Cbz protected **236a** and Boc protected **236b** isoindolinone products in excellent yield. Amides were also well tolerated affording **236c** in high yield. Furthermore, oxazolidinone substituted isoindolinone **236d** was also synthesised in good yield. These substrates have potential as suitable building blocks for further functionalisation, offering an alternative, higher yielding route to the synthetically challenging 3-aminoisoindolinones due to their differential methods of deprotection.

Table 15. Carbamate and Amide Substitution Reactions.

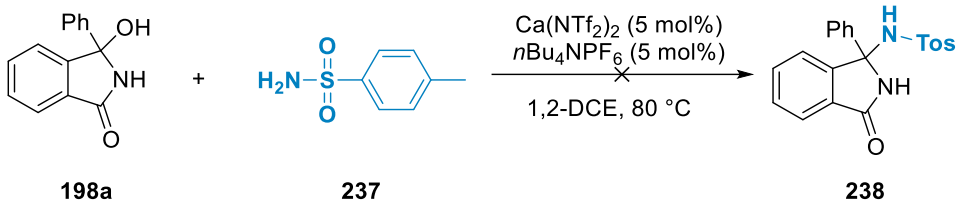




2.3.5.3. Sulfonamides

To complete the study of nitrogen nucleophiles, attention was turned to sulfonamides. The trapping of isoindolinone derived *N*-acyliminium ions with sulfonamides has again seemingly been ignored by the synthetic community, which could offer new avenues to explore regarding biological activity.

The study began by subjecting the 3-hydroxyisoindolinone **198a** to the optimised conditions with p-toluenesulfonamide **237** (Scheme 35) which resulted in no reaction. This can be attributed to the poor nucleophilicity of **237** coupled with its excellent leaving group ability and therefore reaction reversibility.

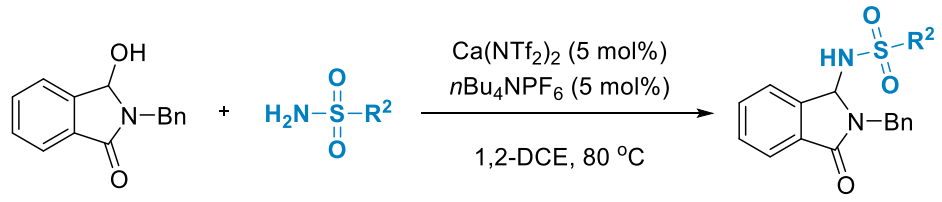


198a **237** **238**

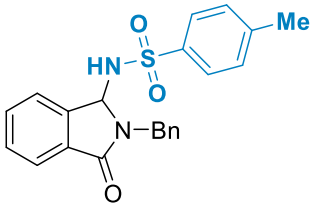
Scheme 35. Attempted reaction of tertairy isoindolinone with p-Toluenesulfonamide.

As with the amine and carbamate nucleophiles, the reactivity was successful when using the *N*-benzyl protected isoindolinones **225** and a range of useful scaffolds employing 5 mol% of the catalyst system were developed (Table 16). The reaction was once again tolerant of electron donating **240a**, **240b** and electron withdrawing sulfonamides **240c** along with various halide substitution patterns **240d**, **240e**, **240f**. Heterocyclic moieties **240g** and unsaturated scaffolds **240h** also worked well affording sulfonamide substituted lactams in good yields.

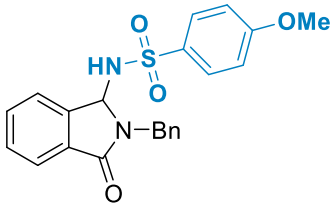
Table 16. Scope of Sulfonamides.



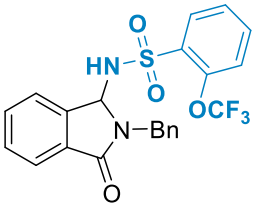
225 **239** **240**



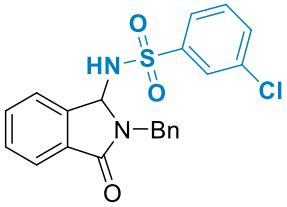
240a, 85%



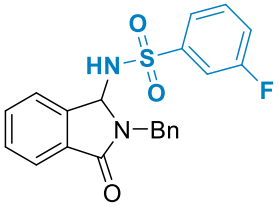
240b, 91%



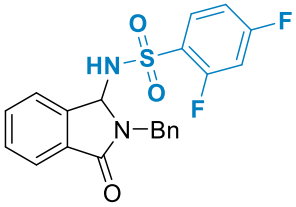
240c, 68%



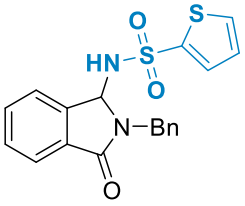
240d, 75%



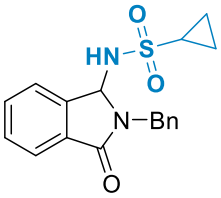
240e, 75%



240f, 60%



240g, 77%



240h, 61%

2.3.6. Proposed Mechanism

A postulated general mechanism is depicted in Figure 23. The active catalyst is understood to be [$CaPF_6NTf_2$] **241**, which is formed upon the mixing of $Ca(NTf_2)_2$ and nBu_4NPF_6. *N*-acyliminium ion **242** is formed by coordination of the catalyst to OH and subsequent displacement of the weakly coordinating PF_6^- anion, which in turn forms complex **243**. Trapping of the *N*-acyliminium ion **242** with an external nucleophile forms intermediate **244**. Re-entry of PF_6^- generates product **245** and water by-product.

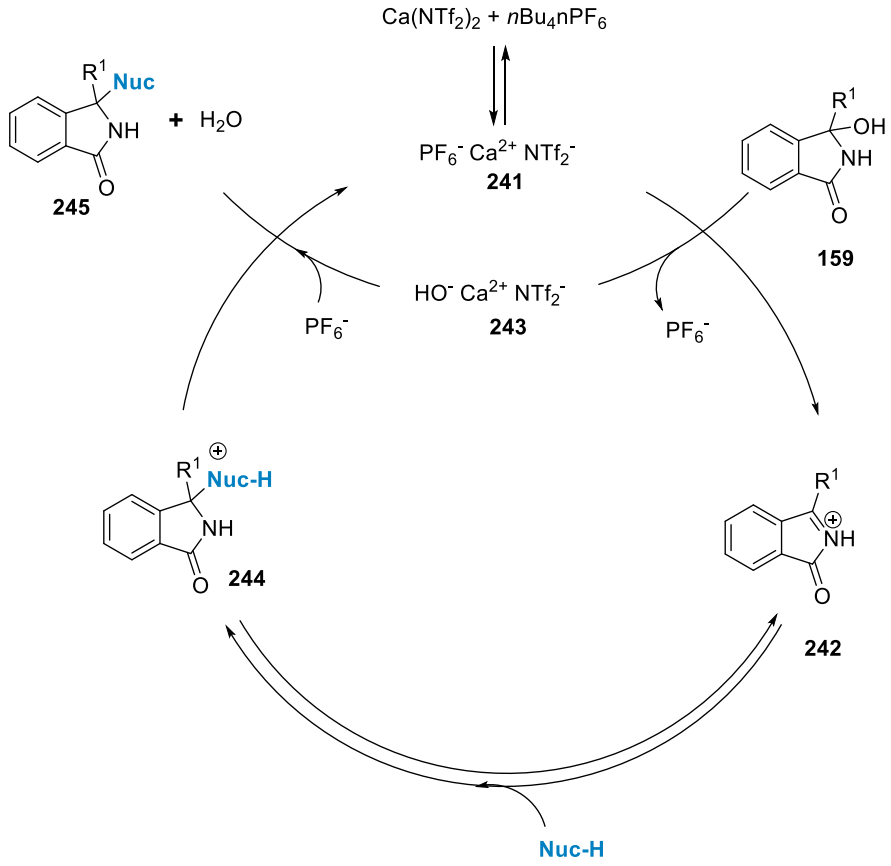


Figure 23. Proposed Catalytic Cycle

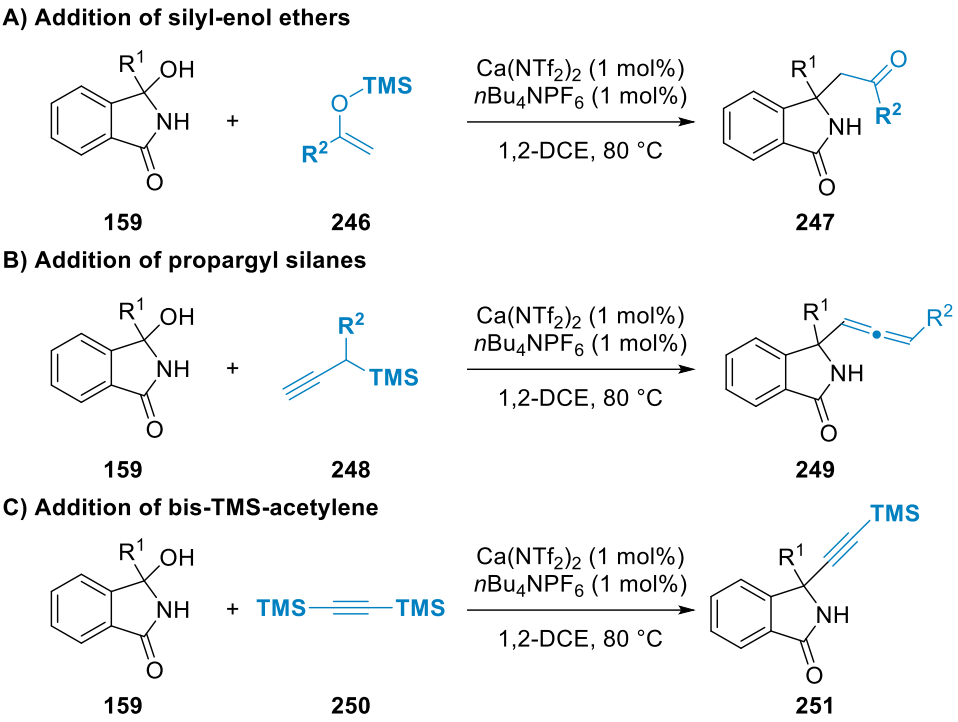
2.4. Conclusions

In summary, a mild and versatile method for the functionalisation of isoindolinones using calcium as a Lewis acid has been developed. The reaction was tolerant to carbon nucleophiles, in the form of 5-substituted indoles, and sulfur and nitrogen containing heteroatomic nucleophiles. The reaction with indoles and thiols proceeded rapidly and smoothly using 1 mol% catalyst loading providing access to 3,3,-disubstituted isoindolinone scaffolds. However, applying this towards nitrogen nucleophiles proved more troublesome. The reactivity with anilines was shown to suffer from chemoselectivity issues, and more basic amines were shown to facilitate side reactions. The addition of less basic nitrogen nucleophiles such as carbamates and sulfonamides resulted in an unstable product forming due to their own respective leaving group ability, aided by the N-H of the lactam and the catalyst. However, it was discovered that by utilising an *N*-Bn 3-hydroxyisoindolinone, the full range of nitrogen nucleophiles was tolerated, preventing any side reactions and reaction reversibility. Amines, carbamates,

amides and sulfonamides were all tolerated providing access to highly desirable and underexplored amino-substituted isoindolinone scaffolds. In developing this methodology, calcium has been shown to be a versatile catalyst that retains catalytic activity in the presence of heteroatomic reactive intermediates and heteroatomic nucleophiles.

2.5. Future Work

Given the mild conditions employed and wide functional group tolerance, there is potential to expand the coupling partner scope beyond those studied by using silyl-enol ethers **246** as nucleophiles (Scheme 36A). Due to their ease of preparation, this would offer a mild, rapid method for the introduction of a ketone moiety resulting in a useful functional handle. Furthermore, other silicon derived nucleophiles could be added in to the *N*-acyliminium ion such as propargyl silanes **248** for access to allenyl substituted lactams **249** (Scheme 36B) and bis-TMS-acetylene **250** for the synthesis of alkynyl substituted isoindolinones **251** (Scheme 36C).

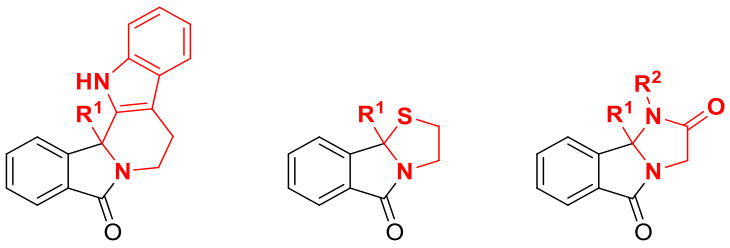


Scheme 36. Proposed addition of silyl-enol ethers (A), propargyl silanes (B) and bis-TMS-acetylene (C) for access to functionalised isoindolinones.

3. Chapter 3: Intramolecular Trapping of *N*-acyliminium Ions

3.1. Introduction

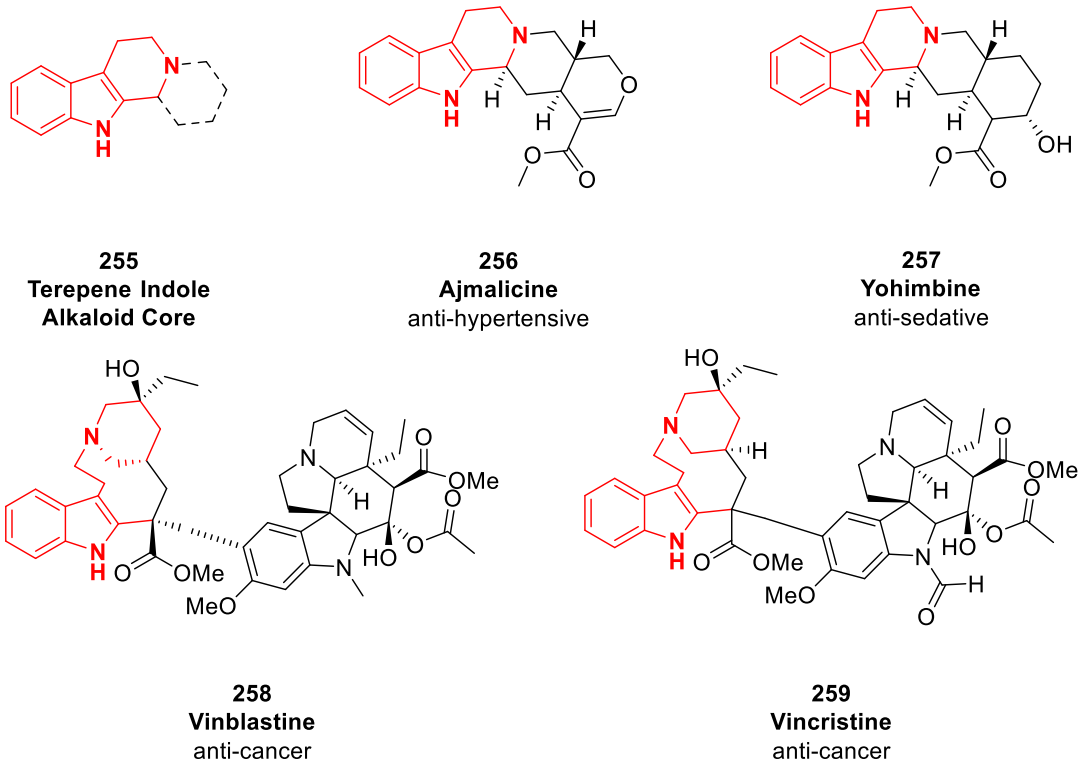
A continuing underlying aim of this project is to develop new synthetic routes to novel compounds that contain medicinally relevant motifs embedded within them. The reason for this is two-fold; there are no or very limited synthetic routes to access these compounds and so this method provides a modular, sustainable, and scalable approach for medicinal chemists wishing to access these compounds for screening. Secondly, given their novelty, any potential medicinal benefits of these compounds are completely unknown so this "plug and play" approach allows substituents to be varied with ease. In particular, targeting γ-lactam derivatives fused with medicinally relevant cores **252-254** is of particular interest (Figure 24).



252 **253** **254**

Figure 24. Target scaffolds within this chapter.

Alkaloids are an important class of naturally occurring and medicinally relevant scaffolds that are prevalent in both natural products and pharmaceuticals.[91] In particular, terpene indole alkaloids **255** are a highly important sub-class of alkaloid, with a diverse range of medicinal properties (Scheme 37). Ajmalicine **256** is a marketed and prescribed anti-hypertensive drug used for the treatment of high blood pressure while Yohimbine **257** is used withing the veterinary industry as an anti-sedative.[92] Vinblastine **258** and Vincristine **259** are both used in chemotherapy courses for treatment of a wide range of cancers. The diverse nature of alkaloids makes them highly desirable targets for synthetic chemists.



Scheme 37. Medicinally relevant terpene indole alkaloids.

Thiazolidines and *N*(acyl),S-acetals are important structural motifs that feature in a range of drugs and natural products (Figure 25). Perhaps the most famous occurrence of this motif is in Penicillin **260**; part of the β-lactam antibiotic family.[93] The isoindolinone motif also features within the HIV-1 reverse transcriptase inhibitor **261**. These compounds bind to an allosteric site of HIV-1 reverse transcriptase, blocking its ability to replicate, and their activity towards this has been reported.[94]

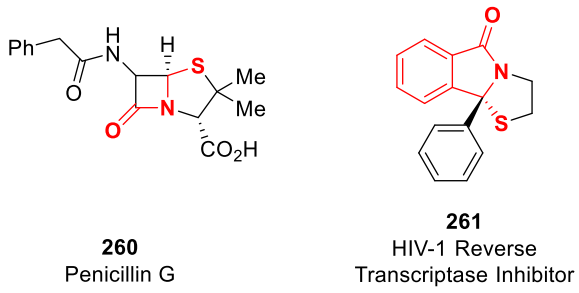


Figure 25. Naturally occurring and pharmacologically relevant *N*(acyl),S-acetals

Furthermore, given the structural similarities between the two scaffolds, any potential anti-microbial properties are yet to be discovered (Figure 26). Penicillin core **262**

contains a β-lactam core fused to a thiazolidine ring system, while **263** contains a γ-lactam core fused to a thiazolidine ring system.

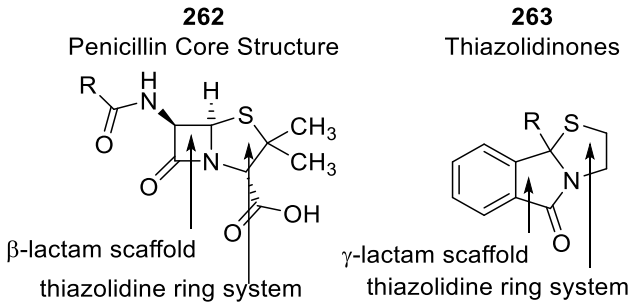
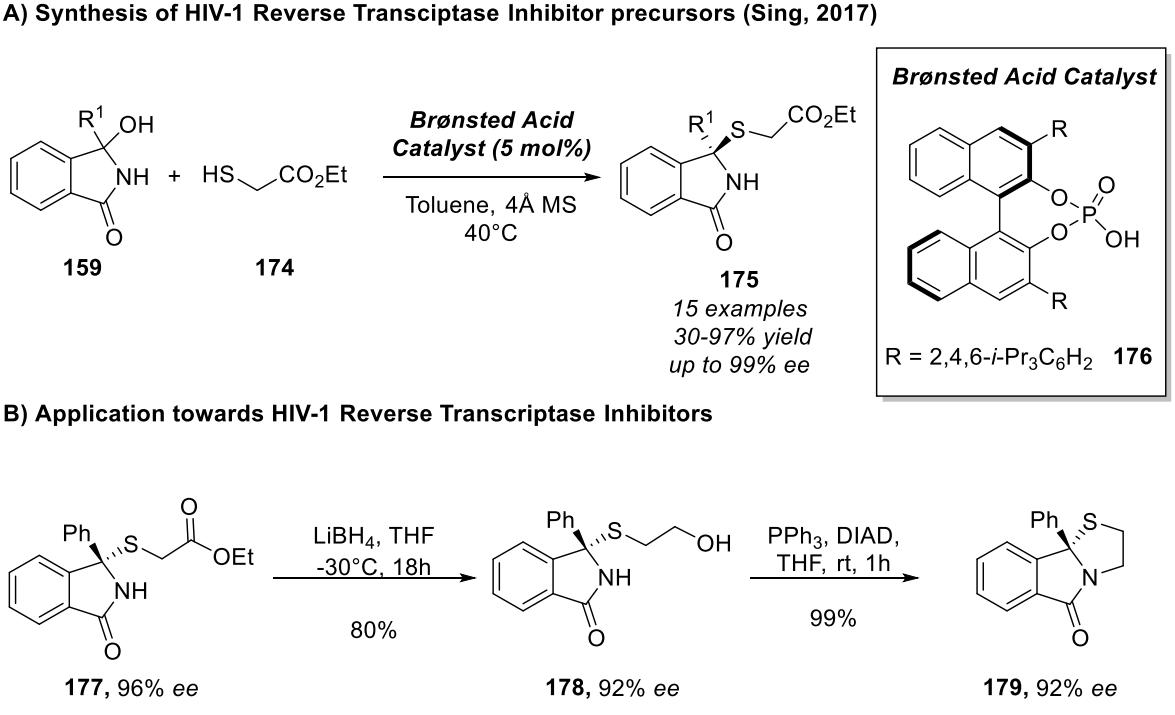


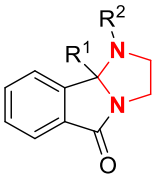
Figure 26. Structural similarities between Penicillin and 275.

Despite their medicinal properties, the only reported method within the literature to access **179** derivatives is *via* a multi-step approach reported by Singh (Scheme 38).[80] Utilising a Brønsted acid catalyst **176**, the authors used *N*-acyliminium ion chemistry to first access **177**, which was then reduced to **178** and subjected to Mitsunobu conditions to access **179**. While successful, it does require multiple steps and harsh reaction conditions therefore demonstrating the need for a milder and more modular approach to access these scaffolds.

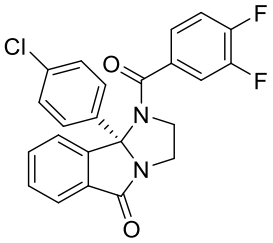


Scheme 38. Synthesis of 277 reported by Singh and their application towards the synsthesis of 281.[80]

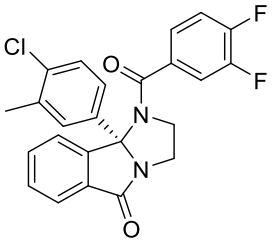
In addition to *N*(acyl),*S*-acetals **179**, fused γ-lactam-imidazolidinone scaffolds **264** have also shown promising medicinal properties (Figure 27). Lindsley identified **265** as a muscarinic acetylcholine receptor negative allosteric modulator (NAM) active a nanomolar quantities with a high CNS penetration.[95] Due to a long half-life of **265**, the same group then reported how **266** has similar potency but with a much needed shorter half-life.[96]. Furthermore, in addition to their CNS penetrating NAM properties, compound **267** has also shown promising anti-viral properties.[97]



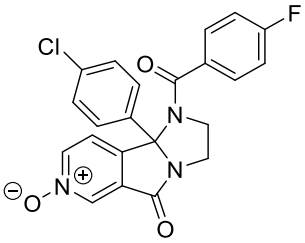
264
fused γ-lactam imidazoline scaffold



265
CNS Modulator
IC_{50} = 300 nm



266
Muscarinic aceylycholine receptor

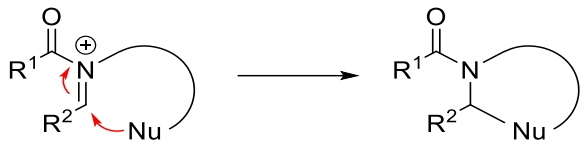


267
RSV Inhibitor
EC_{50} = 0.25 μm

Figure 27. Medicinally relevant fused γ-lactam imidazoline scaffolds.

The medicinal chemists working on the projects described above however did not have a single, modular approach to access these compounds. Instead, they were synthesised *via* multi-step (>4) syntheses from pre-functionalised starting materials. Thus, these medicinally chemistry programs demonstrate how medicinal chemists require modular access to a large library of these compounds with subtle structural modifications which can be rapidly screened.

Given the success of the calcium catalysed intermolecular trapping of *N*-acyliminium ions, it was proposed that these highly reactive intermediates **268** could be trapped intramolecularly to access fused cyclic scaffolds **269** bearing multiple heteroatoms analogous to those described above (Scheme 39).



Scheme 39. Schematic represenation for the intramolecular trapping of *N*-acyliminium ions to access ring systems.

Depending on the nucleophile employed, this methodology would provide access to those highly desirable, aforementioned saturated heterocyclic γ-lactam derivatives **252-254** with either a thiazolidine **253**, 4-imidazolidinone **254** and tryptoline **252** core (Figure 28).

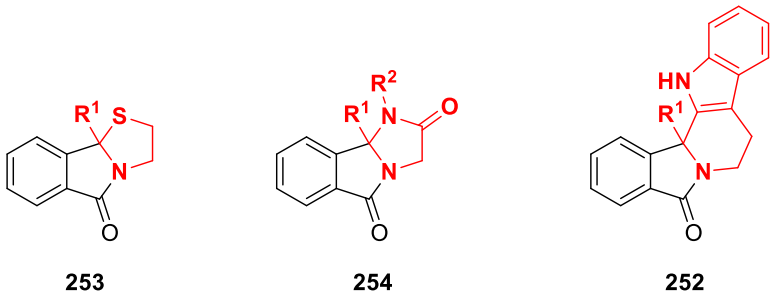
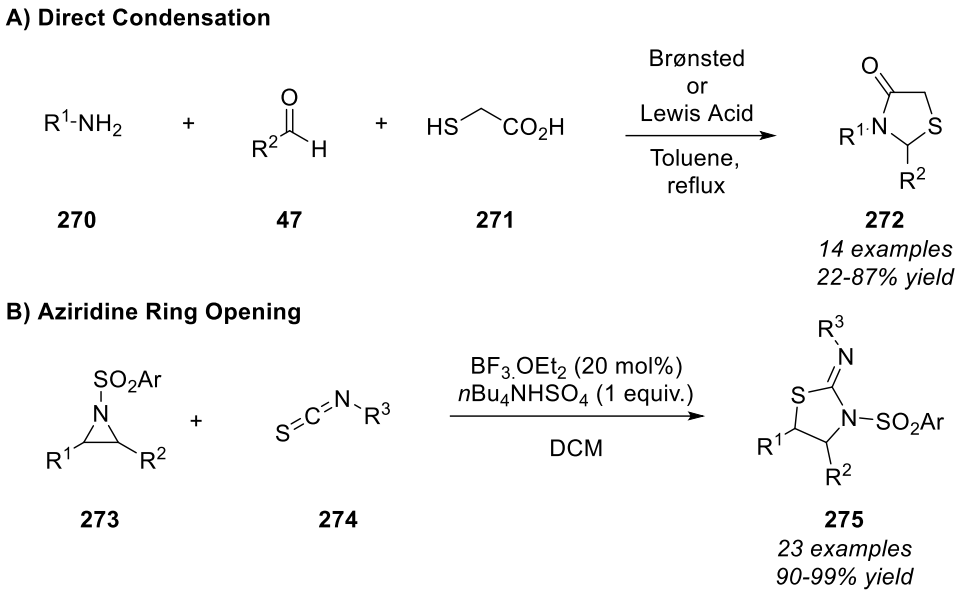


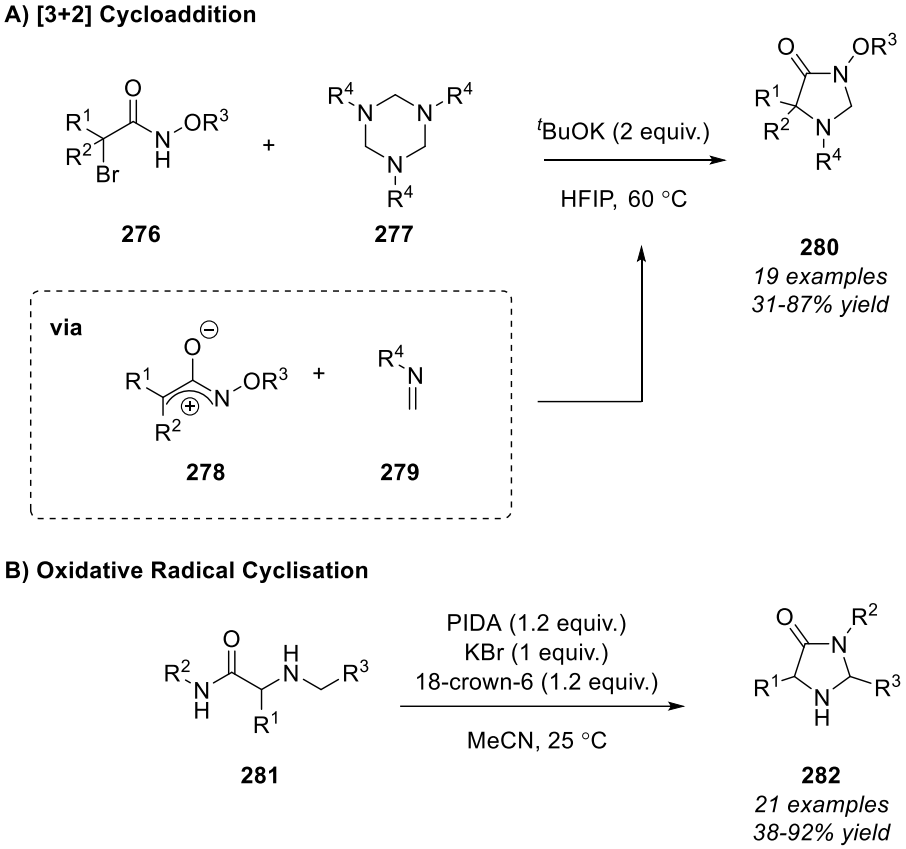
Figure 28. Desired target γ-lactam scaffolds accessed using *N*-acyliminium ion chemistry with the key heterocyclic cores accessed highlighted in red.

Furthermore, the heterocyclic cores embedded within the γ-lactam motif are not trivial to access with limited modular reports for their assembly, and a literature survey offering little inspiration. While tryptoline derivatives **252** can be accessed *via* a traditional Pictet-Spengler reaction,[98] thiazolidine and 4-imidazolidinones are much less trivial to access. Thiazolidine[99] derived cores **272** can be accessed *via* a direct condensation from amines **270**, aldehydes **47** and thioglycolic acid **271** in the presence of a Brønsted or Lewis acid (Scheme 40A).[100] Alternatively, Lewis acid meditated ring opening of aziridines **273** with isothiocyanates **274** also provides access to these scaffolds as reported by Ghorai in 2016 (Scheme 40B).[101] However, a direct condensation requires harsh reaction conditions with limited functional group tolerance, and aziridine ring opening requires access to niche pre-functionalised starting materials.



Scheme 40. Selected examples for the synthesis of thiazolidine scaffolds *via* either a direct condensation (A) or Lewis acid mediated ring opening of aziridines (B).

There are also very few reports on the synthesis of imidazolidinone cores **254**. In 2018, Sun reported a [3+2]-cycloaddition between azaoxallyl cations **278** generated from α-halohydroxamates **276**, with 1,3,5-triazines **277** as formaldehyde derived imine precursors **279** to access 4-imidazolidinone scaffolds **280** (Scheme 41A).[102] In 2021, Hulme reported an oxidative radical cyclisation of benzylamine derived Ugi products **281** to afford 4-imidazolidinone scaffolds **282** (Scheme 41B).[103] This method offers an extra point of diversity to that reported by Sun however it does require stoichiometric quantities of multiple reagents.



Scheme 41. Synthesis of 4-imidazolidnones *via* a [3+2] cycloaddition (A) or oxidative radical cyclisation (B).

Given the limited approaches to access these highly desirable heterocycles utilisation of *N*-acyliminium ion chemistry, using a mild and sustainable Earth abundant Lewis acid catalysis *via* a tethered nucleophile approach poses a desirable route to access these scaffolds.

3.1.1. Intramolecular Trapping of *N*-acyliminium Ions

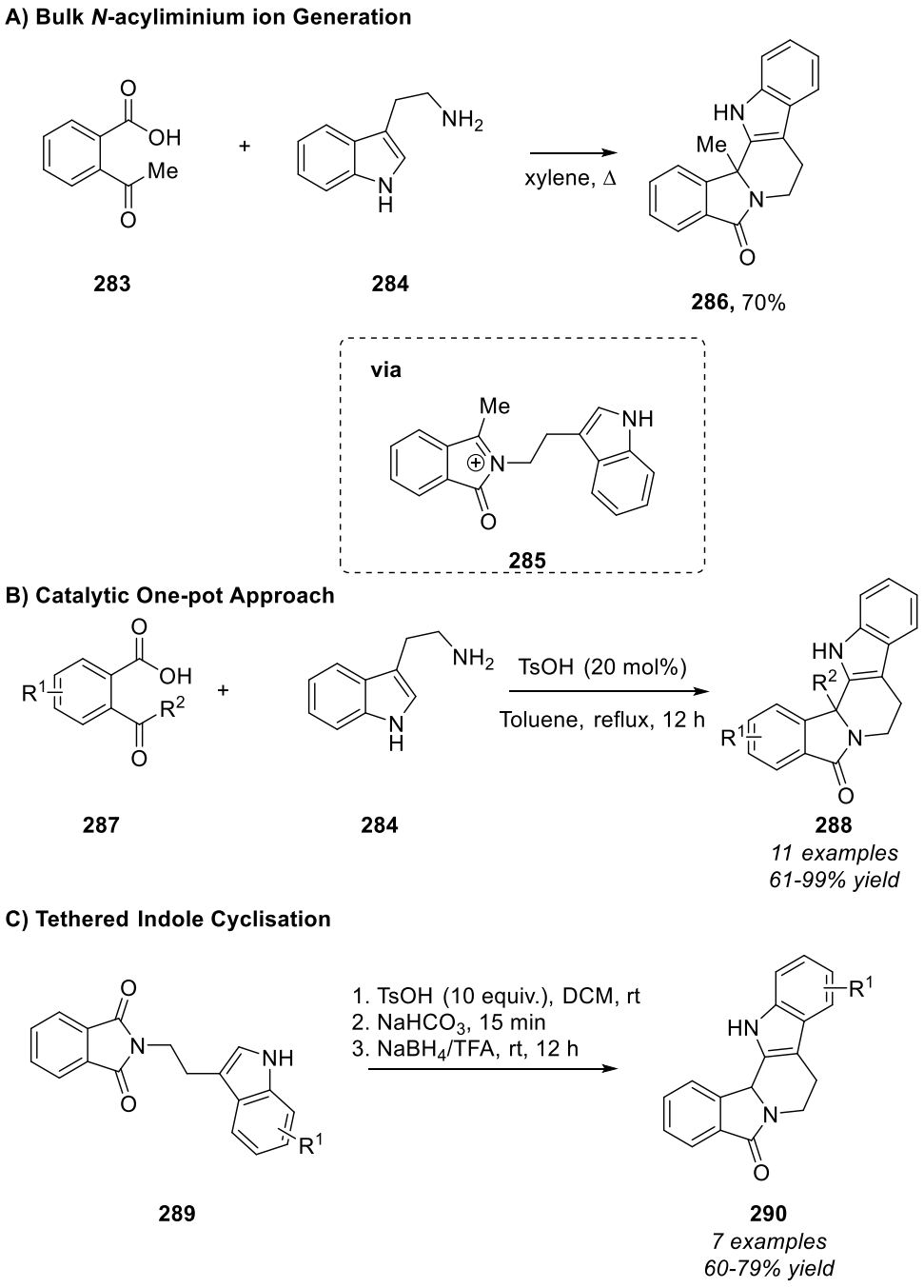
The intramolecular trapping of *N*-acyliminium ions is well documented and has been extensively studied and reviewed.[58] Much of the early work within this field focused on intramolecular cyclisations with carbon-based nucleophiles while more recent developments have focussed on performing this transformation catalytically.

Furthermore, intramolecular trapping of *N*-acyliminium ions with tethered heteroatomic nucleophiles has been far less explored with a noticeable gap within the field. Specifically, trapping isoindolinone derived *N*-acyliminium ions with tethered nucleophiles is of particular interest.

3.1.1.1. Carbon Nucleophiles

The intramolecular trapping of *N*-acyliminium ions with carbon derived nucleophiles has been well explored. Alkenes, alkynes, enolates, allylsilanes, furans and thiophenes have all demonstrated excellent reactivity towards *N*-acyliminium ions.[56]

In particular, *N*-acyliminium ion chemistry has shown continuous promise for accessing terpene indole alkaloids. Traditionally, they can be accessed by a one pot condensation between **283** and tryptamine **284** at high temperature over a prolonged reaction time with the reaction proceeding *via* **285** (Scheme 42A).[104] More recent, milder and catalytic examples include that reported by Wang (Scheme 42B).[105] They reported the reaction of **287** and **284** in the presence of catalytic TsOH provides access to terpene indole alkaloids **288** in good yield. However, they report a competing elimination side reaction which is a frequent occurrence in one pot strategies. To circumvent this, the indole can be tethered to the isoindolinone core **289**, prior to *N*-acyliminium formation, resulting in the reaction taking place in a more controlled manner, as reported by Ramathanan (Scheme 42C). However, this method still requires multiple steps with super-stoichiometric quantities of acid, base and reducing agent all used within this transformation.

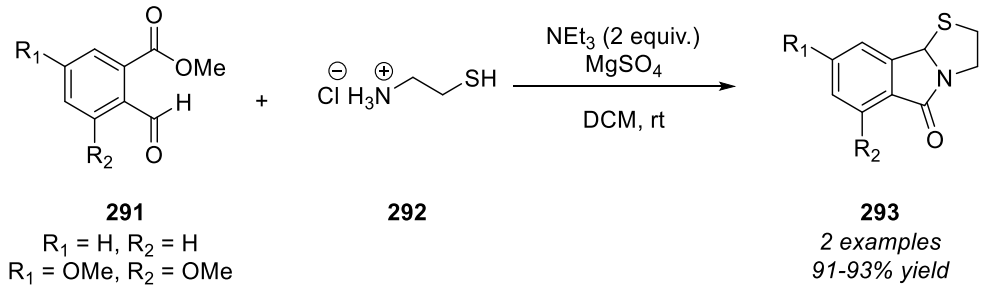


Scheme 42. Intramolecular trapping of *N*-acyliminium ions with indole *via* bulk *N*-acyliminium ion generation (A), catalytic one-pot methodology (B) or by a tethered indole cyclisation approach (C).

3.1.1.2. Sulfur Nucleophiles

In comparison to carbon nucleophiles, the intramolecular trapping of *N*-acyliminium ions with sulfur containing nucleophiles has been much less explored.

A one-pot intramolecular cyclisation strategy was disclosed by Ramstom in 2013 who reported the reaction of **291** and cysteamine salt **292** in the presence of NEt_3 and $MgSO_4$ to afford products **293** in excellent yield (Scheme 43).[106] However this method requires access to pre-functionalised starting material **291** and does not allow access to C3-substituted products.



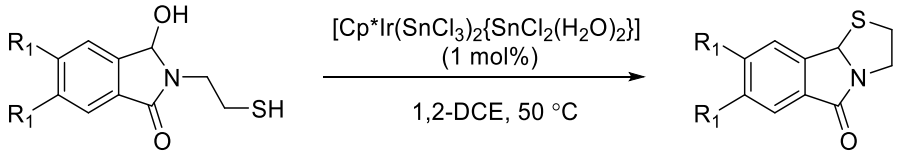
291
R_1 = H, R_2 = H
R_1 = OMe, R_2 = OMe

292

293
2 examples
91-93% yield

Scheme 43. One-pot synthesis of 293.

In 2014, Roy reported an iridium-tritin complex to be a suitable catalyst in activating 3-hydroxyisoindolinones **294** towards *N*-acyliminium ion formation (Scheme 44).[88] They were able to apply this to the cyclisation of a tethered thiol for access to *N*(acyl),S-acetals **295** in excellent yield. However, this was only applied to a very limited substrate scope of two examples using a non-commercially available catalyst with no C3- substitution patterns reported.



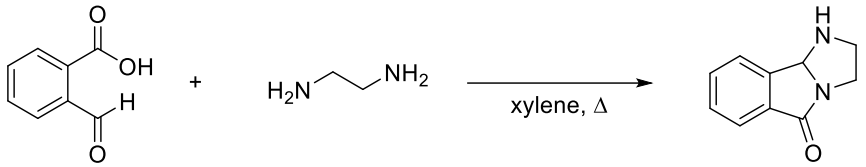
294
R_1 = H, H; Me, Me

295
2 examples
89-95% yield

Scheme 44. Intramolecular cyclisation of tethered thiols using an iridium-tritin catalyst.[88]

3.1.1.3. Nitrogen Nucleophiles

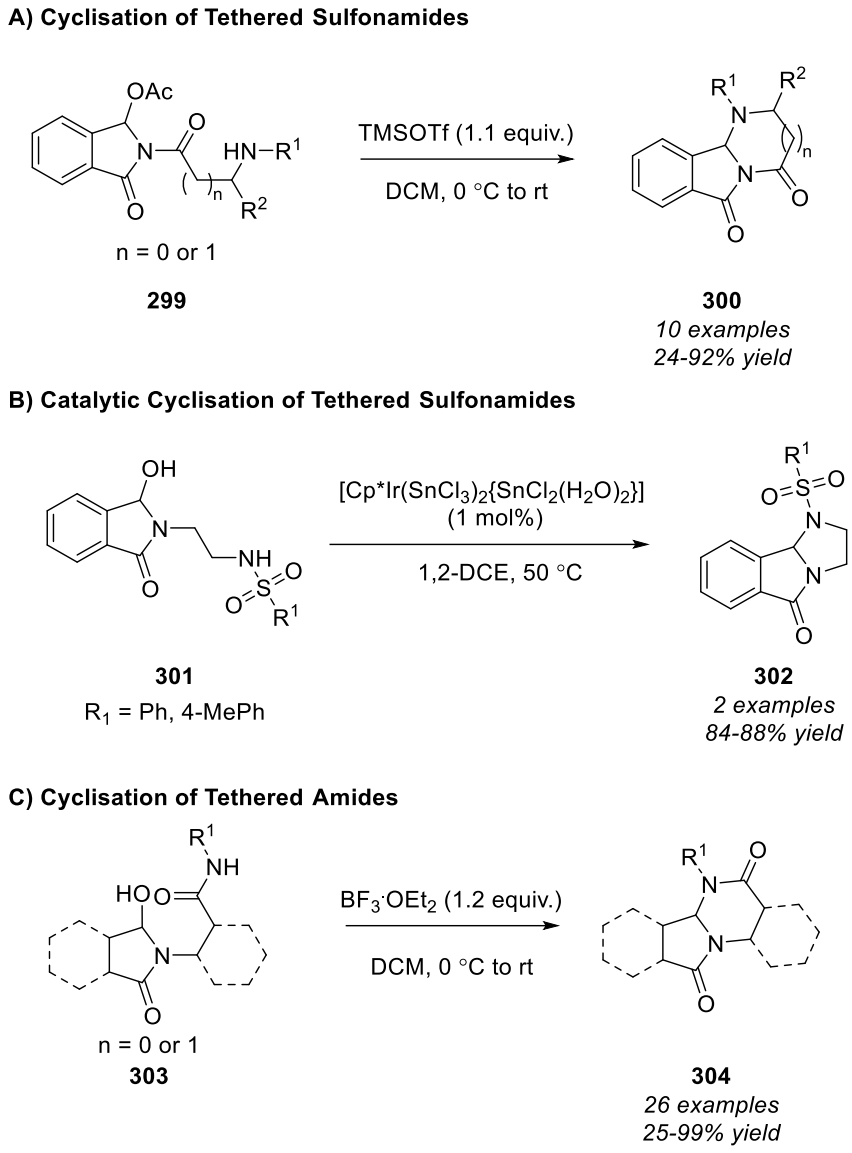
Intramolecular trapping of *N*-acyliminium ions with a tethered nitrogen derived nucleophile can be achieved through a variety of transformations.[107] In particular, accessing isoindolinone fused imidazoline-derived scaffolds is of interest due to there being limited unified and modular methods for their synthesis. The simplest and most traditional route to access these scaffolds is *via* a direct condensation between **296** and ethylenediamine **297** generating bulk *N*-acyliminium ion *in-situ* (Scheme 45).[97] However, this requires high reaction temperatures and only provides access to a single compound **298**.



296 **297** **298**, 70%

Scheme 45. One-pot condensation of 296 and 297 to afford 298.

To incorporate more functionality, Lewis acid mediated generation of *N*-acyliminium ions and subsequent trapping with a tethered nitrogen nucleophile have been reported (Scheme 46). In 2009, Yamada reported a TMSOTf mediated cyclisation of **299** derivatives with a tethered sulfonamide derivative (Scheme 46A).[108] The authors propose that the presence of a sulfonamide over other nitrogen containing nucleophiles proves crucial to the yields due to a S=O stabilising effect of the *N*-acyliminium ion. In addition to the cyclisation of thiols, Roy also showed their methodology could be applied to the cyclisation of sulfonamides **301** affording products **302** in excellent yields (Scheme 46B).[88] In 2021, Saikia reported a $BF_3.OEt_2$ mediated cyclisation of 3-hydroxyisoindolinones with a tethered amide **303** for access to **304** derived scaffolds (Scheme 46C).[109] A variety of tethered amides could be cyclised under these conditions providing access to substituents that were utilised in further diversification.

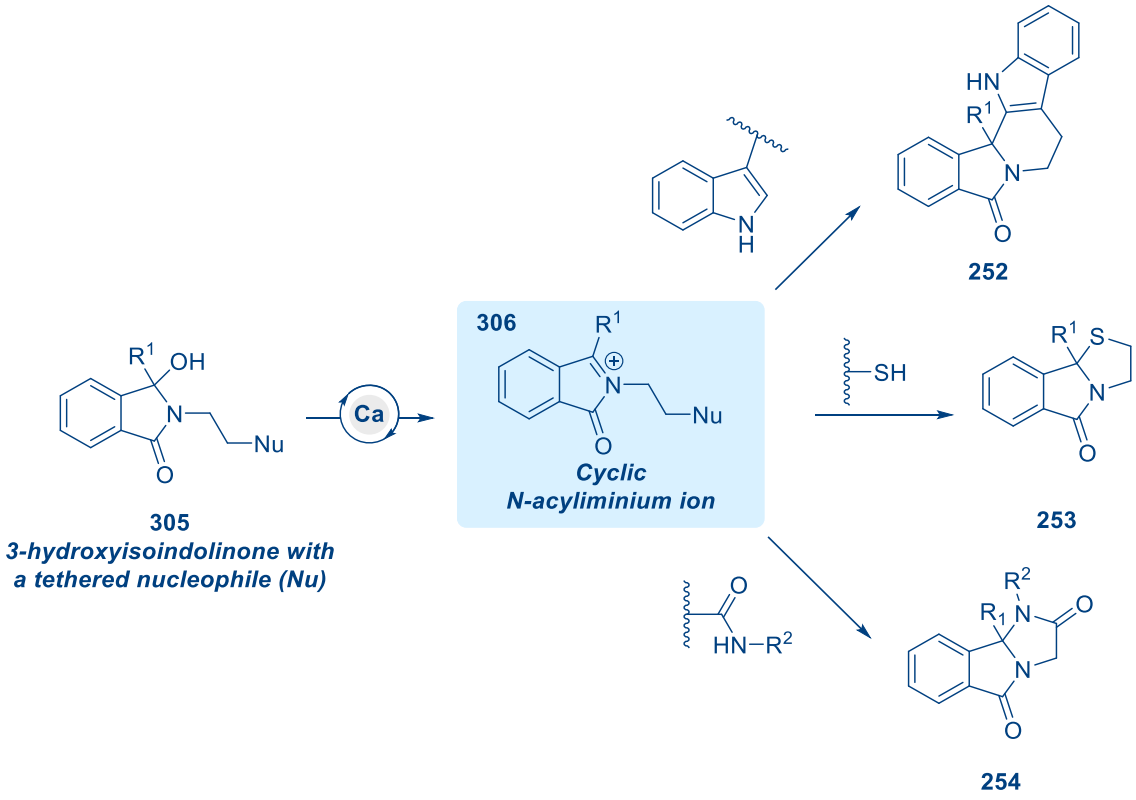


Scheme 46. Lewis acid mediated generation of *N*-acyliminium ions and subsequent trapping with various tethered nitrogen nucleophiles.

While all elegant transformations, the methods described above either require stoichiometric quantities of Brønsted or Lewis acid, use non-commercially available catalysts or are subjected to harsh reaction conditions. Furthermore, the compounds synthesised are C3-substituted, with no examples of 3,3-disubstituted products.

3.2. Aims

The aim of this chapter is to study the calcium catalysed intramolecular trapping of *N*-acyliminium ions with a range of carbon and heteroatomic nucleophiles. It has already been shown that calcium catalysed generation of *N*-acyliminium ions and subsequent trapping with external indoles, thiols, and amides is a highly effective method to access fuctionalised lactams. In this chapter the aim is to develop a library of 3-hydroxyisoindolinones with tethered nucleophiles **305** and subject them to a calcium catalysed dehydrative cyclisation to access novel fused polycyclic γ-lactam derivatives **252**-**254**.



Scheme 47. Proposed calcium catalysed dehydrative cyclisation of 3-hydroxisoindolinones with a tethered nucleophile.

3.3. Results & Discussion

The work described in this section has been published:[110]

A. J. Basson, N. R. Halcovitch and M. G. McLaughlin, *Chem. Eur. J.,* 2022**, 28**, e202201107.

3.3.1. Sulfur Nucleophiles

Firstly, the intramolecular cyclisation reaction with tethered thiols to access complex fused thiazolidinone scaffolds **253** was explored (Figure 29). The trapping of *N*-acyliminium ions with external thiols was successful and it was reasoned an intramolecular variant could be developed with relative ease. As there were no literature examples for the synthesis of 3-hydroisoindolinones with an *N*-tethered thiol, a reproducible and modular synthetic approach to access these starting materials first had to be developed. A continuing drive of this project is to produce scaffolds derived from accessible starting materials and with this in mind, it was postulated the 3-hydroxyisoindolinones could be accessed in a two-step procedure derived from phthalic anhydride **307**, cysteamine **308** and Grignard/organolithium reagents **309** (Figure 29).

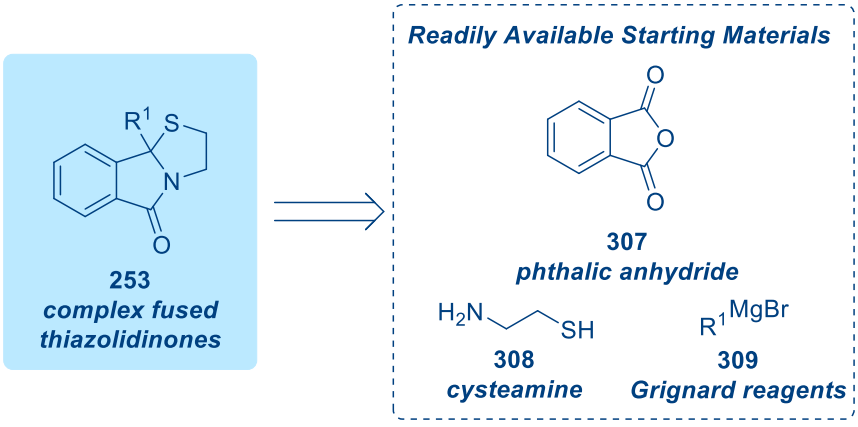
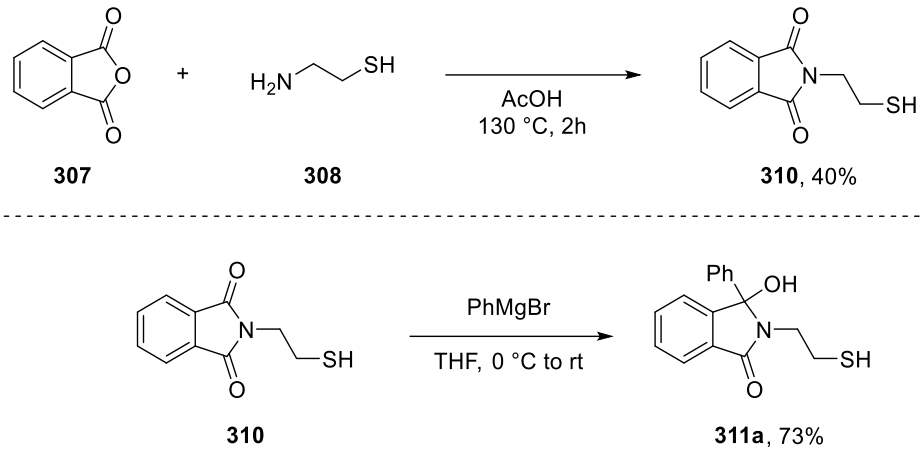


Figure 29. Retrosynthetic strategy for the synthesis of complex fused thiazolidinone scaffolds.

310 was synthesised on a multi-gram scale by condensation of phthalic anhydride **307** with cysteamine **308** in good yield (Scheme 48). Treatment of **310** with 3 equivalents of phenyl magnesium bromide in THF resulted in the formation of **311a** in good yield (Scheme 48).



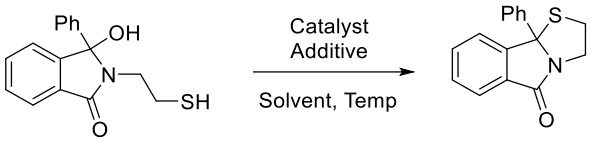
307 308 **310**, 40%

310 **311a**, 73%

Scheme 48. Initial synthesis of 311a.

Optimisation of a calcium catalysed dehydrative cyclisation of **311a** to afford thiazolidinone **312a** was then studied (Table 17). It began by subjecting **311a** to the previously optimised conditions which have been shown to catalytically generate *N*-acyliminium ions.[52] Pleasingly, the reaction rapidly proceeded to completion in high yield (entry 1). Lowering the catalyst loading to 1 mol% had little effect, again producing the desired product in high yield (entry 2). Moving away from halogenated solvents and switching to ethyl acetate, which is considered more green,[111] again had no effect on reaction outcome (entry 3). Given the evident rapid nature of the reaction, whether the temperature of the reaction could be lowered was then studied. To accommodate the decreasing solubility of both **311a** and the $Ca(NTF_2)_2$/$n$$Bu_4NPF_6$ in 1,2-DCE and EtOAc at lower temperatures, attention was then turned to HFIP. The reaction proved just as rapid using 10 mol% of catalyst in HFIP at the lower temperature of 40°C (entry 4). Lowering the catalyst loading further had no effect on yield (entry 5). Decreasing the temperature to room temperature saw a longer reaction time (entry 6) but nonetheless had no effect on yield. To improve functional group applicability, it was decided that running the reaction over a significantly shorter period would be more favourable. Therefore entry 5 was deemed optimal conditions.

Table 17. Optimisation of dehydrative cyclisation with tethered thiol.



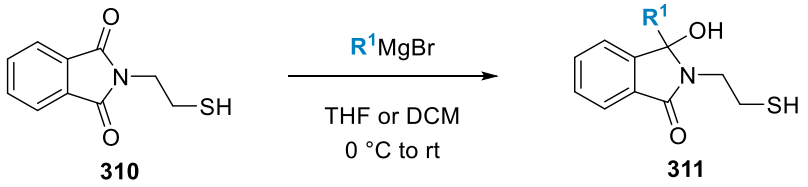
311a 312a

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield[a]
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80ºC	1,2-DCE	15 min	94%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80°C	1,2-DCE	15 min	90%
3	$Ca(NTF_2)_2$	nBu_4NPF_6	1 mol%	80°C	EtOAc	15 min	96%
4	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	40°C	HFIP	15 min	96%
5	**$Ca(NTF_2)_2$**	**nBu_4NPF_6**	**1 mol%**	**40°C**	**HFIP**	**15 min**	**94%**
6	$Ca(NTF_2)_2$	nBu_4NPF_6	1 mol%	rt	HFIP	12 h	94%

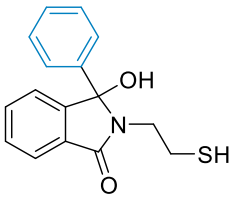
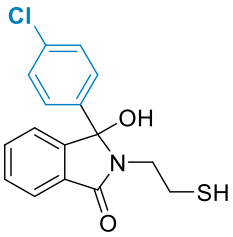
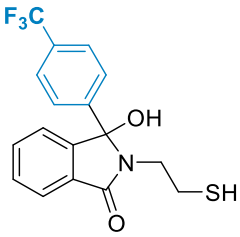
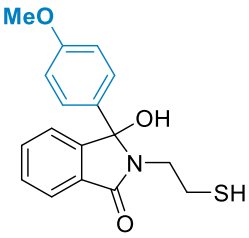
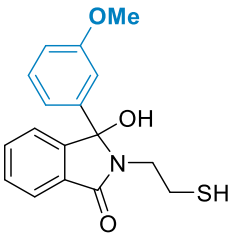
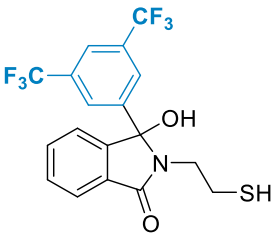
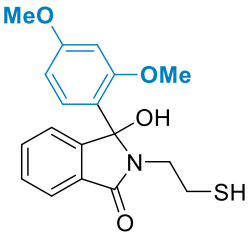
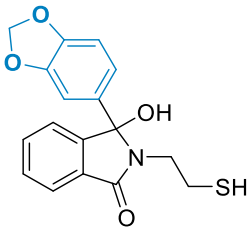
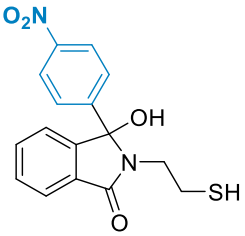
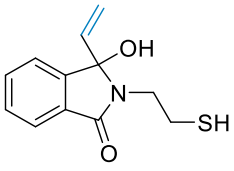
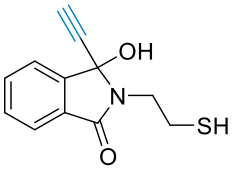
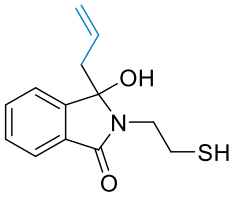
[a] Isolated yields

With the optimised conditions in hand, a library of novel 3-hydroxyisoindolinone scaffolds with a tethered thiol **311** were synthesised (Table 18). In addition to the phenyl-substituted isoindolinone **311a**, halo-substituted **311b**, electron-deficient **311c** and electron-rich substituted isoindolinones **311d** were all synthesised in good yields. *Meta*-substituted aromatics were also tolerated with both electron-rich **311e** and electron-deficient **311f** moieties synthesised in good yield. *Ortho*-substituted aromatics **311g** were tolerated, albeit in diminished yield which could be attributed to the increased steric crowding around the C3 carbon. Attempted synthesis of the acetal-protected isoindolinone **311h** formed a complex inseparable mixture under these conditions with much of the degradation occurring during the formation of the Grignard. When employing the 4-nitro derived Grignard, only trace amounts of product **311i** was observed. Finally, the synthesis of vinyl- **311j**, alkynyl- **311k** and allyl-substituted **311l** isoindolinones was attempted with little success, with all reactions forming complex mixtures and rapid degradation pathways regardless of solvent (THF or DCM) employed.

Table 18. Synthesis of 3-hydroxyisoindolinones with a tethered thiol *via* Grignard addition.

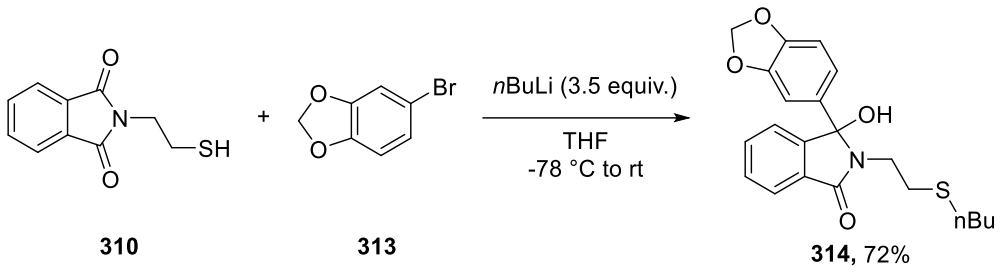


310 → **311**

 **311a**, 73%	 **311b**	 **311c**, 81%
 **311d**, 80%	 **311e**, 80%	 **311f**, 89%
 **311g**, 46%	 **311h**, complex mixture	 **311i**, trace
 **311j**	 **311k**	 **311l**

Dissatisfied with the library of compounds that could be accessed by Grignard addition, whether addition of aryl-lithium species behaved similarly was then studied in an attempt to further develop the library. In particular, incorporating heterocyclic

substituents, which had currently failed using Grignard chemistry were of particular interest. A lithiation of **313** under standard lithiation addition conditions was attempted first (Scheme 49). However, alkylated product **314** was isolated as the major product in 72% yield.

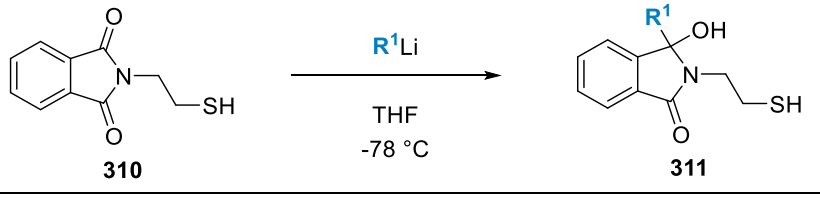


310 **313** **314**, 72%

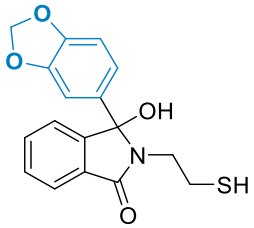
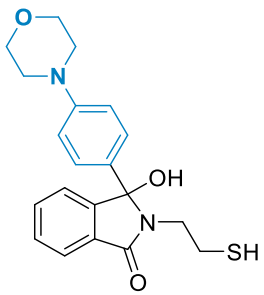
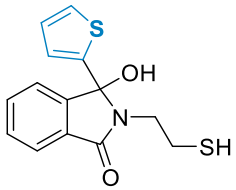
Scheme 49. S-alkylated major product 314 isolated when reaction is warmed to room temperature.

To prevent thiol alkylation ocurring, holding the reaction at -78 °C until full consumption of the starting material followed by quenching the reaction at -78 °C was attempted. This proved successful affording acetal substituted **311m** and morpholine substitued **311n** products in synthetically useful yields (Table 19). Addition of 2-thienyllithium for the synthesis of **311o** was unsuccessful with a complex mixture obtained.

Table 19. Synthesis of 3-hydroxyisoindolinones with a tethered thiol *via* Lithium-halogen exchange.

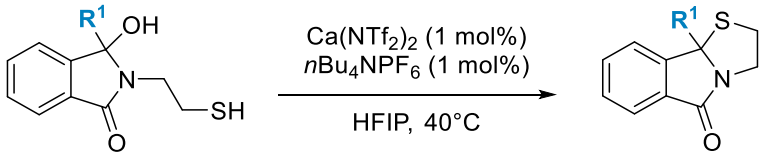


310 **311**

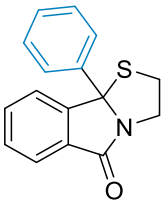
		
311m, 31%	**311n**, 21%	**311o**

The library of 3-hydroxyisoindolinones was then subjected to the calcium catalysed optimised conditions (Table 20). In addition to the optimised phenyl-substituted isoindolinone **312a**, halo-substituted **312b** and electron-deficient **312c** isoindolinones were well tolerated in almost quantitative yields. Electron-donating groups **312d** again work well in excellent yields. Various aromatic substitution patterns were also well tolerated with 3,5- **312e**, 2,4- **312f** and 3-substituted **312g** aromatics, each with varying electronics, all worked well in excellent yields. Furthermore, acetal-derivate **312h** was synthesised in good yield. Lewis basic heterocycles, such as morpholine were less tolerated affording product **312i** in diminished yield. This can be attributed to the nitrogen of the morpholine becoming protonated thereby shutting down the catalytic pathway.

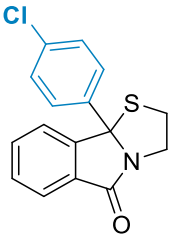
Table 20. Calcium catalysed dehydrative cyclisation with a tethered thiol.



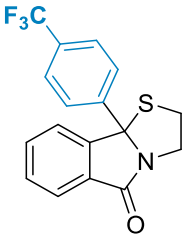
311 312



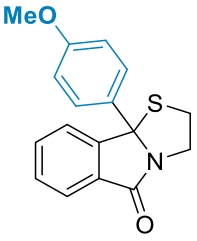
312a, 94%



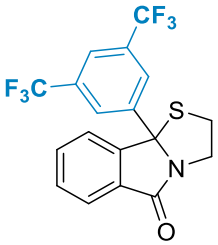
312b, 92%



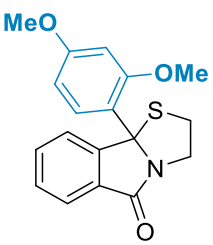
312c, 95%



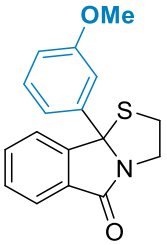
312d, 95%



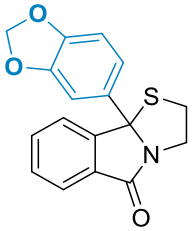
312e, 94%



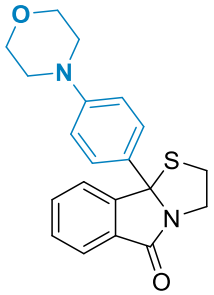
312f, 95%



312g, 94%



312h, 83%



312i, 28%[a]

[a] Starting material reisolated in 53% yield

3.3.2. Carbon Nucleophiles

Due to the success of the addition of external indoles into *N*-acyliminium ions, whether the same reactivity would apply for tethered indoles was then studied. Again, a modular synthetic strategy to realise this goal was devised and it was anticipated that complex fused di-aza-polycyclics **252** could be assembled from readily available phthalic anhydride **307**, tryptamine **284**, and a Grignard reagent **309** (Figure 30).

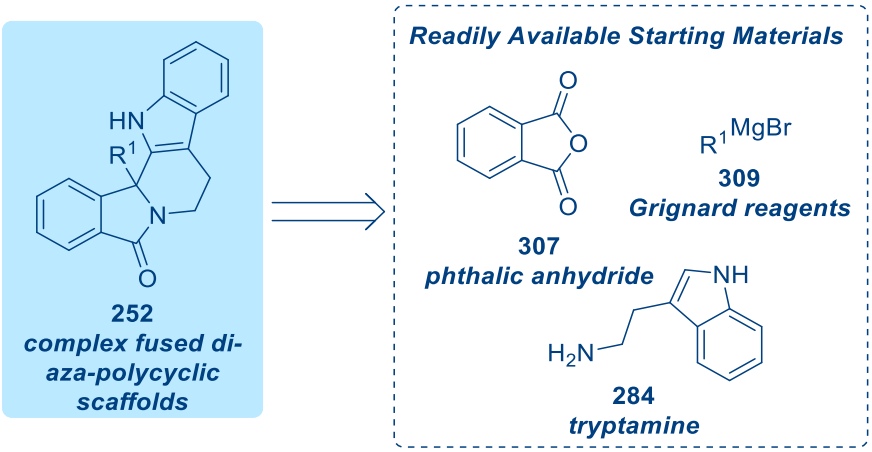
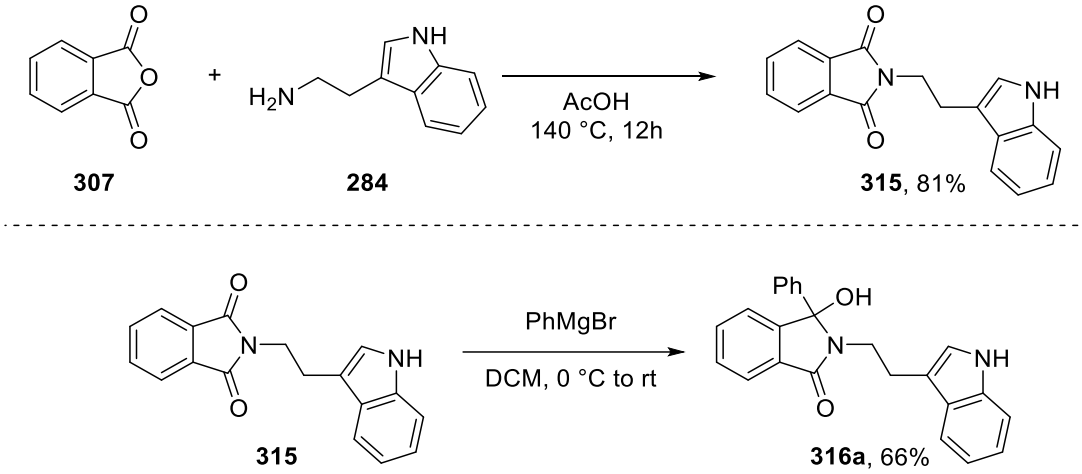


Figure 30. Retrosynthetic strategy for the synthesis of complex fused di-aza-polycyclic scaffolds.

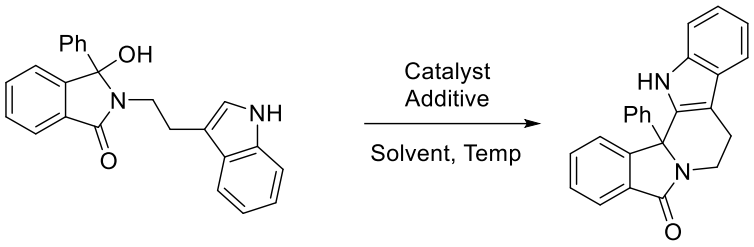
The study began by synthesising **315** on a multi-gram scale by condensation of phthalic anhydride **307** with tryptamine **284** affording common starting material **315** in good yield (Scheme 50). Addition of phenylmagnesium bromide to **315**, afforded 3-hydroxyisoindolinone **316a** with a tethered indole again in good yield (Scheme 50).



Scheme 50. Initial synthesis of 316a in a two step approach.

Optimising the intramolecular cyclisation reaction then began (Table 21). Subjecting **316a** to the previously optimised conditions afforded desired product **317a** in excellent yield (entry 1). Changing the solvent and lowering the temperature, as with the tethered thiols, had little effect on yield (entry 2). Finally lowering the catalyst loading to 1 mol% had no effect on yield affording **317a** in excellent yield (entry 3) which were then deemed optimal conditions.

Table 21. Optimisation of dehydrative cyclisation with tethered indole.



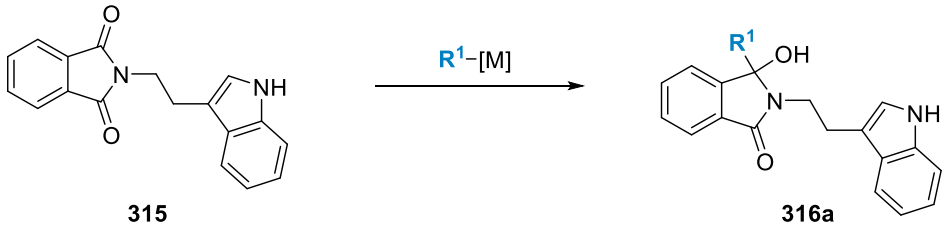
316a **317a**

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield[a]
1	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80ºC	1,2-DCE	1 h	84%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	40°C	HFIP	1 h	80%
3	**$Ca(NTF_2)_2$**	**nBu_4NPF_6**	**1 mol%**	**40°C**	**HFIP**	**1.5 h**	**89%**

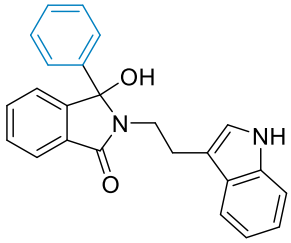
[a] Isolated yields

With the reaction optimised, a range of 3-hydroxyisoindolinones with a tethered indole was synthesised (Table 22), using a similar procedure used for the tethered thiols. As well as the phenyl substituted 3-hydroxy-isoindolinone **316a**, electron-deficient aromatics were also well tolerated providing **316b** and **316c** in good yields. Electron-rich aromatic groups also worked in moderate yield affording **348d** along with both 3,5- and 2,4-aromatic substitution patterns affording **316e** and **316f** respectively. Finally, a range of heterocycles were well tolerated, providing furan substituted **316g,** acetal protected **316h** and pyridyl substituted **316i** scaffolds in good yield.

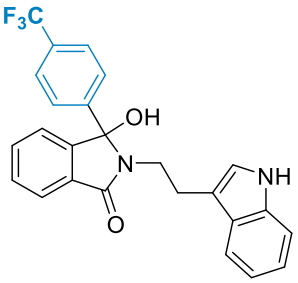
Table 22. Synthesis of 3-hydroxyisoindolinones with a tethered indole *via* either Grignard or organolithium addition.



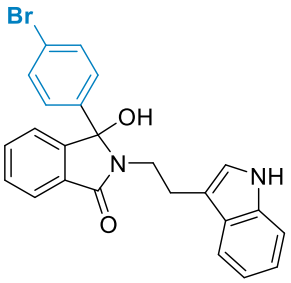
315 **316a**



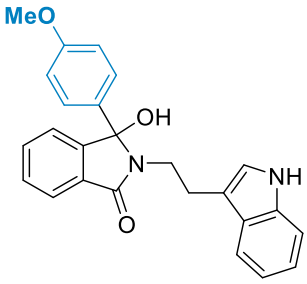
316a, 66%[a]



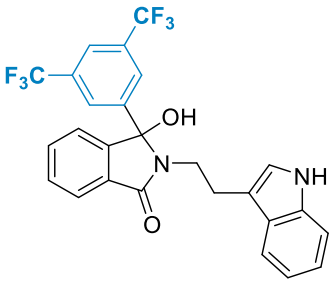
316b, 67%[a]



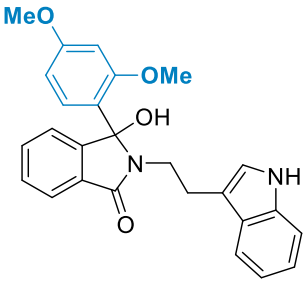
316c, 64%[a]



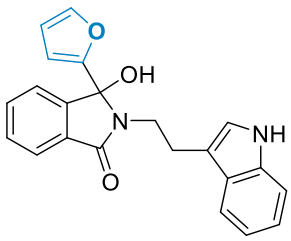
316d, 44%[a]



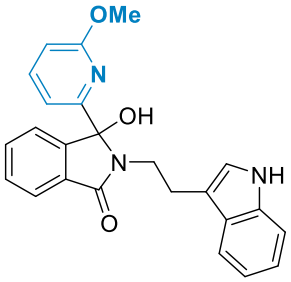
316e, 54%[a]



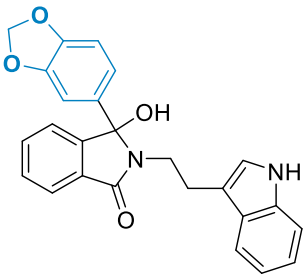
316f, 85%[a]



316g, 54%[b]



316h, 54%[b]



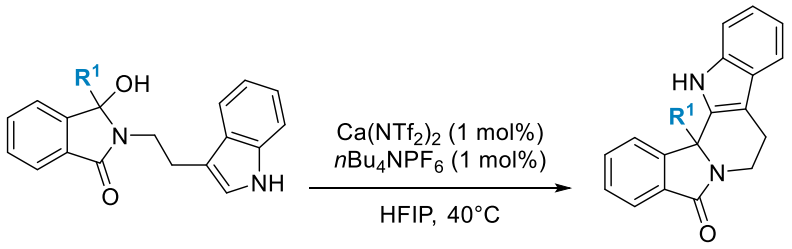
316i, 76%[b]

[a] R^1MgBr addition in DCM, 0°C to rt
[b] R^1Li addition in THF, -78°C to rt

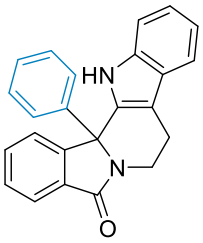
With a diverse library of 3-hydroxyisoindolinones with a tethered indole synthesised, they were then subjected to the optimised conditions (Table 23). This proved to be largely successful with all compounds synthesised in Table 22 affording the complex fused di-aza-polycyclic scaffolds **317**. The reaction proved to be unaffected by

electronics with both electron-deficient **317b, 317c** and electron-rich aromatics **317d** working in high yields. *Meta*-substituted aromatics were again well tolerated affording **349e** in high yield. The 2,4-substituted aromatic afforded product **317f** in slightly diminihsed yield which can be attributed to the increased steric demand. Furan substituted product **317g** could also be accessed in high yield. Extending the substrate scope towards **317h** and **317i** proved to be slightly more troublesome. Subjecting **317h** to the optimised conditons saw no reaction take place after 16 h with unreacted starting material isolated. It was postulated that the Lewis basic pyridyl substituent was indeed poisoning the Brønsted acidic calcium/HFIP catalyst **318** (Figure 31). To circumvent this, the catalyst was tuned by changing the solvent to 1,2-DCE thereby inhibiting the Brønsted acidic pathway and utilising the calcium complex solely as a Lewis acid **319**. This proved to be successful and afforded product **317h** in high yield. Finally, the cyclisation of **317i** proved to be slower than the optimised 1h and required 12h for full consumption of starting material. This resulted in the formation of product **317i** in a much lower yield due to the partial deprotection of the acetal under the acidic conditions employed.

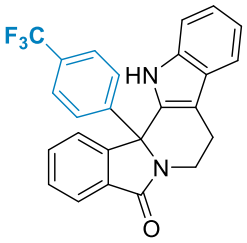
Table 23. Calcium catalysed dehydrative cyclisation with a tethered indole.



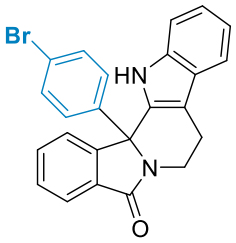
316 **317**



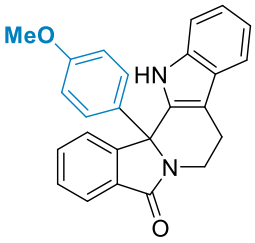
317a, 89%



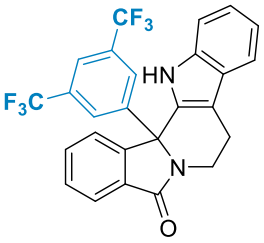
317b, 87%



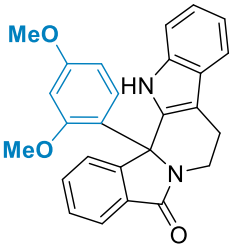
317c, 94%



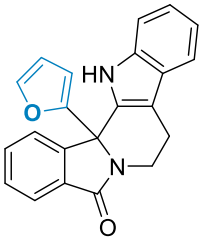
317d, 92%



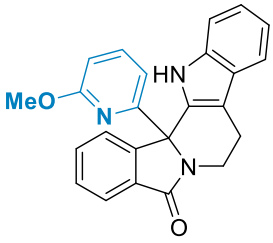
317e, 91%



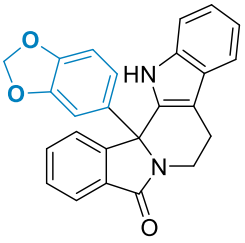
317f, 70%



317g, 82%



317h, 93%[a]



317i, 21%

[a] reaction carried out in 1,2-DCE at 80 °C using 1 mol% catalyst

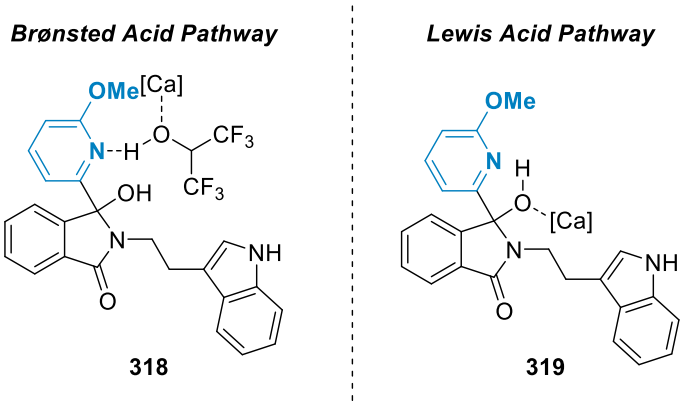


Figure 31. Differing pathways for generation of the *N*-acyliminium ion *via* either a Brønsted acidic Ca/HFIP complex or a Lewis acidic calcium species.

To further demonstrate the "druglikeness" of the library of compounds, a crystal of **317a** was grown and anyalysed (Figure 33). A study has shown that molecules with increasing sp^3 character may lead to an increase in clinical success.[112] While the aromatic nature of the compounds may provide vital π-π stacking interactions, the 3-dimensional "bowl" shape that the compound adpots may provide access to additional protein-ligand interactions which would otherwise not be accessible with flat compounds. This shows that not only do these scaffolds contain a large amount of functionality, but are also engineered to occupy 3-dimensional spaces, owing to the incorporation of the C3 functionality.

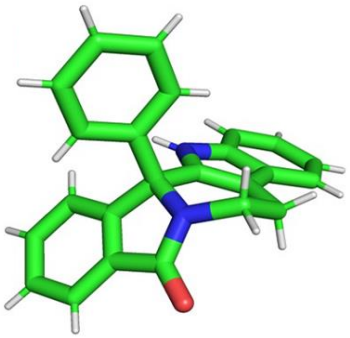


Figure 32. Crystal structure of 317a.

3.3.3. Nitrogen Nucleophiles

Next, whether tethered nitrogen containing nucleophiles would cyclise and display similar reactivity under the same conditions was then studied. However, it was anticipated these would be more troublesome due to their differing reactivity to carbon and sulfur nucleophiles in the intermolecular variant of this transformation. Firstly, imidazolidinone motifs **254** were targeted and it was again reasoned that a modular synthetic route could be devised to access these scaffolds from readily available starting materials: phthalic anhydride **307**, amines **320**, Grignard reagents **309** and the amino acid glycine **321**. (Figure 33).

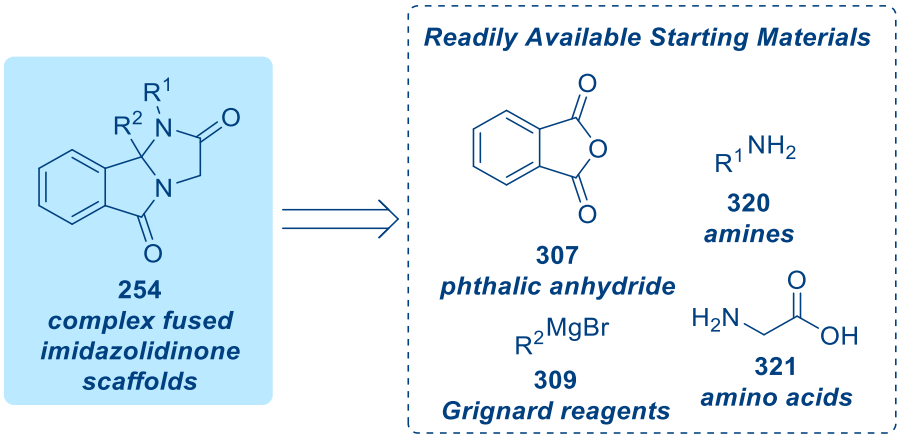
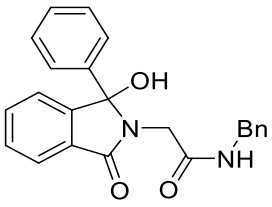


Figure 33. Retrosynthetic strategy for the synthesis of complex fused imidazolidinone scaffolds.

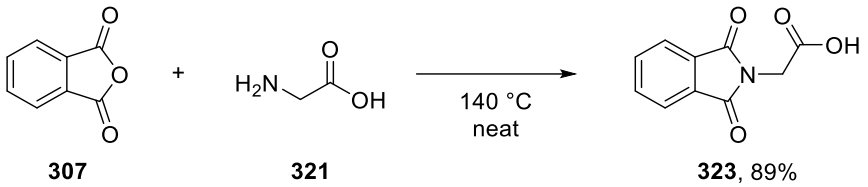
Following the above retrosynthetic strategy, **325a** was identified as the initial target compound for optimisation (Figure 34).



325a

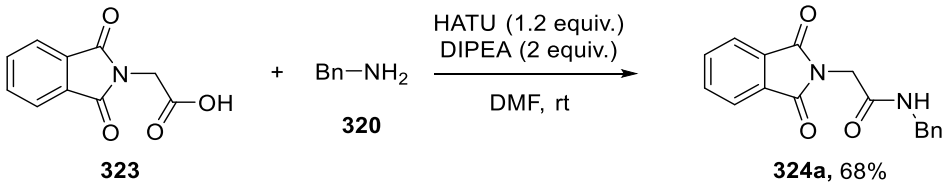
Figure 34. Target compound for optimisation.

Assembly of **325a** began by synthesising **323** on a multi-gram scale from phthalic anhydride **307** and glycine **321,** in a condensation reaction which was high yielding (Scheme 51).



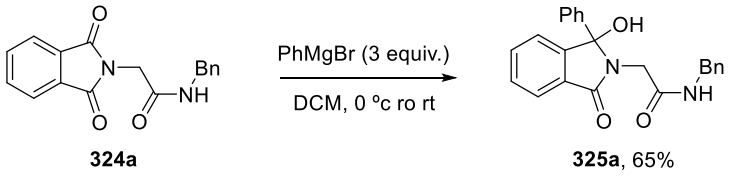
Scheme 51. Synthesis of 323 by condensation of phthalic anhydride with glycine.

An amide coupling reaction between **323** and benzylamine **320** using HATU as the coupling reagent afforded product **324a** in good yield (Scheme 52).



Scheme 52. Synthesis of 324a by amide coupling reaction.

Addition of phenyl magnesium bromide into **324a** afforded target compound **325a** in good yield (Scheme 53).

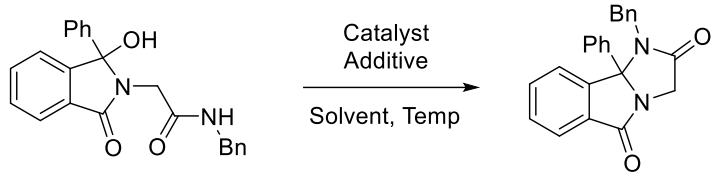


Scheme 53. Synthesis of 325a by Grignard addition.

With target precursor **325a** synthesised, optimisation began for the calcium catalysed dehydrative cyclisation (Table 24). Subjecting **325a** to conditions previously optimised for the addition of amides to *N*-acyliminium ions afforded product **326a** in low yield (entry 1). Changing the solvent to EtOAc resulted in decomposition of the starting material (entry 2). Furthermore, subjecting **325a** to the same conditions utilised for tethered thiols and indoles also proved unsuccessful with decomposition of the starting material being observed (entry 3). Given 1,2-DCE had shown the most promising results, further optimisation using this solvent was attempted to improve the yield. Increasing

the temperature to 100 °C significantly improved the reaction outcome affording product **326a** in excellent yield (entry 4). Additionally, increasing the catalyst loading saw improved reaction time with little effect on yield (entry 5). Finally, the reaction did not proceed at the elevated temperature without the catalyst, even at prolonged reaction times (entry 6). Due to the elevated temperatures employed and significantly shorter reaction times, entry 5 was deemed optimal conditions.

Table 24. Optimisation of dehydrative cyclisation with a tethered amide.

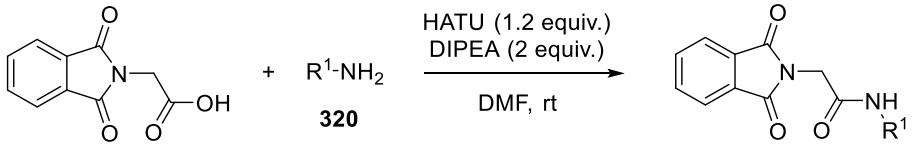


325a **326a**

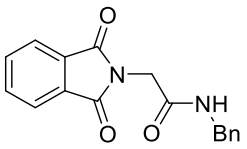
Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80ºC	1,2-DCE	12 h	29%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80°C	EtOAc	12 h	decomp
3	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40°C	HFIP	12 h	decomp
4	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	100°C	1,2-DCE	4 h	88%
5	**$Ca(NTF_2)_2$**	**nBu_4NPF_6**	**20 mol%**	**100°C**	**1,2-DCE**	**15 min**	**85%**
6	-	-	-	100 °C	1,2-DCE	12 h	n.r

With the reaction optimised, the multi-step assembly of a library of **325a** derivatives was then studied by firstly performing an amide coupling reaction on **323** (Table 25). In addition to the benzyl substituted amide **3241a,** other benzyl substituted amides could also be coupled affording **324b** in good yield. Both acyclic **324c** and cyclic amides **324d** could also be accessed in good yields. Finally, aniline derived amines were also coupled affording amides **324e** and **324f** in moderate yields.

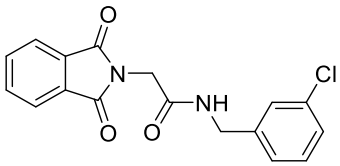
Table 25. Synthesis of phthalimide derivatvies with a tethered amide by an amide coupling reaction.



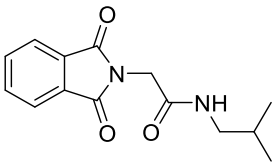
323 **324**



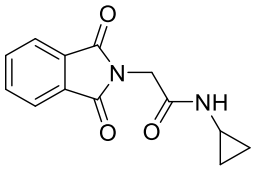
324a, 68%



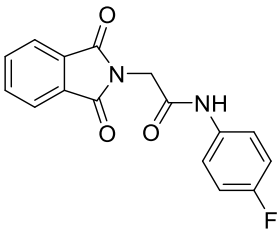
324b, 59%



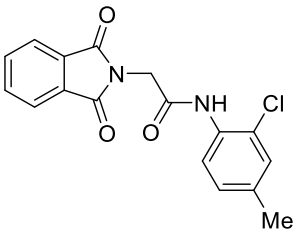
324c, 67%



324d, 71%



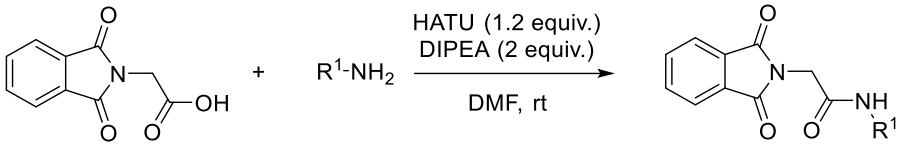
324e, 51%



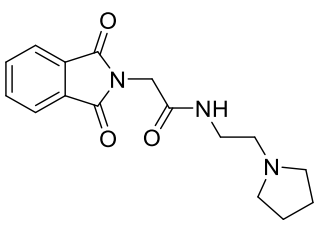
324f, 46%

More complex, heterocyclic derived amines were also attempted under the amide coupling conditions (Table 26). However, the pyrrolidine derived amide **324g** could not be synthesised under the conditions employed with unreacted starting material re-isolated. A complex mixture was obtained when attempting to synthesise the 2-chloro-pyridine substituted product **324h**. Trace amounts of pyrimidine substituted product **324i** was synthesised however the product could not be isolated in synthetically useful yield.

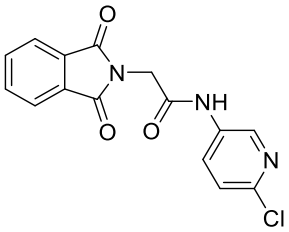
Table 26. Unsuccessful subtrates in the amide coupling reaction.



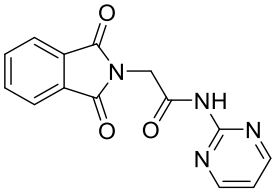
323 **320** **324**



324g



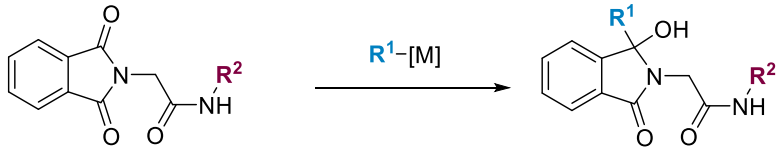
324h



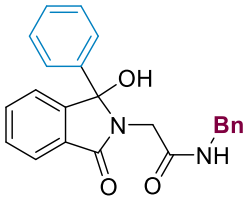
324i

With a library of phthalimide derivatives **324** synthesised with varying tethered amides, the scaffolds were then subjected to Grignard or organolithium addition conditions for the synthesis of a range of 3-hydroxyisoindolinones with a tethered amide **327** (Table 27). In addition to the phenyl-substituted product **327a**, electron deficient products **327b** and **327c** were also synthesised in good yield. Electron-rich product **327d** was also synthesised in good yield. Finally, both oxygen and nitrogen derived heterocyclic products were also synthesised in synthetically useful yields affording **327e** and **327f** respectively. To complete the starting material library, phenyl magnesium bromide was then added to the range of amides synthesised in Table 25 affording products **327g**-**327k** all in moderate, synthetically useful yields.

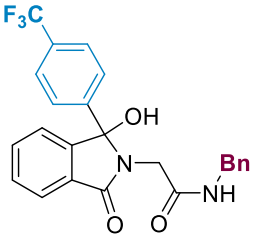
Table 27. Synthesis of 3-hydroxyisoindolinones with a tethered amide *via* either Grignard or organolithium addition.



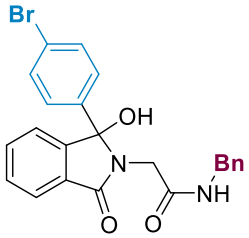
324 **327**



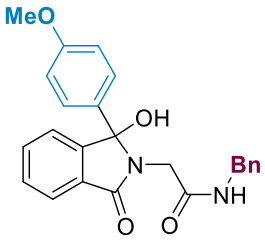
327a, 65%[a]



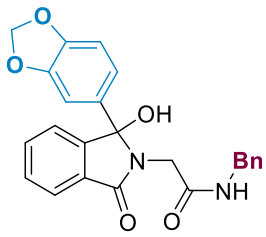
327b, 64%[a]



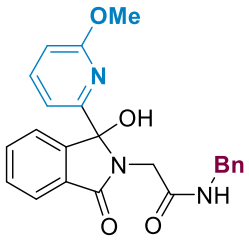
327c, 44%[a]



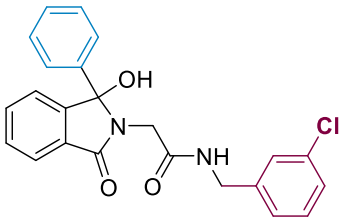
327d, 60%[a]



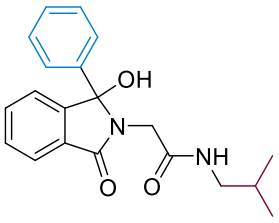
327e, 38%[b]



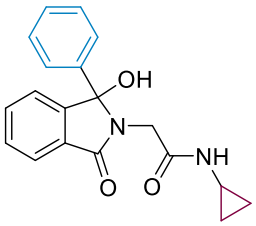
327f, 15%[b]



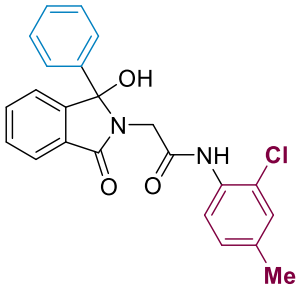
327g, 56%[a]



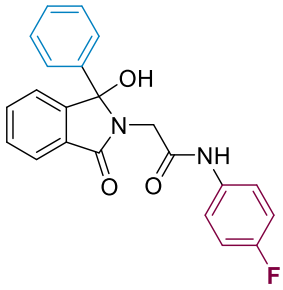
327h, 59%[a]



327i, 40%[a]



327j, 42%[a]

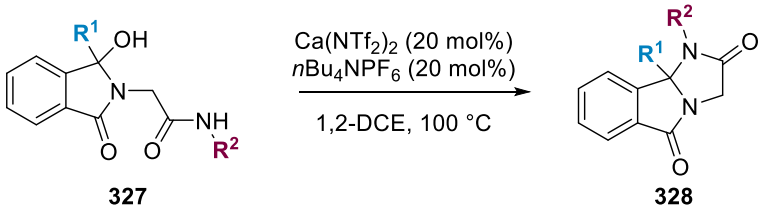


327k, 63%[a]

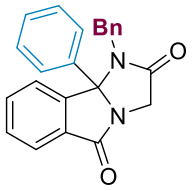
[a] R_1MgBr addition in DCM, 0°C to rt
[b] R_1Li addition in THF, -78°C to rt

With the library of 3-hydroxyisoindolinones synthesised, they were then subjected to the optimised conditions for the synthesis of a library of imidazolidinones **328** (Table 28). The variation with respect to the 3-position of the isoindolinone, derived from the Grignard reagent was first investigated. In addition to phenyl substation **328a**, electron-withdrawing groups were also tolerant affording **328b** and **328c** in good yields. Electron-rich aromatics were also tolerated affording **328d** in high yield. Oxygen and nitrogen derived heterocycles were also well tolerated affording **328e** and **328f** respectively in good yields. The reactivity derived from the amine of the initial amide coupling reaction was then studied. Further benzyl substituted amides could be cyclised in good yield affording **328g** along with both acyclic and cyclic saturated derivates affording **328h** and **328i** again in good yield. Finally aniline derived amides could also be cyclised affording **328j** and **328k** albeit in slightly lower yields compared to the other examples. This can be attributed to the lower nucleophilicity of the aniline amides which resulted in a less clean reaction and trace impurities being detected.

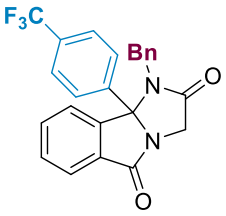
Table 28. Calcium catalysed dehydrative cyclisation with a tethered amide.



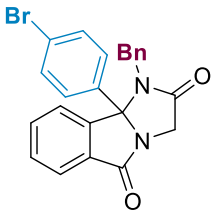
327 **328**



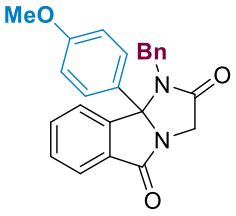
328a, 82%



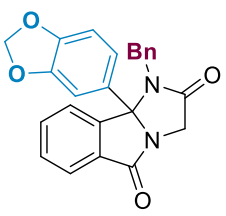
328b, 72%



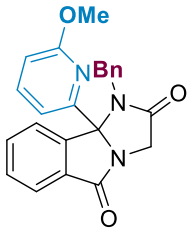
328c, 86%



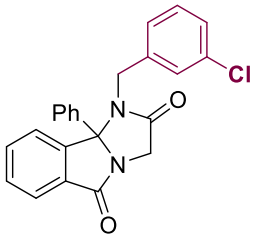
328d, 80%



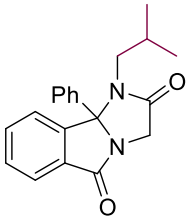
328e, 84%



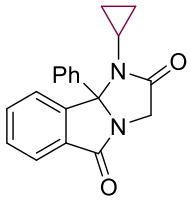
328f, 75%



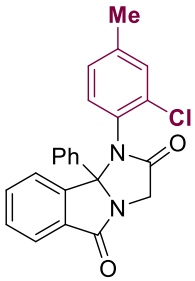
328g, 81%



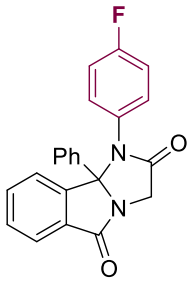
328h, 81%



328i, 82%



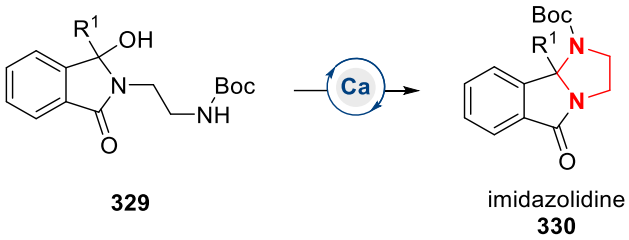
328j, 74%



328k, 53%

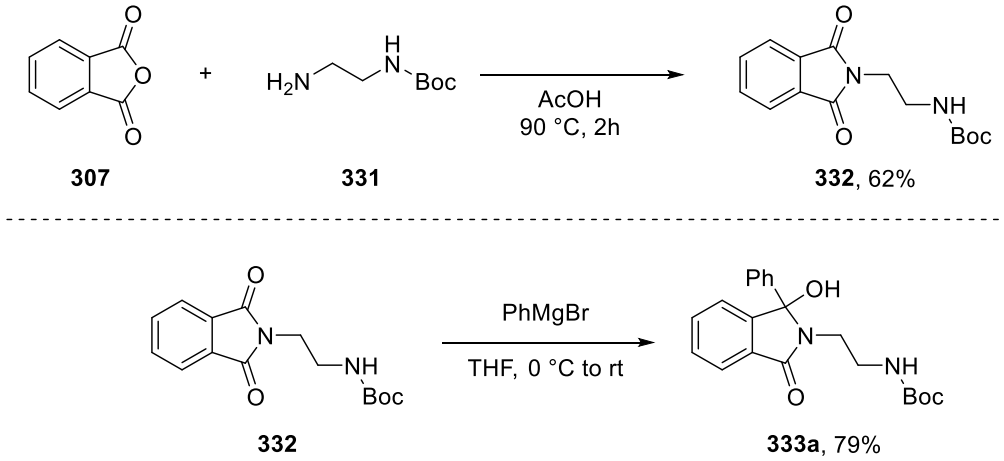
With a library of imidazolidinones synthesised, the cyclisation of tethered carbamate protected amines to access imidazolidines was then explored (Scheme 54). In particular, the cyclisation of the *N*-Boc carbamate derivative **329** to **330** was of interest due to

having an easily removable protecting group thereby offering scope for further functionalisation.



Scheme 54. Desired route to access imidazolidines.

A similar route to that used for the thiazolidines to access the 3-hydroxyisoindolinone precursor **333a** with an *N*-Boc protected tethered carbamate was used (Scheme 55)**.** An initial condensation with phthalic anhydride **307** and *N*-Boc-ethylenediamine **331** afforded phthalimide **332** in good yield. A subsequent Grignard addition to **332** afforded **333a** in good yield (Scheme 55).

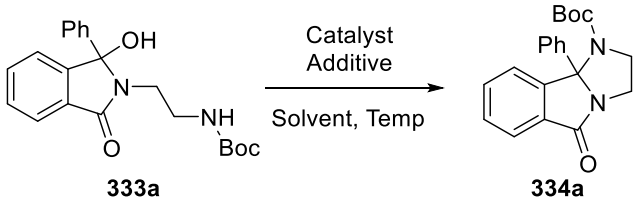


Scheme 55. Initial synthesis of 333a in a two-step approach.

With a large batch of **333a** synthesised, optimisation of the dehydrative cyclisation to afford **334a** was studied (Table 29). Subjecting **333a** to previously optimised conditions afforded product **334a** in moderate yield (entry 1) with the mass balance consisting of unreacted starting material. To drive the reaction to completion, the catalyst loading was increased which resulted in a decrease in yield (entry 2). Increasing the catalyst loading further resulted in a further decrease in yield (entry 3). Isolation of side-products provided some insight into this trend with *N*-Boc deprotection of **333a** occurring under

the reaction conditions, particularly at higher catalyst loadings. Furthermore, a possible thermal or Lewis acid catalysed *N*-Boc deprotection was also taking place aided by the catalyst. Thermal *N*-Boc deprotection alone is unlikely as temperatures of 150 °C are typically required without a catalyst.[113] Lowering the temperature to 60 °C saw a decrease in yield, with unreacted starting material remaining, in both 1,2-DCE and EtOAc (entries 4 and 5) while performing the reaction in MeCN inhibited the reaction fully (entry 6). Given the promising results obtained using HFIP earlier in this study, a range of conditions using HFIP as the solvent was then screened. Full consumption of **333a** was now observed using 10 mol% catalyst loading in HFIP at 60 °C with **334a** forming in moderate yield (entry 7). Decreasing the temperature to 40 °C saw an increase in yield (entry 8) and lowering the temperature further to room temperature had little effect on yield (entry 9). Lowering the catalyst loading to 1 mol% at 40 °C saw **334a** forming in almost quantitative yield (entry 10). Decreasing the temperature however resulted in a more sluggish reaction (entry 11). Due to its mildly acidic nature, a control reaction without catalyst was performed to ensure HFIP alone did not facilitate the cyclisation in which no reaction was observed (entry 12). Finally, the reaction was probed without addition of the additive whereby no reaction was observed (entry 13). In summary, entry 10 was deemed optimal conditions.

Table 29. Optimisation of dehydrative cyclisation with a tethered amide.



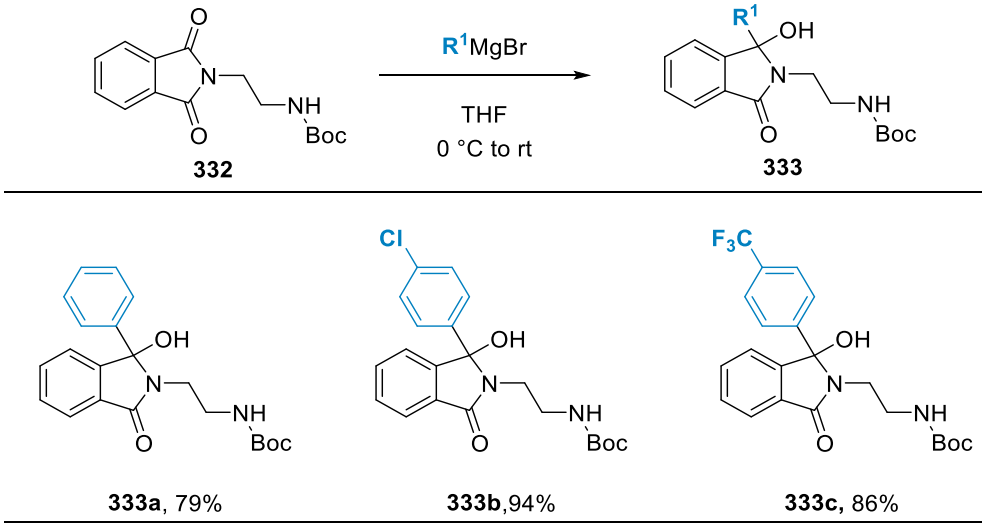
333a **334a**

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80ºC	1,2-DCE	12 h	61%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80°C	1,2-DCE	12 h	49%
3	$Ca(NTF_2)_2$	nBu_4NPF_6	20 mol%	80°C	1,2-DCE	12 h	42%
4	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	60°C	1,2-DCE	12 h	44%[a]
5	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	60°C	EtOAc	12 h	46%[a]
6	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	60°C	MeCN	12 h	n.r
7	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	60°C	HFIP	15 min	58%
8	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40°C	HFIP	12 h	79%
9	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	rt	HFIP	12 h	74%
10	**$Ca(NTf_2)_2$**	**nBu_4NPF_6**	**1 mol%**	**40°C**	**HFIP**	**12 h**	**93%**
11	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	rt	HFIP	12 h	58%[a]
12	-	-	-	rt	HFIP	12 h	n.r
13	$Ca(NTf_2)_2$	-	1 mol%	40°C	HFIP	12 h	n.r

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

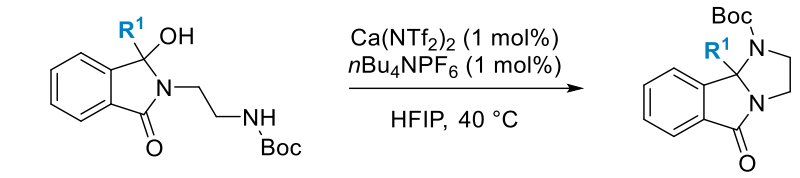
With the optimised conditions in hand a small library of 3-hydroxyisoindolinones with a tethered *N*-Boc carbamate were synthesised (Table 30). In addition, the phenyl substituted **333a**, chloro- and trifluoromethyl substituted products **333b** and **333c** were also synthesised respectively in good yield.

Table 30. Synthesis of 3-hydoxyisoindolinones with a thethered *N*-Boc carbamate.

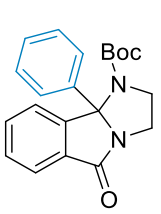


The library of 3-hydroxyisoindolinones **333** were then subjected to the optimised conditions (Table 31). However, when the reaction was performed with **333b** only trace amounts of product **334b** was detected. A similar trend was observed with **333c** in which no reaction took place. This was attributed to the more electron-deficient 3-hydoxyisoindolinones being slower to activate due to strengthening of the carbon-oxygen bond resulting from the electron-withdrawing nature of the aryl group, thereby making the lone pair of the oxygen less available. This may potentially result in protonation of the carbamate being more favourable and therefore shutting down reaction pathway. Increasing the temperature of the reaction had little effect, with increasing complex mixtures being formed, as observed in the initial optimisation.

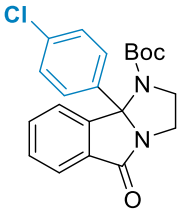
Table 31. Calcium catalysed dehydrative cyclisation with a tethered *N*-Boc carbamate.



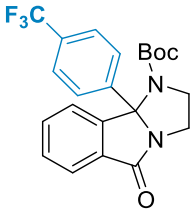
329 **334**



334a, 93%

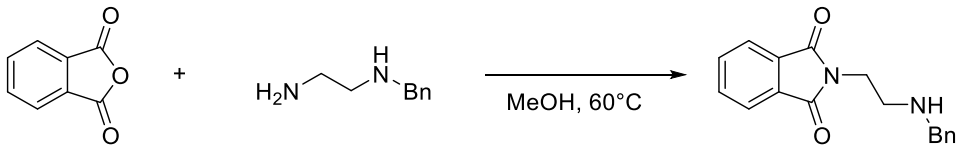


334b, n.r.



334c, n.r.

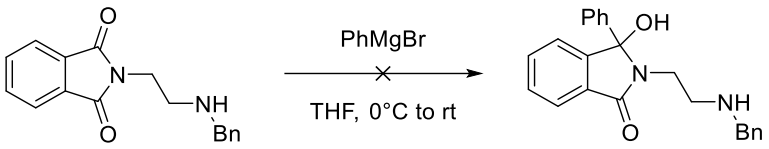
As the cyclisation of amides and carbamates have been studied, whether the same methodology could be applied to amines providing an alternative way to access imidazolidines was investigated. **336** was first synthesised by condensation of **307** and **335** in methanol (Scheme 56).



307 **335** **336,** 32%

Scheme 56. Synthesis of 336 by condensation.

Subjecting **336** to a Grignard addition however resulted in a complex mixture of products being obtained (Scheme 57). This is possibly due to initial deprotonation of the *N*-Bn amine resulting in a highly reactive nucleophile which could also cyclise into the carbonyl of the phthalimide or dimerise with another molecule of **336**. The same reaction was also attempted at a lower temperature without any improvement in reaction outcome.



336 337

Scheme 57. Attempted synthesis of 337 by Grignard addition.

3.3.4. Proposed Mechanism

Based on the computational work carried out by Lebeouf,[36] it is postulated the mechanism for the cyclisation of tethered thiols and indoles proceeds *via* a calcium-HFIP mediated Brønsted acid pathway (Figure 35). The Brønsted acidic calcium-HFIP complex **338** protonates the hydroxy group of the 3-hydroxyisoindolinone **311** resulting in the formation of *N*-acyliminium ion **339** *via* loss of water. Intramolecular trapping of the *N*-acyliminium ion with the tethered nucleophile results in protonated intermediate **342** which is deprotonated by the NTf^- ligand on complex **341** thereby generating product **253** and complex **343**. Regeneration of the catalyst occurs *via* an intramolecular proton transfer between the protonated NTf^- ligand and a hexafluoroisopropoxide ligand.

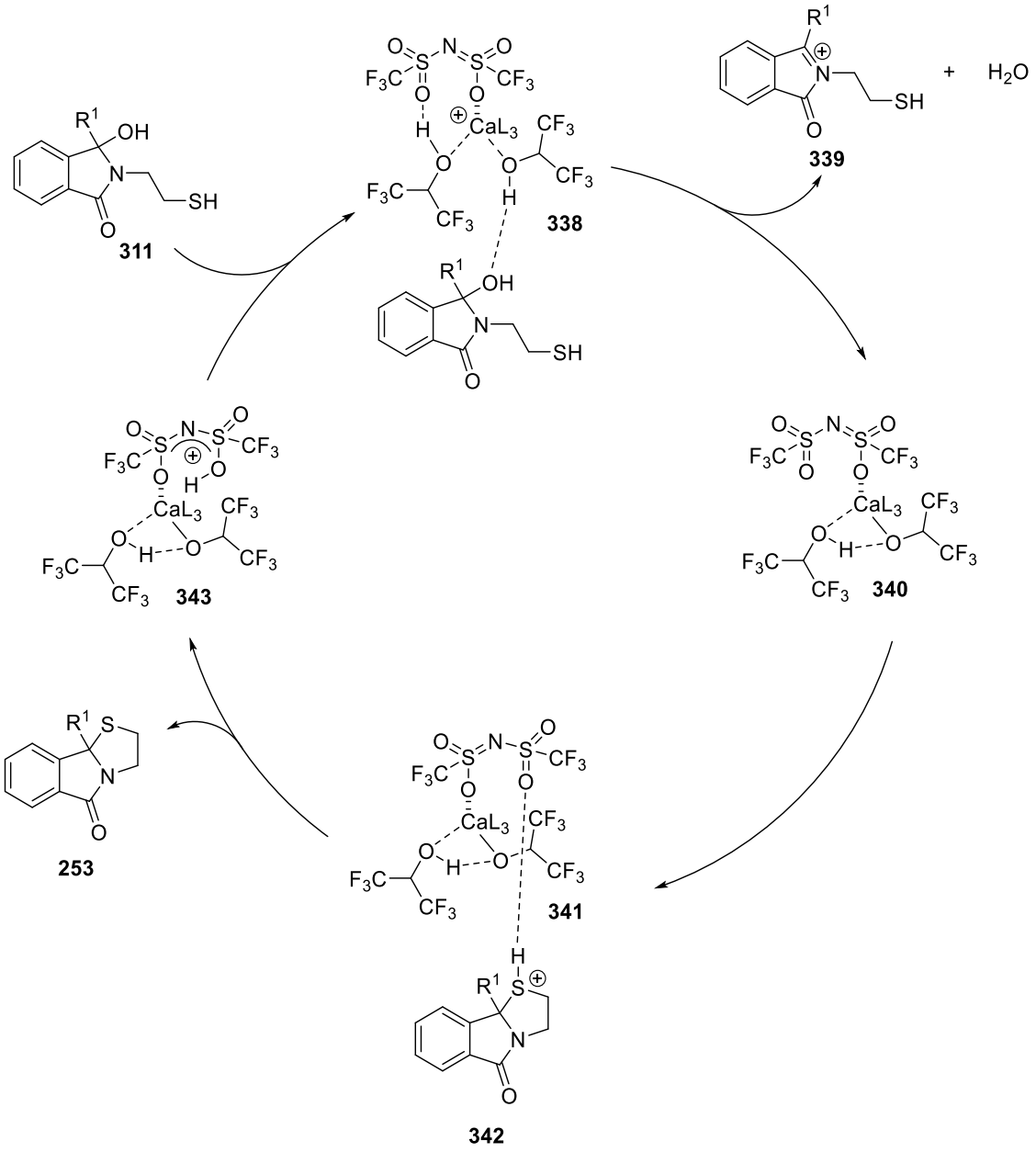


Figure 35. Proposed mechanism for the calcium-HFIP catalysed dehydrative cyclisation with a tethered thiol.

3.4. Conclusions

In summary, the intramolecular trapping of *N*-acyliminium ions with carbon, sulfur and nitrogen containing nucleophiles has been demonstrated. A modular route to access a library of 3-hydroxisoindolinone derivatives with varying tethered nucleophiles has been developed, which have been subjected to an optimised dehydrative cyclisation to afford fused heterocyclic γ-lactam scaffolds. Tethered thiols and indoles were cyclisation under Bronsted acidic conditions utilising a 1 mol% of a calcium-HFIP complex formed *in-situ.* Cyclisation of nitrogen derived nucleophiles utilised calcium as a Lewis acid, in which a range of tethered amides could be cyclised to afford fused imidazolidinone scaffolds. The methodology however could not be reliably extended to carbamates or amines. In utilising either a Brønsted or Lewis acidic calcium catalyst, it has been shown how the reactivity can be tuned by judicious choice of solvent depending on the tethered nucleophile employed.

3.5. Future Work

The work carried out in this chapter provides modular access to complex fused scaffolds with ease under mild conditions. While the nucleophiles employed provide a good seminal investigation into the calcium catalysed intramolecular trapping of isoindolinone derived *N*-acyliminium ions, it opens several new avenues for further investigation into this transformation.

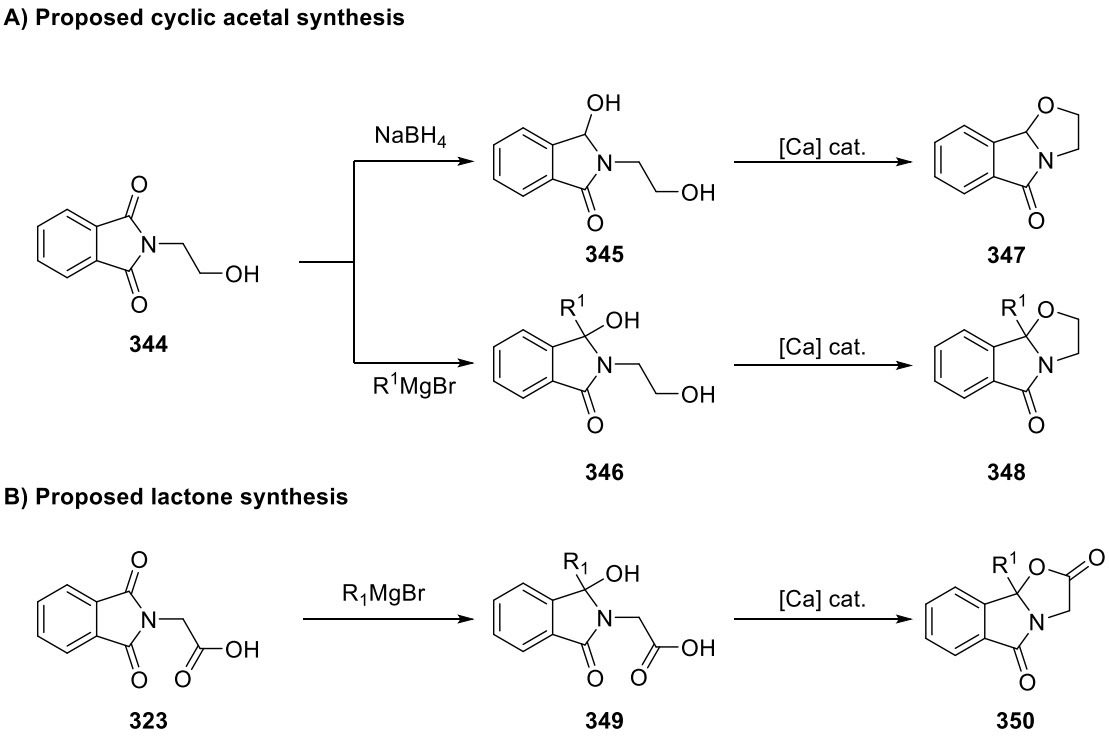
3.5.1. Solvent Controlled Cyclisation

The inhibition of the HFIP mediated cyclisation pathway in the presence of Lewis basic functionalities could offer a distinct advantage in overcoming chemoselectivity issues should this methodology be applied to larger scaffolds or as part of a total synthesis.

3.5.2. Nucleophiles Employed

In this chapter, thiol, nitrogen, and indole derived carbon nucleophiles were studied. Investigating whether oxygen nucleophiles would cyclise under similar conditions would be advantageous. An initial condensation between phthalic anhydride and amino ethanol would provide access to the common precursor **344** with a tethered alcohol

(Scheme 58A). Manipulation of **344** by either Grignard addition, if the tethered alcohol is tolerated tolerated, or reduction would result in the formation of **345** and **346** respectively and subjection to the calcium catalysed dehydrative conditions would provide access to cyclic acetals **347** and **348** respectively. Furthermore, manipulation of **323** synthesised earlier in the chapter under the same conditions described above has the potential for access to lactone motif **350** (Scheme 58B).

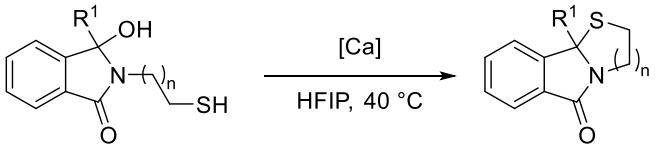


Scheme 58. Proposed calcium catalysed synthesis of cyclic acetals (A) and lactones (B).

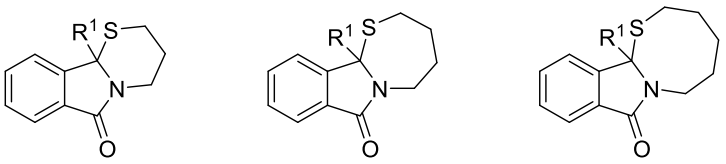
3.5.3. Ring Size

As the starting materials employed are readily available, the methodology developed in this chapter could be applied to the synthesis of larger ring sizes **352a-352c** with relative ease. By swapping out the cysteamine used in the initial condensation, amino-thiol derivatives of longer chain lengths, could be synthesised under the same conditions (Table 32).

Table 32. Proposed access to larger ring sizes.



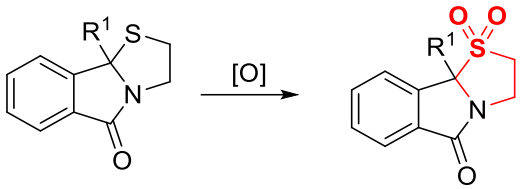
351 **352**



352a **352b** **352c**

3.5.4. Applications of Products

The scaffolds synthesised in this chapter were designed to not only be valuable fragment library molecules in themselves but also to bear several useful functional handles for further manipulation. For example, oxidation of **253** to the sulfone derivative **353** would provide access to desirable cyclic sulfones which have been under-explored in medicinal chemistry and shown to be bioisosteric of the carbonyl motif (Scheme 59).[114]



253 **353**

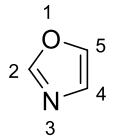
Scheme 59. Oxidation of products to medicinally relevant sulfones.

4. Chapter 4: Intermolecular Trapping of *N*-acyliminium ions with isocyanides; access to oxazoles and thiazoles

4.1. Introduction

4.1.1. Oxazoles

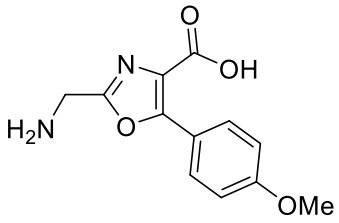
Oxazoles **354** are highly important motifs present in various natural products and pharmaceuticals (Figure 36).



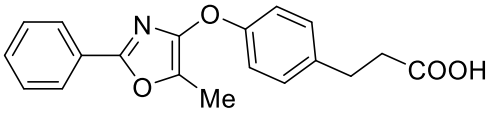
354

Figure 36. Oxazole Structure.

The oxazole motif is prevalent in a range of medicinally relevant compounds which display anti-bacterial, -fungal, -viral, -cancer, -inflammatory and -diabetic properties.[115] For example, compound **355** has shown activity against cancer[116] and **356** shown promise as a treatment for diabetes.[117] Compounds **357** and **358** have shown anti-bacterial[118] and anti-viral[119] properties respectively (Figure 37). This demonstrates the wide-ranging nature of the oxazole moiety in medicinally relevant scaffolds and supports the continual need for new methods to access these privileged scaffolds with increasing demand for molecular complexity.



355



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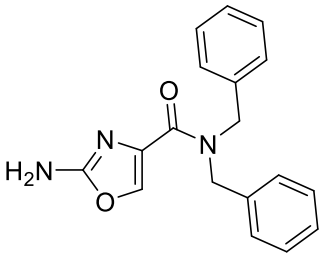

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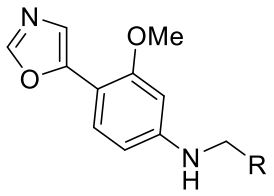


358

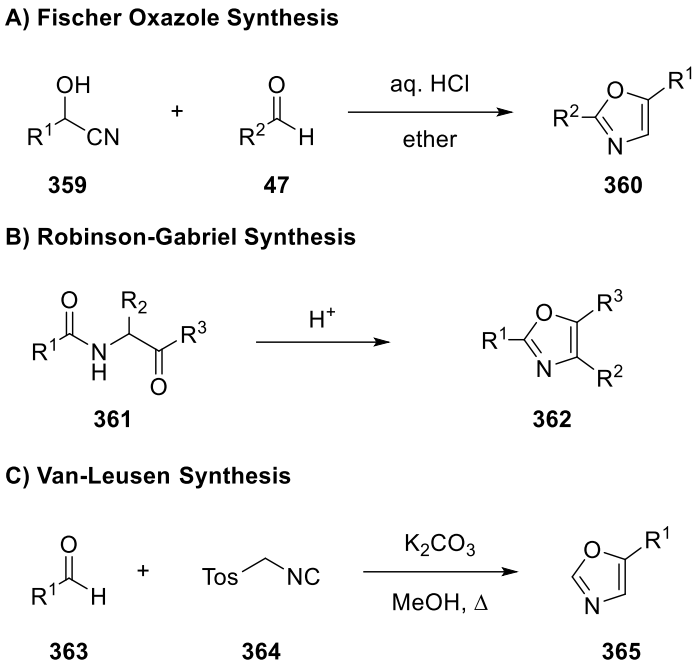
Figure 37. Medicinally relevant oxazoles

4.1.1.1. Synthesis of Oxazoles

Due to their extensive prevalence, the assembly of oxazoles is continually attracting the interest of synthetic chemists. In particular, medicinal chemists continually require rapid access to functionalised heterocycles with useful synthetic handles, from simple, readily available starting materials.

4.1.1.2. Traditional Methods

Traditionally, the oxazole motif is synthesised through a variety of routes (Scheme 60). This includes that reported by Fischer in 1896.[120] Treatment of cyanohydrin **359** with an aldehyde **47** in the presence of aqueous HCl resulted in the formation of 2,5-disubstituted oxazoles **360** (Scheme 60A). Access to 2,4,5-trisubstituted oxazoles was then reported by Robinson and Gabriel respectively in 1909 and 1920.[121, 122] The 2-acylamino ketone **361** cyclises to form oxazole **362** in the presence of acid producing water as the by product (Scheme 60B). Van-Leusen reported synthesis of 5-substituted oxazoles by reaction of an aldehyde **363** with tosylmethylisocyanide **364** in the presence of a base (Scheme 60C).[123] While these are elegant and robust seminal methods, they require stoichiometric quantities of acid or base at elevated temperatures which somewhat limits functional group tolerance. Furthermore, the products of these reactions offer limited scope for further diversification.



Scheme 60. Traditional methods for accessing oxazoles.

Transition metal catalysed approaches have gained considerable interest in recent years, however it is their synthesis in a more sustainable manner, without the use of precious transition metals that is highly desirable.[124]

4.1.2. Synthesis of 5-aminooxazoles

The installation of an amine derivative at the 5-position of an oxazole offers the addition of a useful synthetic handle for further functionalisation making it a desirable building block (Figure 38).

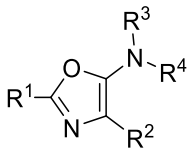
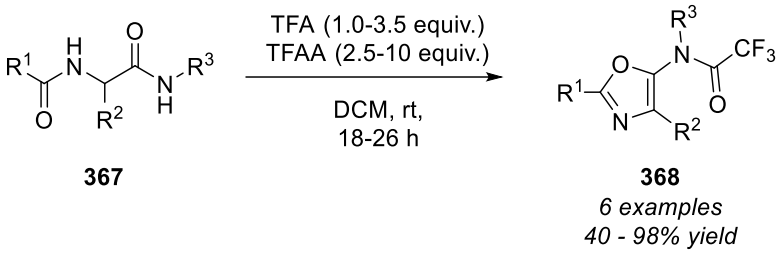


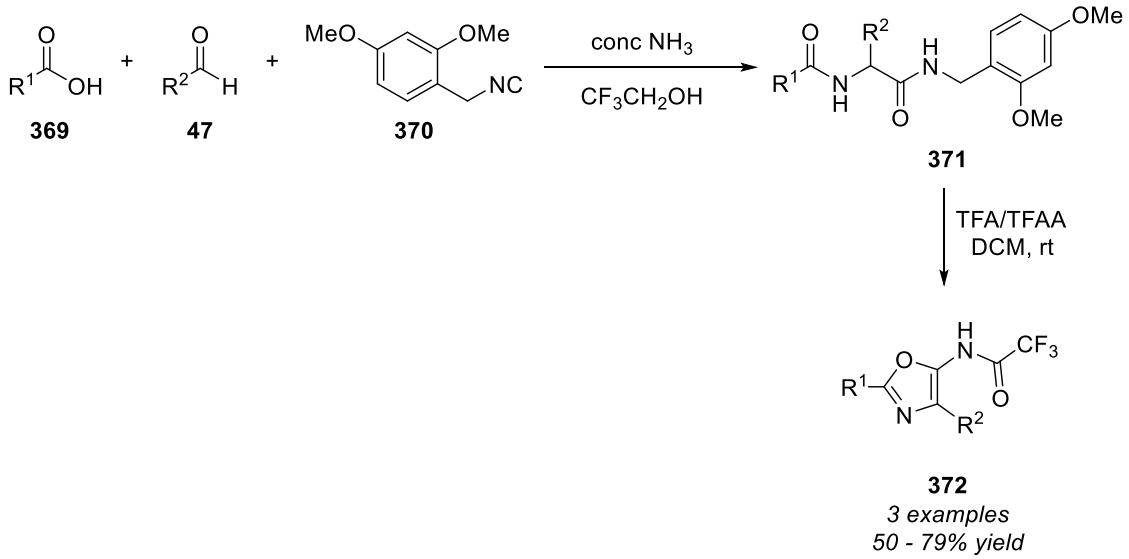
Figure 38. 5-aminooxazole structure.

One of the earliest reports for the synthesis of 5-aminooxazoles was by Lipshutz in 1983 who reported a TFA/TFAA mediated dehydrative cyclisation of diamide precursors **367** (Scheme 61). They also explored the functionalisation of oxazole products **368** by *N*-alkylation and C-alkylation (when R_1 = Me).[125]



Scheme 61. TFA/TFAA mediated dehydrative cyclisation of diamides to afford 5-amidosubstituted oxazoles.

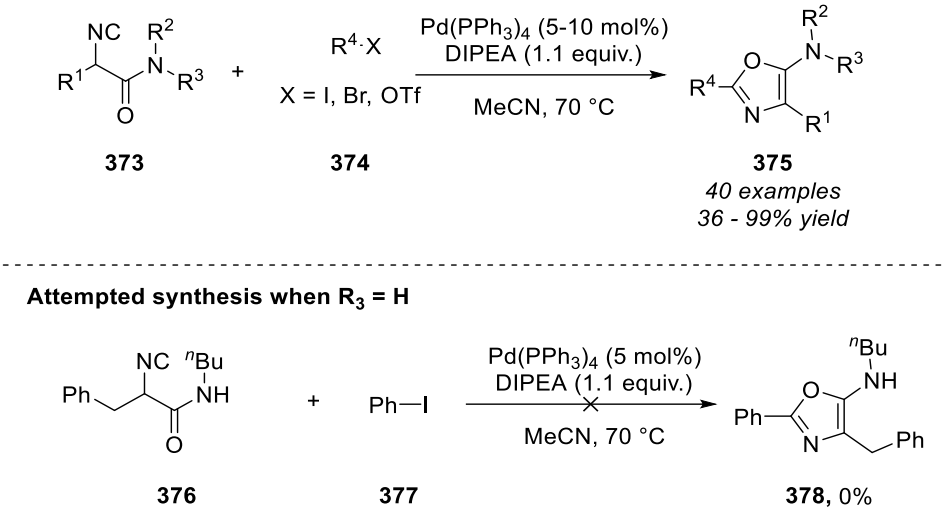
Inspired by Lipshutz's work, Chen and co-workers found that a modified Ugi reaction with ammonia and trifluoroethanol as solvent results in the formation of a diamide **371** in which both amides formed are secondary.[126] Applying the same methodology reported by Lipshutz the authors disclosed a small library of 5-amidooxazoles **372** in a more modular approach (Scheme 62). The diamide precursors **371** also display similar reactivity upon treatment with Burgess reagent[127] for the synthesis of 5-sulfamidooxazoles which was reported by Serafini in 2021.[128]



Scheme 62. Modified Ugi MCR for access to di-secondary amides which undergo dehyrdative cyclisation to afford 5-amidooxazoles.

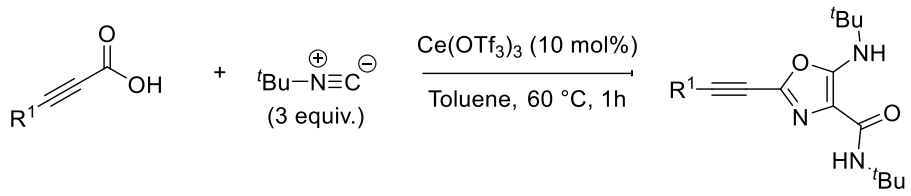
In more recent years, further advancements have been made focussing on catalytic methods to access 5-aminooxazoles. In 2014, Zhu and co-workers reported a transition metal catalysed approach to access 5-aminooxazoles from α-isocyanoacetamides **373** and an aryl, vinyl or alkynyl triflate **374** (Scheme 63).[129] Utilising catalytic $Pd(PPh_3)_4$ and

stoichiometric DIPEA a range of 5-aminooxazoles **375** was reported. The authors disclose a limitation of this work is that the reaction does not proceed in the presence of secondary α-isocyanoacetamides **376** which somewhat limits any diversification.



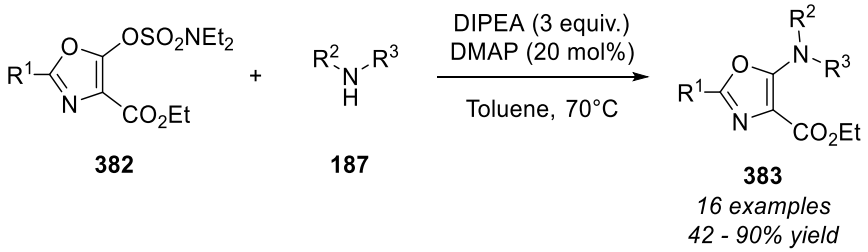
Scheme 63. Synthesis of 5-aminooxazoles *via* a palladium catalysed cyclisation of α-isocyanoacetamides.[129]

Then in 2020, Wang and co-workers reported a cerium triflate catalysed cascade reaction of alkynyl carboxylic acids **379** and tert-butyl isocyanide **380** to afford a range of 5-aminooxazoles **381** (Scheme 64).[130] Building on an earlier report which used stoichiometric zinc bromide,[131] the authors describe a catalytic approach which also has useful 2-alkynyl functional handle in addition to the 5-amino group. Several of the compounds synthesised also demonstrated good activity against gastric cancer cells further supporting the continuing importance to develop new ways to access these compounds. However, the products synthesised, although heavily substituted, have only two sites of diversification, with both the 5-amino-substituent and 4-amido-substituent being derived from the isocyanide.



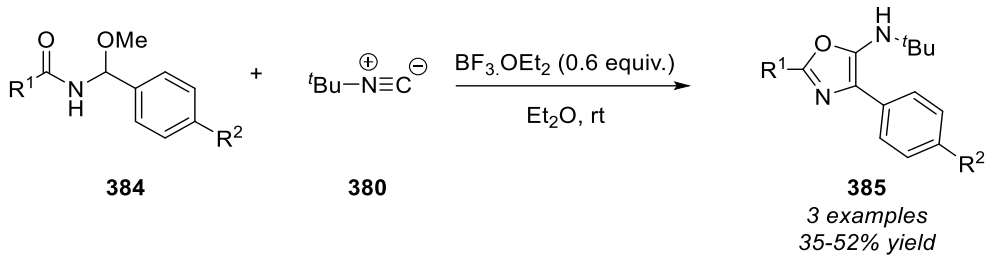
Scheme 64. Synthesis of 5-aminooxazoles *via* a $Ce(OTf)_3$ catalysed cascade reaction of carboxylic acids and isocyanides.[130]

Further methods for the incorporation of an amino-group at the 5-position of the oxazole also include that reported by Arndt in 2022.[132] The authors reported the reaction of 5-oxazoyl-sulfamates **382** with various nucleophiles including amines, thiols and phenols, afforded a range of 5-aminooxazoles **383** (Scheme 65). While an elegant reaction affording a diverse range of compounds, it does require the oxazole motif to be pre-installed which limits modularity.



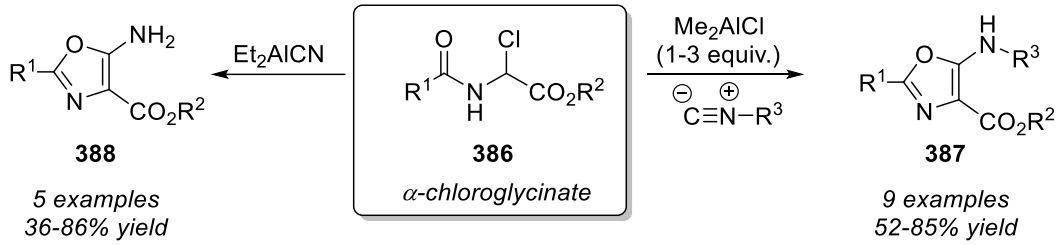
Scheme 65. Synthesis of 5-aminooxazoles from 5-Oxazoyl-sulfamates.[132]

It is the synthesis of 5-aminooxazoles using *N*-acyliminium ion chemistry that is of particular interest and this was first reported in 1972 (Scheme 66).[133] Using $BF_3.OEt_2$ as a Lewis acid, and *N*-acyl-*N,O*-acetals **384** as *N*-acyliminium ion precursors, a small substrate scope was probed using *t*-butyl isocyanide **380**. Despite using "catalytic" quantities of $BF_3.OEt_2$, the turnover is not reflected in the yields obtained.



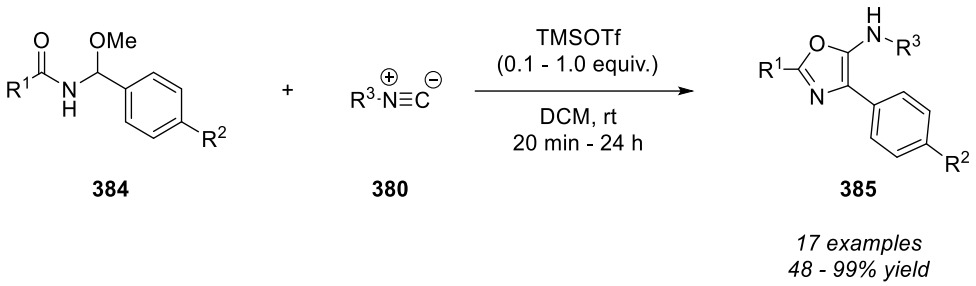
Scheme 66. First report of the sythesis of 5-aminooxazoles using *N*-acyliminium ion chemistry.

In 2010, Ciufolini developed this further using α-chloroglycinates **386** as *N*-acyliminium precursors (Scheme 67).[134] Nucleophilic attack of isocyanides in the presence of a super-stoichiometric amount of Me_2AlCl or Et_2AlCN afforded a range of 5-alkylamino **387** or 5-amino oxazoles **388** respectively.



Scheme 67. Synthesis of 5-aminooxazoles using chloroglycinate precursors.[134]

More recently, synthesis of 5-aminooxazoles using isocyanides has been reported by Ukaji (Scheme 68).[135] Using TMSOTf, a range of 5-aminooxazoles were developed. While this work provided an expansion of that reported by Killion in 1972, the substrate scope provided is somewhat limited, with naphthyl, 4-bromo-, 4-nitro- and 4-methoxy- phenyl substituted products being reported. Methyl substituted aromatics required stoichiometric amounts of Lewis acid and the R^2 position is varied only with methyl and bromine.



Scheme 68. Synthesis of 5-aminooxazoles reported by Ukaji.[135]

The above examples all demonstrate significant contributions to the assembly of 5-aminooxazoles, however challenges still remain with regards to catalyst loading and functional group tolerance.

4.2. Aims

The aim of this chapter is to develop a mild and robust calcium catalysed route to access highly functionalised 5-aminoozaxoles **389** from easily accessible *N*-acyl-*N,O*-acetals **103** and isocyanides **390** (Figure 39). *N*-acyl-*N,O*-acetals **436** have been chosen here due to their intrinsic stability over hemiaminals (R^3 = OH). Firstly, the aim is to explore whether calcium can be used to catalytically generate acyclic *N*-acyliminium ions **104** from *N*-acyl-*N,O*-acetals, and subject this to an elimination, dehydration, cyclisation strategy to access 5-aminooxazoles. Due to the origin of the starting materials, this will allow assembly of the oxazole from readily available amides **109**, aldehydes **47** and amines **391**. It is anticipated that this method has advantages over traditional methods due to the mild conditions employed.

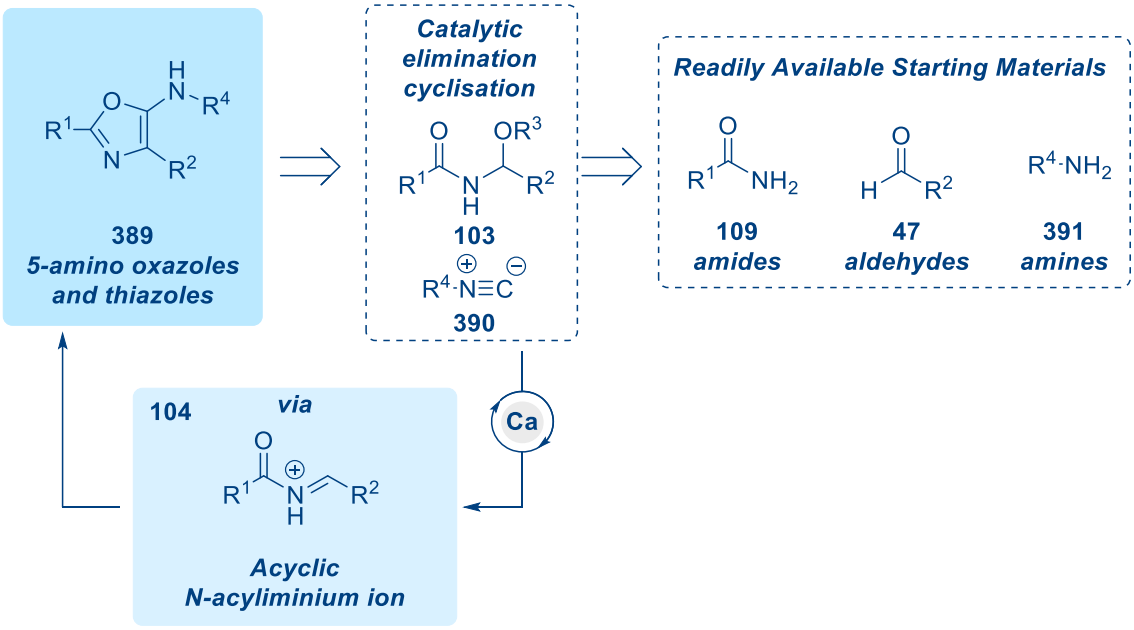


Figure 39. Proposed synthesis of 5-aminooxazoles using a calcium catalysed transformation. Substituents on the oxazole can be easily varied from amides, aldehydes and isocyanides.

4.3. Results & Discussion

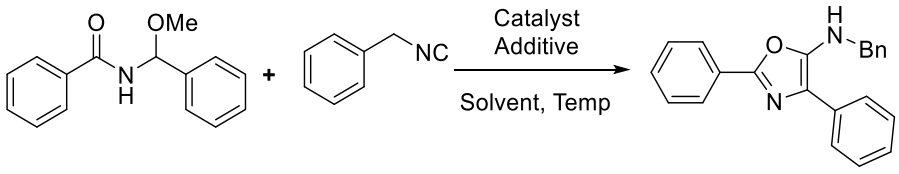
The work described in this section has been published:[136]

A. J. Basson and M. G. McLaughlin, *Chem. Sus. Chem.,* 2021**, 14**, 1696.

4.3.1. Optimisation Studies

The investigation began by studying the reaction of **392a**, synthesised according to a literature procedure,[137] with benzyl isocyanide **393** which was chosen due to the resulting oxazole having a useful protecting group (Table 33). When **392a** and **393** were subjected to 10 mol% of catalyst and additive at room temperature no reaction took place with unreacted starting material re-isolated (entry 1). Increasing the temperature to 40 °C had no effect on reaction outcome (entry 2). Raising the temperature to 80 °C afforded product **394** in both a moderate NMR and isolated yield (entries 3 and 4). In an attempt to improve the yield, the reaction was repeated at 60 °C however this resulted in a decreased yield (entry 5). Switching to an alternative Lewis acid catalyst proved to be less efficient (entry 6) and using a Brønsted acid catalyst resulted in a complex mixture being obtained (entry 7). The reaction was also repeated using the same conditions reported by Ukaji[135] and this proved unsuccessful (entry 8). Finally, the reaction was performed without any catalyst or additive in which no reaction took place (entry 9).

Table 33. Optimisation for the synthesis of 5-aminooxazoles with benzyl isocyanide.



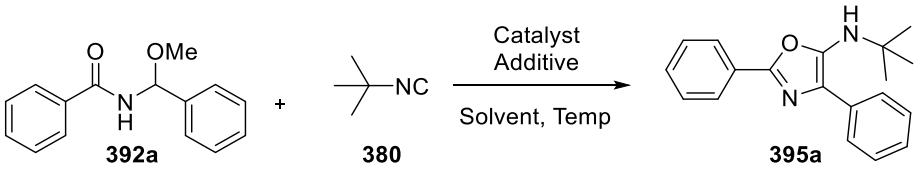
392a **393** **394**

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	r.t	DCM	12 h	n.r
2	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40 °C	DCM	12 h	n.r
3	$Ca(NTF_2)_2$	nBu_4NPF_6	10 mol%	80 °C	1,2-DCE	10 min	61% [a]
4	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	1,2-DCE	10 min	55%
5	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	60 °C	1,2-DCE	15 min	22%
6	$Mg(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	1,2-DCE	10 min	31%
7	$HNTf_2$	-	10 mol%	50 °C	DCM	12 h	mixture
8	TMSCl	-	1. equiv	r.t	1,2-DCE	1 h	mixture
9	-	-	-	80 °C	1,2-DCE	2 h	n.r

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Dissatisfied with the yields obtained using benzyl isocyanide, the reaction using tert-butyl isocyanide was also studied to investigate whether the isocyanide was the source of the decreased yields obtained. The investigation began by employing **392a** and tert-butyl isocyanide **380** to the conditions that resulted in the highest yield when employing benzyl isocyanide (entry 1, Table 34). The reaction proceeded to completion in 5 mins producing product **395a** in high yield. Lowering the catalyst loading to 1 mol% saw a significant increase in reaction time with a slight decrease in yield (entry 2). Increasing the catalyst loading to 5 mol% again rapidly produced the product in high yield (entry 3). It was reasoned that balancing reaction time with catalyst loading, 5 mol% was optimum. With the underlying aim of using calcium as a sustainable catalyst, a solvent screen was performed using more environmentally friendly solvents (entries 4-7). The reaction proceeded to 99% conversion with an isolated yield of 92% when ethyl acetate was employed as the solvent. This was unprecedented due to ethyl acetate being widely expected to poison the catalyst. Thus, to confirm the reaction was indeed calcium catalysed, a reaction in the presence of 2,6-ditertbutylpyridine was performed (entry 8), ruling out a Brønsted acid catalysed pathway. The reaction was also carried out without the presence of the additive, in which the reaction becomes extremely sluggish demonstrating the important nature of the additive.

Table 34. Optimisation for the synthesis of 5-aminooxazoles with tert-butyl isocyanide.



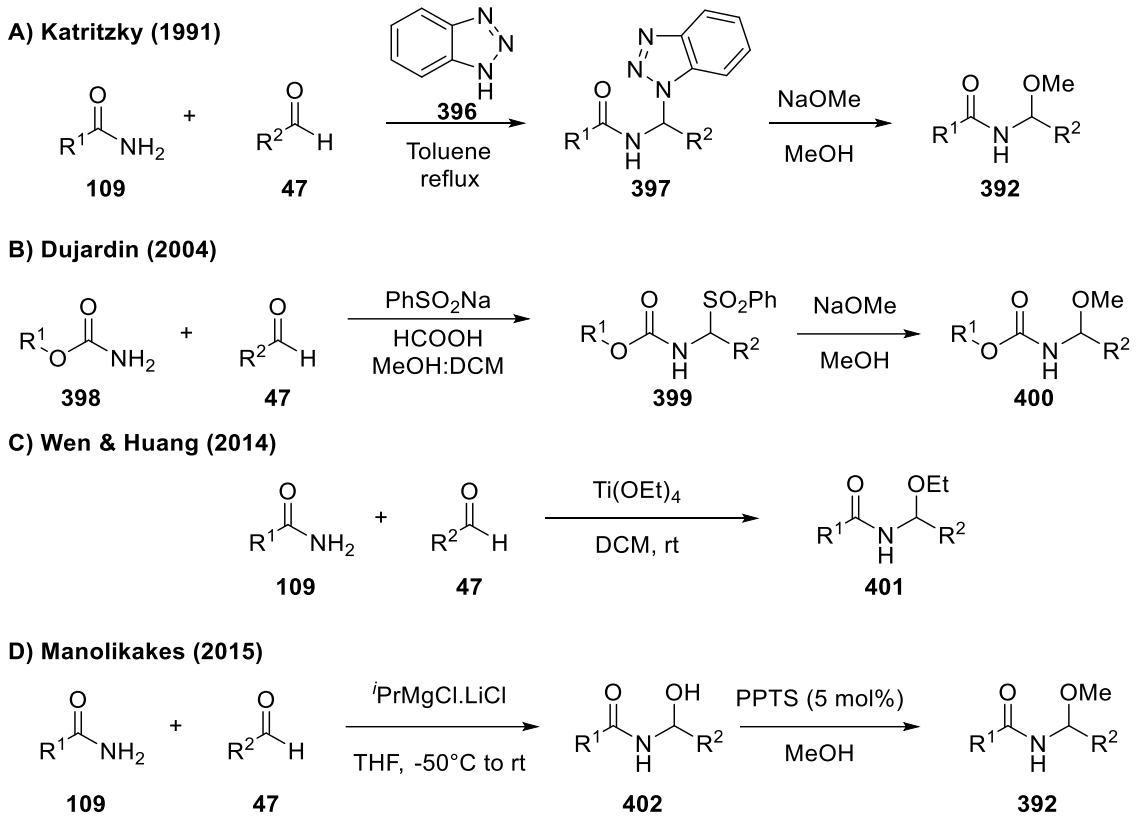
392a **380** **395a**

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80ºC	1,2-DCE	5 min	83%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80°C	1,2-DCE	2h	73%
3	$Ca(NTF_2)_2$	nBu_4NPF_6	5 mol%	80°C	1,2-DCE	15 min	86%
4	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80°C	EtOAc	1h	99%[a]
5	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80°C	EtOAc	1h	92%[b]
6[a]	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80°C	MeCN	12h	53%[a]
7	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80°C	Acetone	12h	0%
8	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80°C	EtOAc	1h	96%[a,c]
9	$Ca(NTf_2)_2$	-	5 mol%	80°C	EtOAc	1h	2%[a]

a NMR yield using 1,3,5-trimethoxybenzene as an internal standard
b isolated yield
c reaction carried out in presence of 2,6-Di tertbutyl pyridine

4.3.2. Preparation of Starting Materials

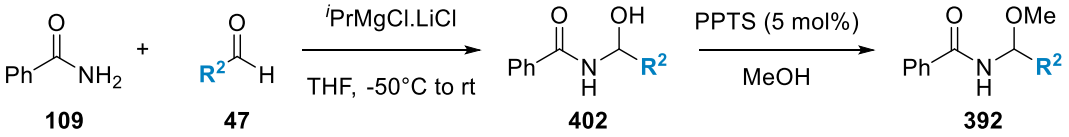
Starting material synthesis began by studying access to *N*-acyl-*N,O*-acetals which are useful *N*-acyliminium ion precursors. Methods for their preparation has been recently reviewed[138] and they are typically prepared by traditional synthesis or electrochemically. The use of electrochemical equipment somewhat limits the usability of these methods by other groups. As such, following a survey of traditional synthetic routes four methods were identified (Scheme 69) which provided modular access to the acyclic acetal motifs required. Katritzky first reported a two-step process with benzotriazole intermediate **397** followed by reacting with sodium methoxide (Scheme 69A).[139] In 2004, Dujardin reported a two-step process *via* α-amido sulfone intermediate **399** to afford a range of carbamate protected acetals **400** (Scheme 69B).[140] The reactivity of the α-amido sulfone intermediates have also been explored as *N*-acyliminium ion surrogates and has been extensively studied and reviewed.[141, 142] More recently, Wen and Huang reported a one-step approach using titanium ethoxide and were able to react primary amides and carbamates with aldehydes directly (Scheme 69C).[143] One year later, citing irreproducibility of Wen and Huang's approach, Manolikakes reported a two-step procedure by first forming hemiaminal **402** by initial deprotonation with ^{i}PrMgCl.Li followed by treatment with catalytic PPTS in methanol to afford acetal **392** (Scheme 69D).[137]

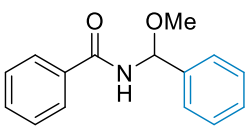


Scheme 69. Summary of the synthesis of *N*-acyl-*N,O*-acetals used in this chapter, reported by Katritzky,[139] Dujardin,[140] Wen & Huang,[143] Manolikakes[137]

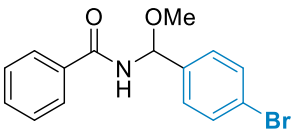
The first approach studied was inspired by the method developed by Manolikakes.[137] Due to their instability, hemiaminals **402** were isolated by recrystallisation then immediately subjected to transacetalisation to afford products **392**. Using commercially available benzamide **109**, the range of aldehydes that could be reacted under these conditions was initially studied (Table 35). In addition to the phenyl-substituted acetal **392a**, halo-substituted acetals also worked well in moderate yield **392b-392d**. Furthermore, more electron-deficient substituents were also tolerated in good yield affording **392e** and **392f**.

Table 35. Synthesis of *N*-acyl-*N,O*-acetals using Manolikakes' procedure.

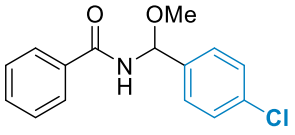




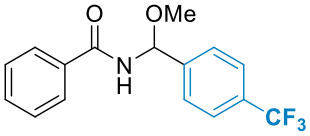
392a, 79%



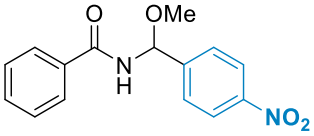
392b, 47%



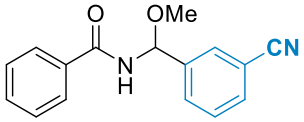
392c, 53%



392d, 71%



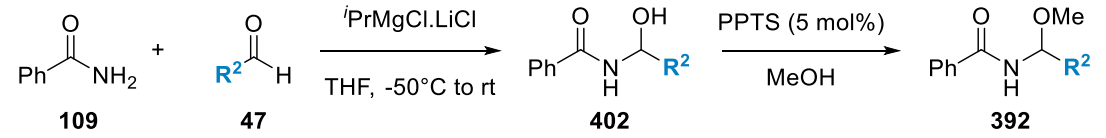
392e, 66%

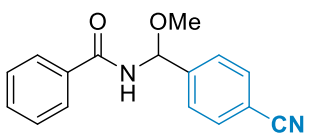


392f, 64%

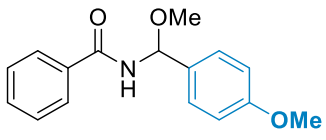
Unfortunately, this methodology was not tolerant to all functional groups. The substrates synthesised in Table 35 are all derived from electron-deficient aldehydes. The 4-cyano substituted hemiaminal **392g** proved unreactive when subjected to the transacetalisation conditions with the unreacted hemiaminal reisolated (Table 36). Furthermore, electron-rich aldehydes also proved intolerant to this method and **392h-392i** could not be synthesised under these conditions. Preparation of their hemiaminal precursors proved to be much slower (12 h vs 1.5 h), even at higher temperatures (-10 °C) along with the transacetalisation step providing both a mixture of product and degradation back to the corresponding amide and aldehyde. A rapid degradation profile of the remaining product was then observed when subjected to column chromatography marking these electron-rich acetals incredibly acid sensitive. Additionally, furan **392j** and thiophene substituted acetals **392k** also proved troublesome using this method with a complex mixture of products obtained during the hemiaminal formation.

Table 36. Unsuccessful substrates using Manolikakes' method.

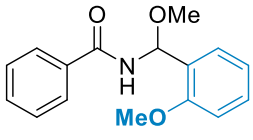




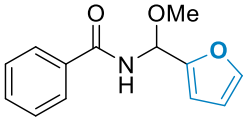
392g



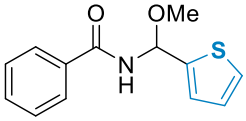
392h



392i



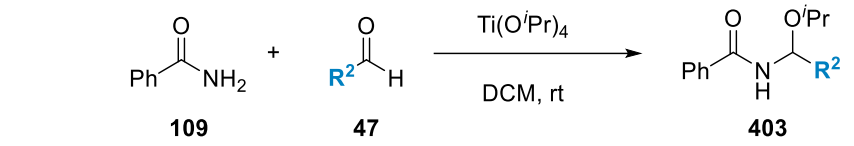
392j



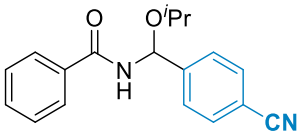
392k

To further expand the library of *N*-acyl-*N,O*-acetals, attention was then turned towards the procedure reported by Wen and Huang[143] swapping $Ti(OEt)_4$ for $Ti(O^iPr)_4$ due to it being more readily available. Pleasingly, this procedure was complimentary to that reported by Manolikakes and allowed access to some of the compounds that could not be synthesised using their method (Table 37). Further aryl-substituted acetals were synthesised in moderate yields with 4-cyano **403a** and 3-methyl **403b** substituents. Naphthyl-substituted acetal **403c** was also synthesised in moderate yield. Both thiophene **403d** and furan **403e** substituted acetals could be accessed *via* this procedure allowing incorporation of heterocyclic motifs. Finally, alkyl substituted acetals could also be accessed in synthetically useful yield **403f**.

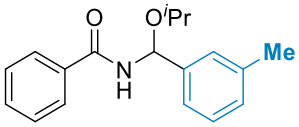
Table 37. Synthesis of *N*-acyl-*N,O*-acetals with varying aldehyde components using an adapted procedure reported by Wen & Huang.



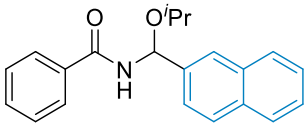
109 **47** **403**



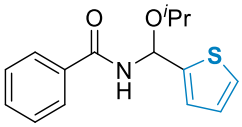
403a, 59%



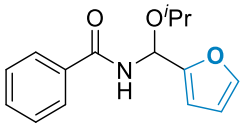
403b, 33%



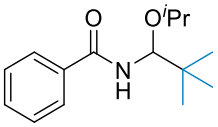
403c, 59%



403d, 33%



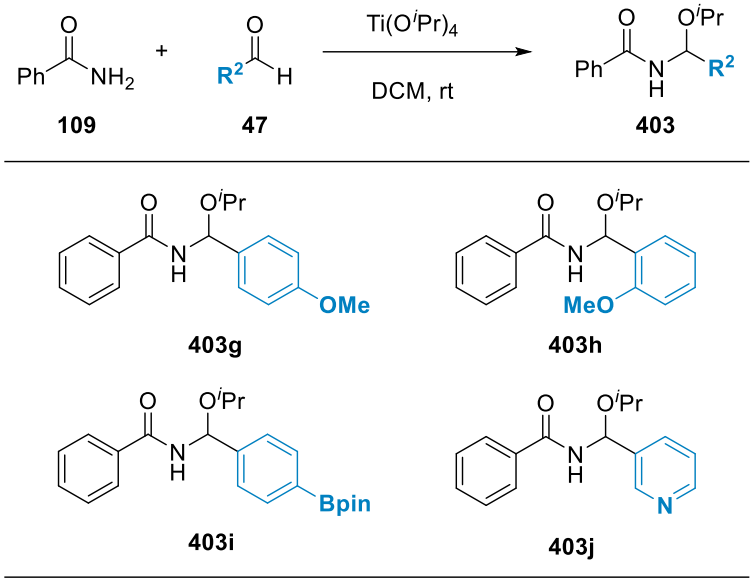
403e, 33%



403f, 27%

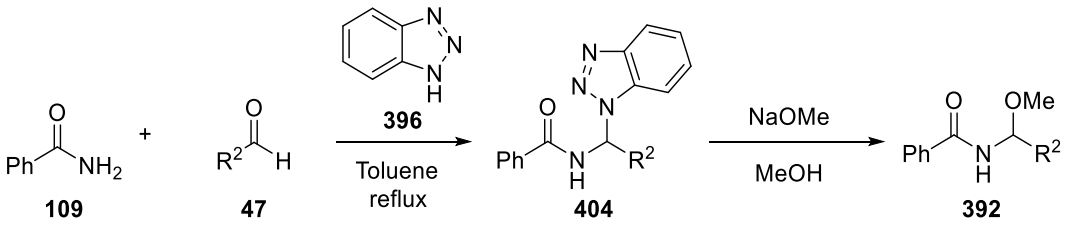
As with Manolikakes' procedure, this procedure also had some limitations. Again, access aryl-substituted aromatics containing electron-rich functionalities **403g** and **403h** was unsuccessful under these conditions (Table 38). While the acetals formed, a rapid degradation profile during their purification was again observed. It was not possible to isolate any product in synthetically useful yield and the amide and aldehyde were reisolated. Recrystallisation attempts prior to column chromatography also provided a mixture of product and benzamide. Furthermore, the boronic ester substituted acetal **403i** and pyridyl substituted product **403j** also proved unsuccessful with a complex mixture of products being obtained in both cases.

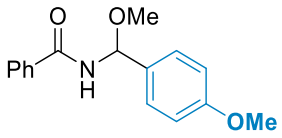
Table 38. Unsuccessful substrates using Wen & Huang's adapted procedure.



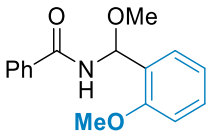
To fully explore the reactivity with respect to the aldehyde component, and any electron-rich aldehydes had so far proven unsuccessful, attention was turned to the method reported by Katritzky (Table 39).[139] These reactions did not proceed cleanly, and added to this, purification was confined to recrystallisation due to their instability in column chromatography. High purity of the benzotriazole intermediate **404** proved crucial to obtaining synthetically useful yields of **405** here. Trituration with diethyl ether and recrystallisation from methanol was found to be successful. Subjecting **404** to sodium methoxide in methanol followed by further recrystallisation afforded the para-substituted **405a** and ortho-substituted **405b** products in useful yields without the need for column chromatography (Table 39).

Table 39. Synthesis of electron-rich *N*-acyl-*N,O*-acetals using an adapted procedure reported by Katritzky.[139]





392l, 11%

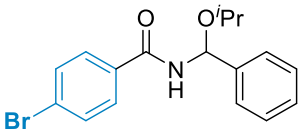


392m, 40%

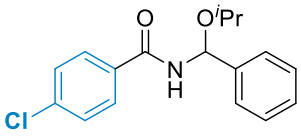
With a library of *N*-acyl-*N,O*-acetals synthesised with various aldehyde components focus was then turned to variation derived from the amide component **109**, in keeping with the overall aims of developing a modular synthetic route. The focus here was solely on the method reported by Wen and Huang as this allowed assembly of the products in a single step and was tolerant to a wider range of substrates (Table 40). The reaction proved tolerant to halogenated amides **407a** and **407b**, along with electron-deficient amide **407c.** *Meta*-substituted halogenated amides were also tolerated affording the 3,5-disubstituted and 3-substituted products **407d** and **407e** in useful yields. Electron-rich amides were also tolerated affording **407f** in useful yield and *ortho* weakly donating substituents were also tolerated affording **407g** in low yield. Heterocyclic amides were tolerated affording furan- and thiophene-substituted acetals **407h, 407i** again in useful yields. Finally, cyclohexyl-substituted acetal **407j** was synthesised in useful yield.

Table 40. Synthesis of *N*-acyl-*N,O*-acetals with varying amide components using an adapted procedure reported by Wen & Huang.[143]

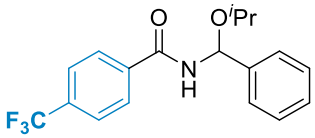
405 **406** **407**



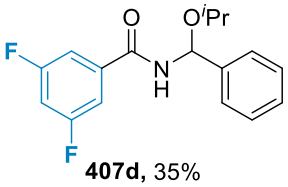
407a, 16%



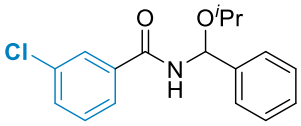
407b, 23%



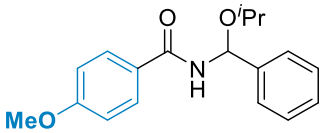
407c, 30%



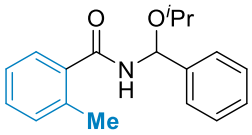
407d, 35%



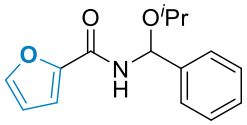
407e, 33%



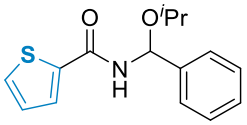
407f, 26%



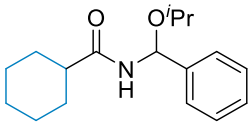
407g, 14%



407h, 21%



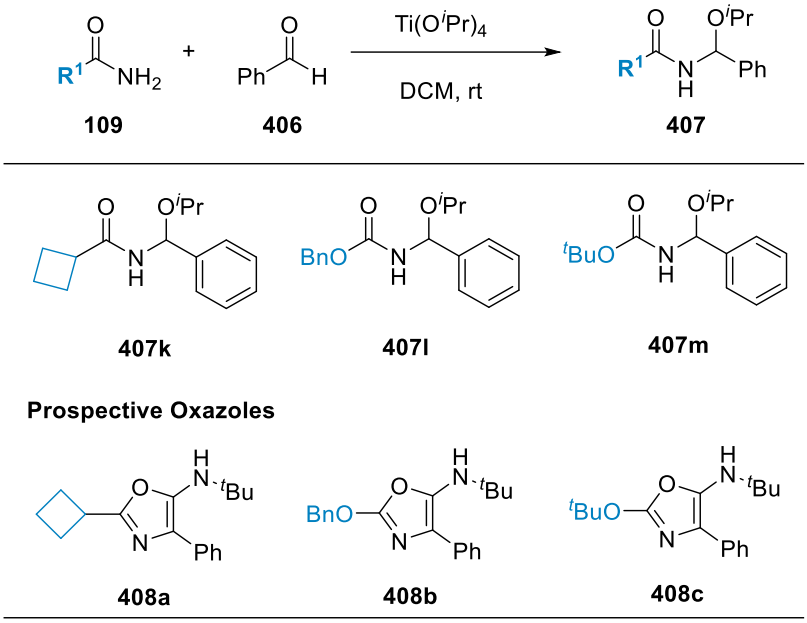
407i, 24%



407j, 10%

Other substituents were also attempted under the same conditions, however these proved to be unsuccessful (Table 41). Firstly, the attempted cyclobutyl acetal **407k** resulted in the formation of a complex mixture. In addition to amide substituted acetals, whether carbamate substituted acetals **407l** and **407k** could be cyclised under the optimised conditions for access to **408b** and **408c** was attempted. However, when reacting with benzyl- and tertbutyl carbamate, unreacted starting material was reisolated in both cases.

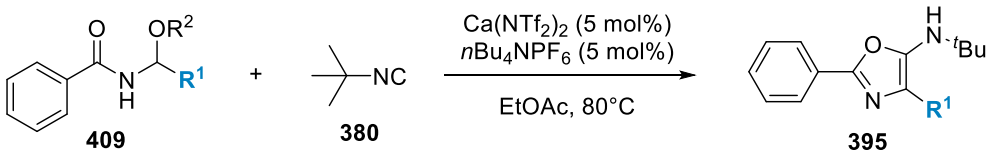
Table 41. Attempted synthesis of further alkyl-substituted acetals and carbamate substituted acetals and their prospective oxazole products.



4.3.3. Development of Substrate Scope

With the optimised conditions in hand, the substrate scope to access a range of 5-amino-oxazoles was probed (Table 42). It should be noted here the use of methyl or isopropyl derived *N,O*-acetals (**462**, R^2= Me or ^{i}Pr) has no significant impact on reaction outcome. This began by studying the reactivity derived from the aldehyde component of the acetal resulting in variation at the 4-position of the oxazole. Halogenated electron-withdrawing groups worked well, providing the desired oxazoles in high yield (**395b-395d**). Stronger electron-withdrawing groups were also tolerated providing the oxazole products in good yield (**395e-395g**). Electron-donating groups were again tolerated affording the desired oxazole in synthetically useful yields (**395h-395j**). Finally, heterocycles in the form of thiophene were tolerated (**395k**) along with naphthyl derivatives (**395l**).

Table 42. Functionalised Oxazoles - Aldehyde Variation

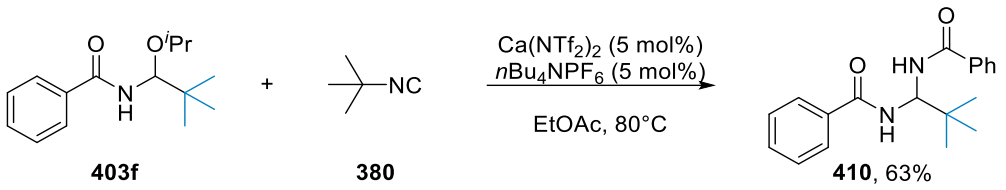


409 + 380 → 395

395a, 92%	**395b**, 91%	**395c**, 87%
395d, 89%	**395e**, 71%	**395f**, 72%
395g, 90%	**395h**, 90%	**395i**, 93%
395j, 40%	**395k**, 58%	**395l**, 90%

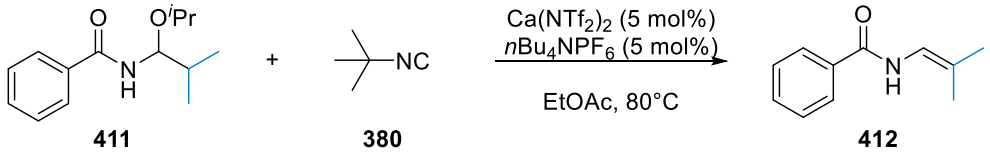
R^2 =Me for 395a, 395b, 395c, 395d, 395e, 395g, 395h, 395j
R^2 = ^{i}Pr for 395f, 395i, 395k, 395l

While the above examples demonstrate access to a diverse range of 4-substituted-5-amino-oxazoles, the functional group tolerance is not without its limitations. When the optimised conditions were applied to saturated systems **403f**, the bis-amide product **410** was the sole product (Scheme 70). This is most likely due to decomposition of the *N*-acyliminium ion *via* hydrolysis.



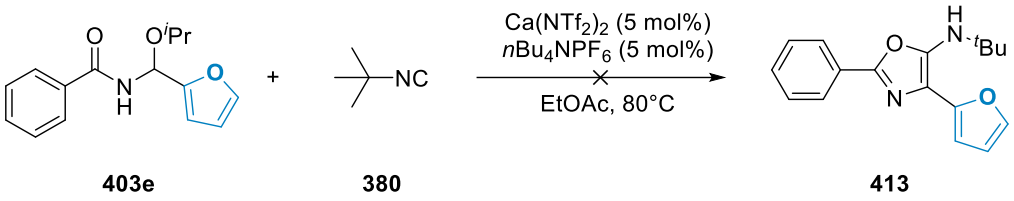
Scheme 70. Formation of bis-amide derivative when aplied to saturated systems

Only tertiary substituted alkyl moieties were attempted here as any protons beta to the nitrogen have shown a tendency to eliminate upon formation of the *N*-acyliminium ion resulting in the formation of an enamide **412** (Scheme 71).



Scheme 71. Formation of enamide when using alkyl substituents.

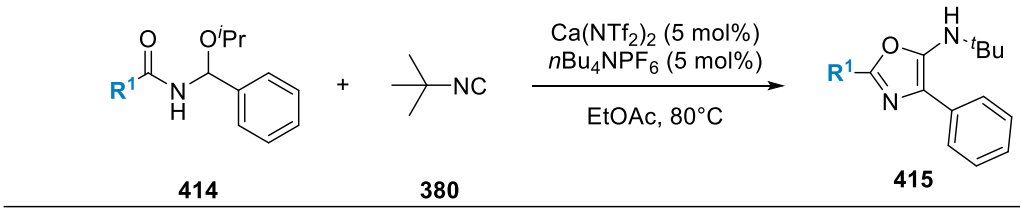
Furthermore, when the furan substituted *N*-acyl-*N,O*-acetal **403e** was employed, a complex mixture of inseparable products was obtained (Scheme 72). This was unsurprising given the acetal precursor is analogous to the precursor used in a Piancatelli reaction, in which calcium catalysed transformations have been reported.[35, 36, 144]



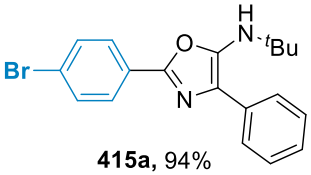
Scheme 72. Attempted Synthesis of furan substituated 5-amino-oxazoles

To continue with the modular approach, attention was then turned to functionalisation arising from the amide component of the *N*-acyl-*N,O*-acetal, resulting in variation of the 2-position of the 5-amino-oxazole (Table 43). This proved to be more fruitful, with both electron-withdrawing (**415a**-**415f**) and electron-donating (**415g**) groups being tolerated in high yields. Heterocycles such as furan and thiophene were both well tolerated (**415h**-**415i**) and the reaction was also undeterred by steric factors arising from ortho substituted aromatics (**415j**).

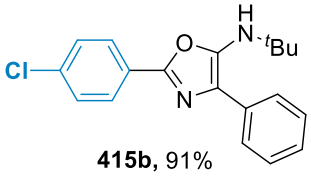
Table 43. Functionalised Oxazoles - Amide Variation



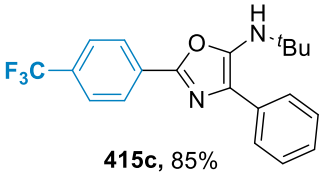
414 380 415



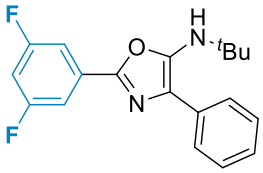
415a, 94%



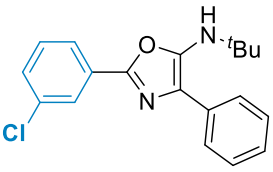
415b, 91%



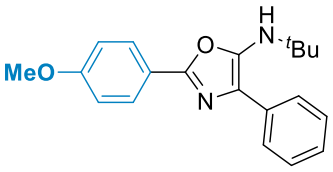
415c, 85%



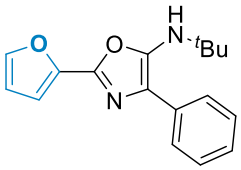
415d, 91%



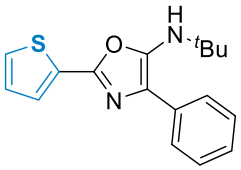
415e, 91%



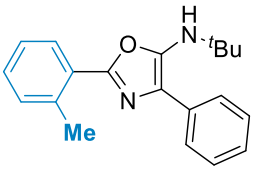
415f, 97%



415g, 65%

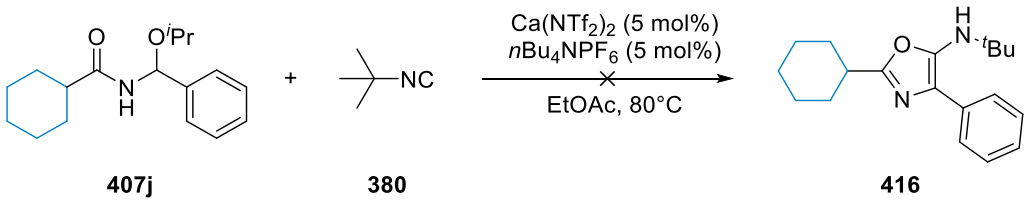


415h, 89%



415i, 95%

As with the 4-substituted-5-amino-oxazoles, reactivity towards saturated derivatives was then studied. When the cyclohexyl acetal **407j** was subjected to the optimised conditions, a rapid degradation profile was observed, which resulted in a complex mixture being isolated (Scheme 73). ^{1}H NMR studies provided some insight into this, with traces of aldehyde being detected suggesting decomposition of **407j**.



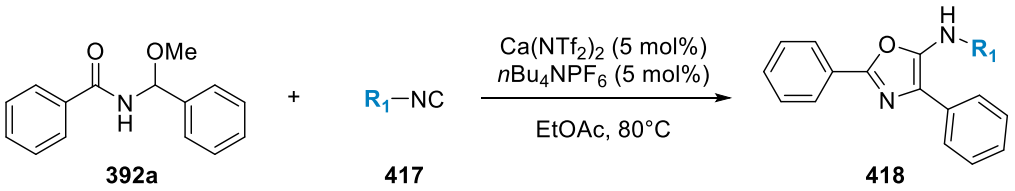
407j 380 416

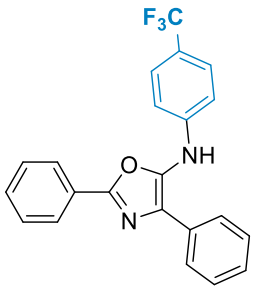
Scheme 73. Attempted synthesis of alkyl substituted 5-amino-oxazoles

Finally, to ensure the methodology was fully modular, a range of isocyanides were then studied (Table 44) which allows for the direct installation of the amine functionality. Aryl isocyanides with electron-withdrawing (**418a**-**418c**), electron-donating (**418d**) and

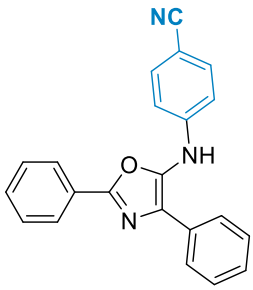
mixed electronic groups (**418e**) were all tolerated in good to excellent yields. Other alkyl isocyanides were successful with benzyl (**418f**) and cyclohexyl (**418g**) offering alternative unsaturated derivatives with the former being a versatile protecting group and yield comparable to the initial optimisation carried out in Table 33

Table 44. Functionalised Oxazoles - Isocyanide Variation

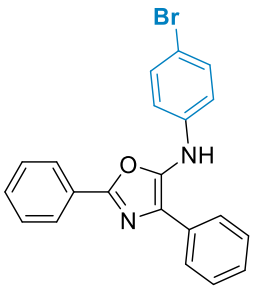




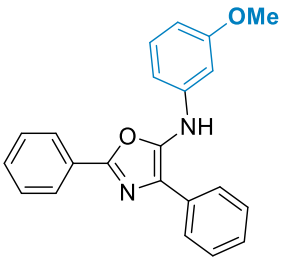
418a, 81%



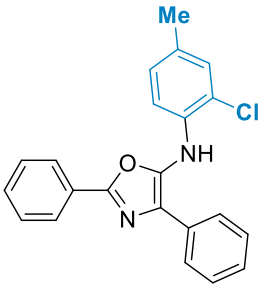
418b, 86%



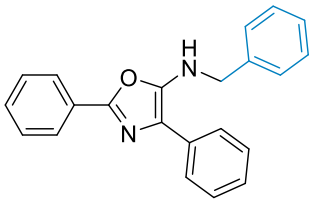
418c, 82%



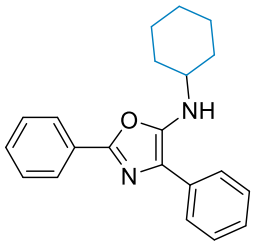
418d, 51%



418e, 86%



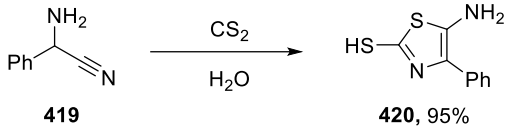
418f, 55%



418g, 62%

4.3.4. Application to Thiazoles

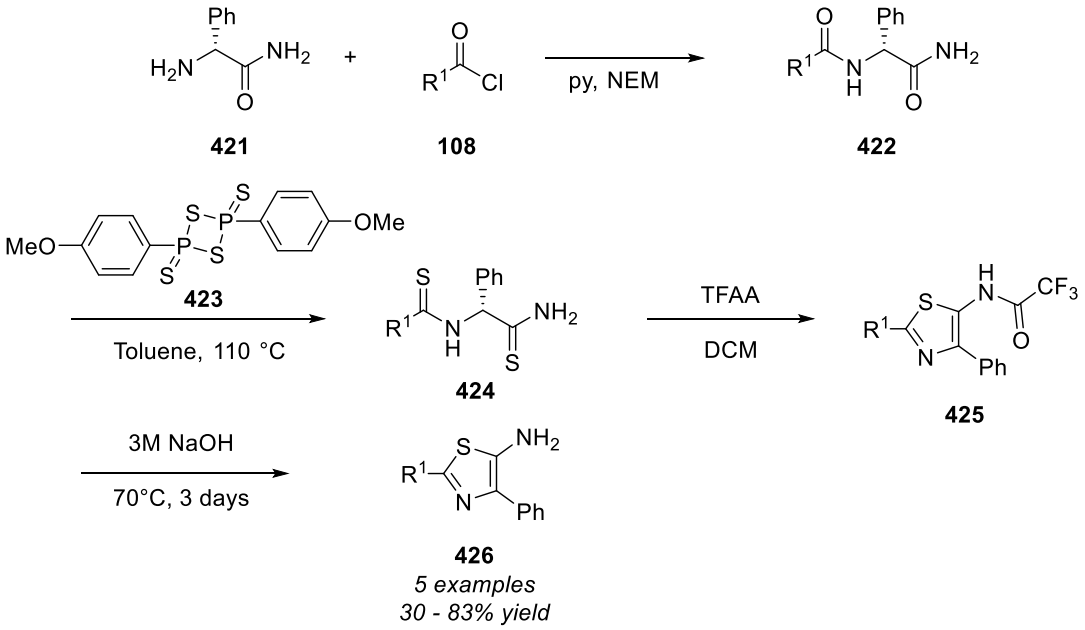
Whether this elimination-cyclisation methodology could be applied to the synthesis of 5-aminothiazoles was then studied. Traditionally, 5-aminothiazoles are accessed using the Cook-Heilbron synthesis which was reported in 1947.[145] The reaction of an α-amino-nitrile **419** with carbon disulfide under basic conditions results in the formation of a 5-aminothiazole derivative **420** (Scheme 74). While a useful initial report, the use of carbon disulfide is required which limits usability within laboratories.



419 **420**, 95%

Scheme 74. Cook-Heilbron synthesis of 5-aminothiazoles.[145]

More recently, Chen and co-workers reported a stepwise approach to 5-aminothiazoles from *N*-phenylglycinamide **421** (Scheme 75). This approach involved reacting **421** with a range of acid chlorides **108** followed by reacting with Lawessons' reagent **423** to give thioamide **424**. This intermediate was immediately reacted with trifluoroacetic anhydride to give 5-amidooxazoles **425** and could be deprotected under basic conditions to give a library of 5-aminothiazoles **426**. The authors do not observe any regioselectivity issues in the dithionation, cyclisation step with no oxazole product being detected meaning this method offers control of the 2-position of the thiazole.

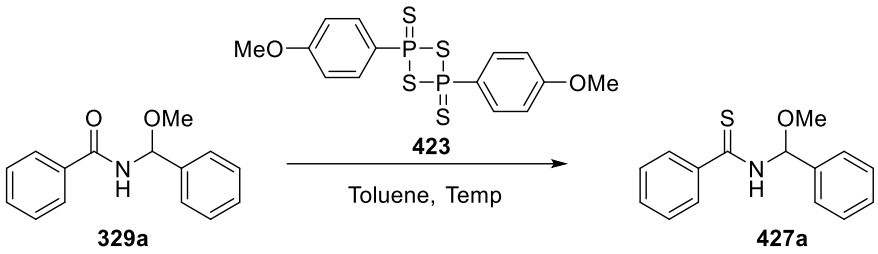


Scheme 75. Synthesis of 5-aminothiazoles *via* a thionation, TFAA cyclisation, deptroction sequence.[146]

As the synthesis of 5-aminothiazoles is reported sparingly within the literature, a modular and sustainable method to access them would be advantageous. Added to this, 2-aminothiazoles have shown continuous promise in medicinal chemistry suggesting amino-substituted thiazoles would be highly desirable building blocks for medicinal chemists.[147]

To access 5-aminothiazoles using this dehydrative-addition-cyclisation methodology, access to a range of *N*-thioacyl-*N,O*-acetals **427** was first required . As a library of *N*-acyl-*N,O*-acetals had already been synthesised, it was first postulated whether this library could be thionated directly using Lawessons' reagent (Table 45). When subjecting **392a** to Lawesson's reagent **423** at 110 °C decomposition of the starting material was observed and a complex mixture was obtained (entry 1). Lowering the temperature further resulted in the same outcome (entries 2,3 and 4).

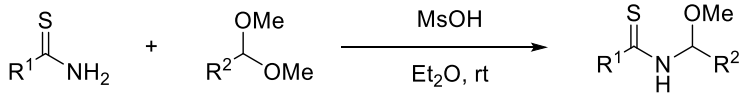
Table 45. Attempted thionation of 392a using Lawessons' reagent.



329a 427a

Entry	Temp	Time	Yield
1	110 ºC	12 h	decomp.
2	80 °C	12 h	decomp.
3	60 °C	12 h	decomp.
4	40 °C	12 h	decomp.

A survey of the literature found the synthesis *N*-thioacyl-*N,O*-acetals **427** is reported once,[148] using thioamides **428** and dimethyl acetals **429** in the presence of methanesulfonic acid (Scheme 76).

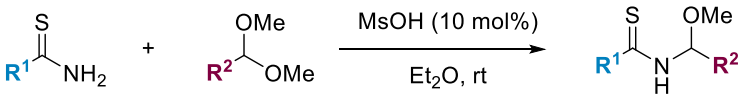


428 **429** **427**

Scheme 76. Synthesis of *N*-thioacyl-*N,O*-acetals reported in the literature.[148]

Upon repeating the reaction, it was found that using catalytic MsOH proved to be more successful resulting in cleaner reactions and a small library of *N*-thio-acyl-*N,O*-acetals were synthesised (Table 46). In addition to phenyl substituted product **427a**, the 4-bromo-substituted products **427b** and **427c** could also be synthesised in synthetically useful yields. Utilising the methodology reported by Huang[143] and Manolikakes[137] for the synthesis of *N*-acyl-*N,O*-acetals proved unsuccessful when using a thioamide **428** in place of an amide. An inseparable complex mixture of products was obtained in both cases.

Table 46. Synthesis of *N*-thio-acyl-*N,O*-acetals by an adapted literature procedure.

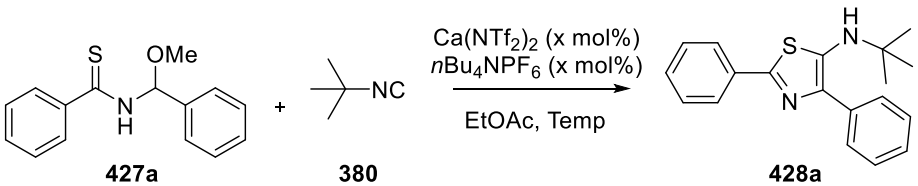


428 **429** **427**

427a, 24%	**427b**, 36%	**427c**, 34%

When **427a** was subjected to the optimised conditions, product **428a** formed in an acceptable yield of 67% (entry 1, Table 47). To improve this yield further, some small modifications to the reaction conditions were made. Increasing the temperature to 100 °C initially had little effect (entry 2), as did increasing the catalyst loading at 80 °C (entry 3). However, a combination of higher catalyst loading, and higher temperature, was found to provide the desired 5-aminothiazole **428a** in high yield (entry 4).

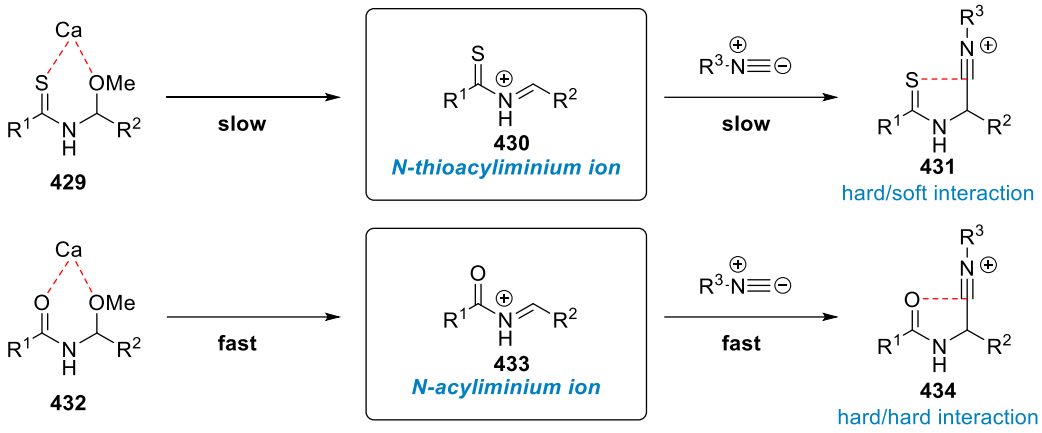
Table 47. Modification of optimised conditions for the synthesis of 5-aminothiazoles.



427a **380** **428a**

Entry	Loading	Temp	Yield
1	5 mol%	80 °C	67%
2	5 mol%	100 °C	70%
3	10 mol%	80 °C	63%
4	**10 mol%**	**100 °C**	**83%**

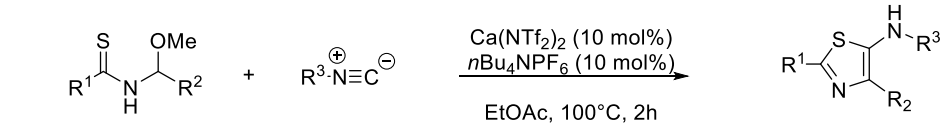
The re-optimised conditions and improvement in reaction outcome and yield can be readily explained (Scheme 77). Firstly, the formation of the *N*-thioacyliminium ion **430** is slower due to a weaker interaction with the calcium centre **429**. At lower catalytic loadings the reaction proceeded much slower with slight decomposition being observed and it was reasoned generating larger quantities of *N*-thioacyliminium ion would result in a cleaner reaction. Secondly, the cyclisation of the nitrilium ion **431** would also be slower, again due to a hard-soft interaction between the nitrilium and sulfur atom of the thioamide, and a higher temperature would help facilitate this step and drive the reaction to completion.

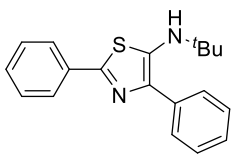


Scheme 77. Comparison of reactivity of 5-aminothiazole formation compared to 5-aminooxazole.

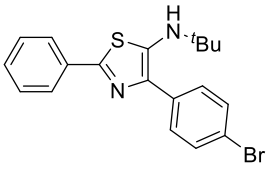
A range of *N*-thioacyl-*N,O*-acetals was then subjected to the modified reaction conditions (Table 48). Firstly, subjecting the library of starting materials **427** to *tert*-butyl-isocyanide **435** proved successful forming products **436a-436c** in good yield. Changing the isocyanide to cyclohexyl-isocyanide also proved successful forming products **436d-436f** again in good yield.

Table 48. Synthesis of 5-aminothiazoles

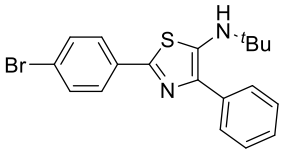




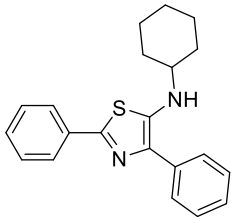
436a, 83%



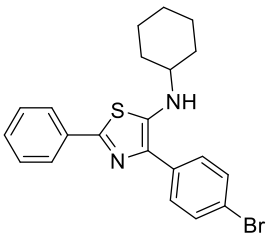
436b, 76%



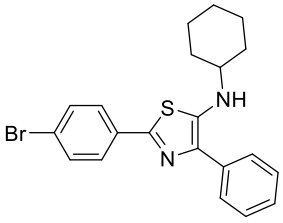
436c, 89%



436d, 63%



436e, 60%



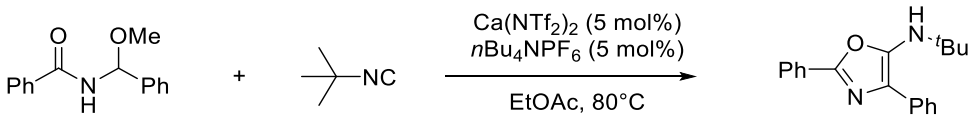
436f, 65%

When applied to aryl isocyanides, a complex mixture of products was obtained with rapid degradation of the starting material being observed. This can be attributed to the

N-thioacyliminium ion being less electrophilic coupled with a less nucleophilic aryl isocyanide.[65] These findings were comparable to others,[135] with this methodology unable to improve on this.

4.3.5. Catalytic Studies

Given one of the underlying aims of this project is to produce complex heterocycles using sustainable methodology, the reusability of the catalyst was a necessary requirement of the study. Although, it is not reusable in the traditional sense, whether the catalyst can tolerate multiple turnovers was investigated. This was studied by setting up a model reaction for the synthesis of **395a** as normal. Upon completion of the reaction after 20 mins, an aliquot was taken to calculate the NMR yield and subsequently the same flask was recharged with a further 1 equivalent of **392a** and 1.2 equivalent of isocyanide **380** (Scheme 78).



392a **380** **395a**

Scheme 78. Model reaction for iterative additions of 476 and 422 to the same reaction vessel.

The flask was recharged with reagents 4 times. As shown in Figure 41 the catalyst can tolerate 3 full turnovers without any noticeable decrease in yield and an 82% overall yield. After 5 additions the overall yields drops to 51% with the mass balance being unreacted starting material. The retardation of the reaction can be better depicted in Figure 41 whereby the increasing about of starting material can be seen by the increase in amount of the doublet at δ 9.18 ppm (N-H). This suggests catalyst poisoning whereby super-stoichiometric amounts of alcoholic by-products are coordinating to the calcium centre.

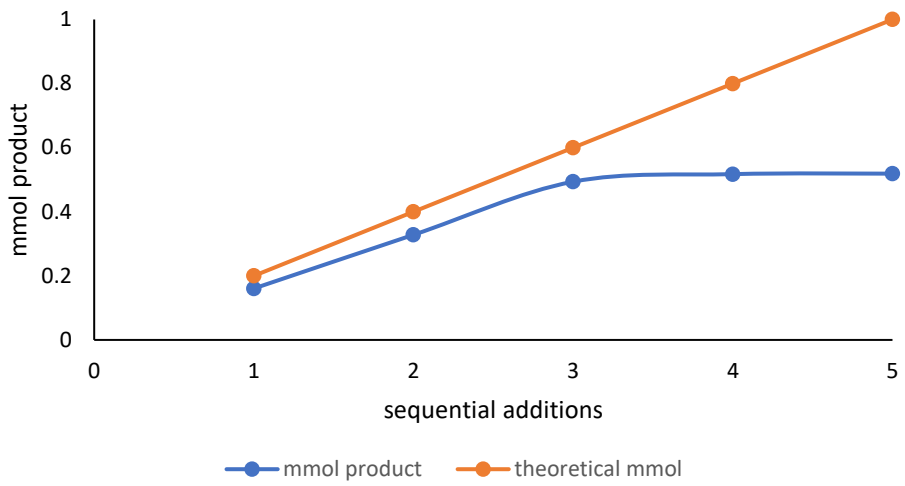


Figure 40. Graph showing the mmol of product formed after each consective addition of starting material with the theoretical number of mmol. The mmol of product was calculated usig ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

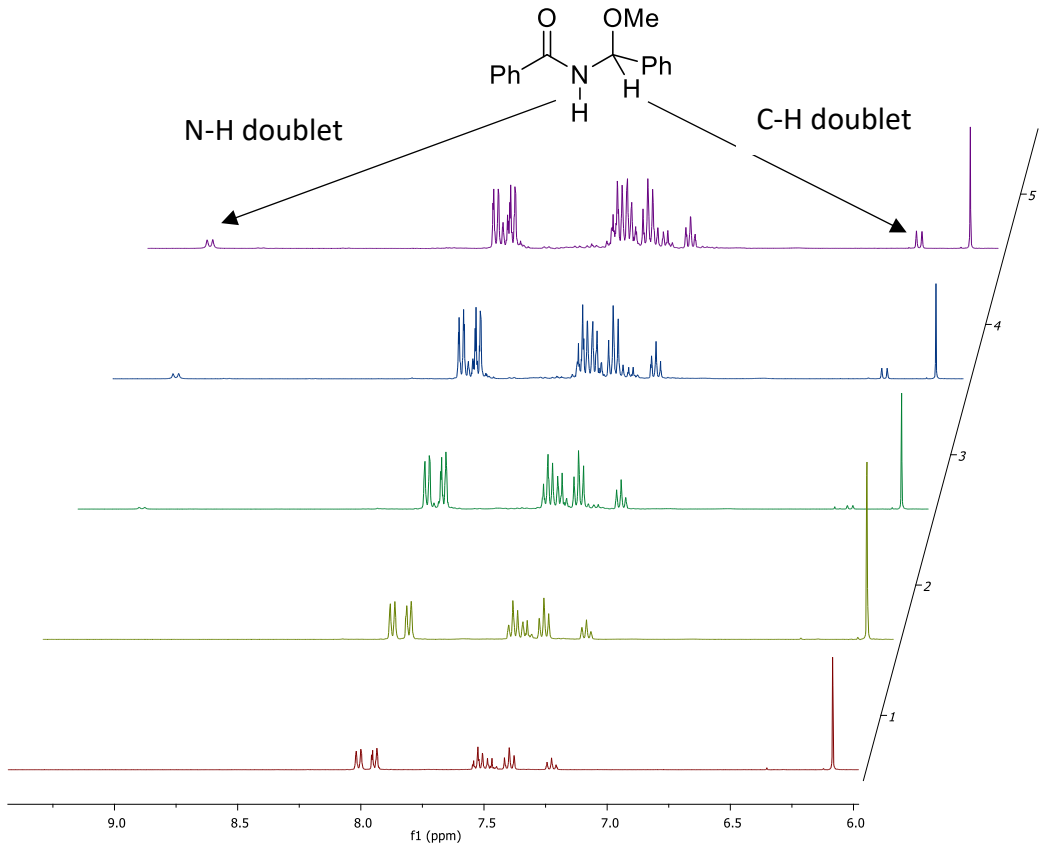


Figure 41. Stacked spectra of ^{1}H NMR aliquots taken at each sequential addition. The first addition is at the bottom, with the increasing concentration of starting material being observed by the appearrance of the doublet at δ9.18 ppm.

These results show the catalyst is indeed reusable and can facilitate three full cycles without any effect on yield. It also demonstrates that the calcium catalyst is largely unhindered by the super-stoichiometric amounts of alcoholic by-products produced.

4.3.6. Proposed Mechanism

A proposed catalytic cycle for the formation of 5-aminooxazoles is depicted below (Figure 42). Combination of the catalyst precursors forms the active catalyst [PF_6^- $Ca^{2+}NTf_2^-$] **241**. This in turn results in the formation *N*-acyliminium ion **104** and the intermediate **437**. Trapping of the *N*-acyliminium ion with an external isocyanide **438** results in the formation of nitrilium intermediate **439**. The subsequent trapping of the nitrilium ion by cyclisation forms intermediate **440** while simultaneously, re-entry of weakly coordinating PF_6^- results in the liberation of the methanol by-product. Aromatisation of **440** forms product **389**. In addition to the proposed catalytic cycle depicted below, there is an alternative mechanism that cannot be discarded, whereby

isocyanide **438** reacts directly with *N*-acyliminium **104** in a concerted [4+1]-cycloaddition.

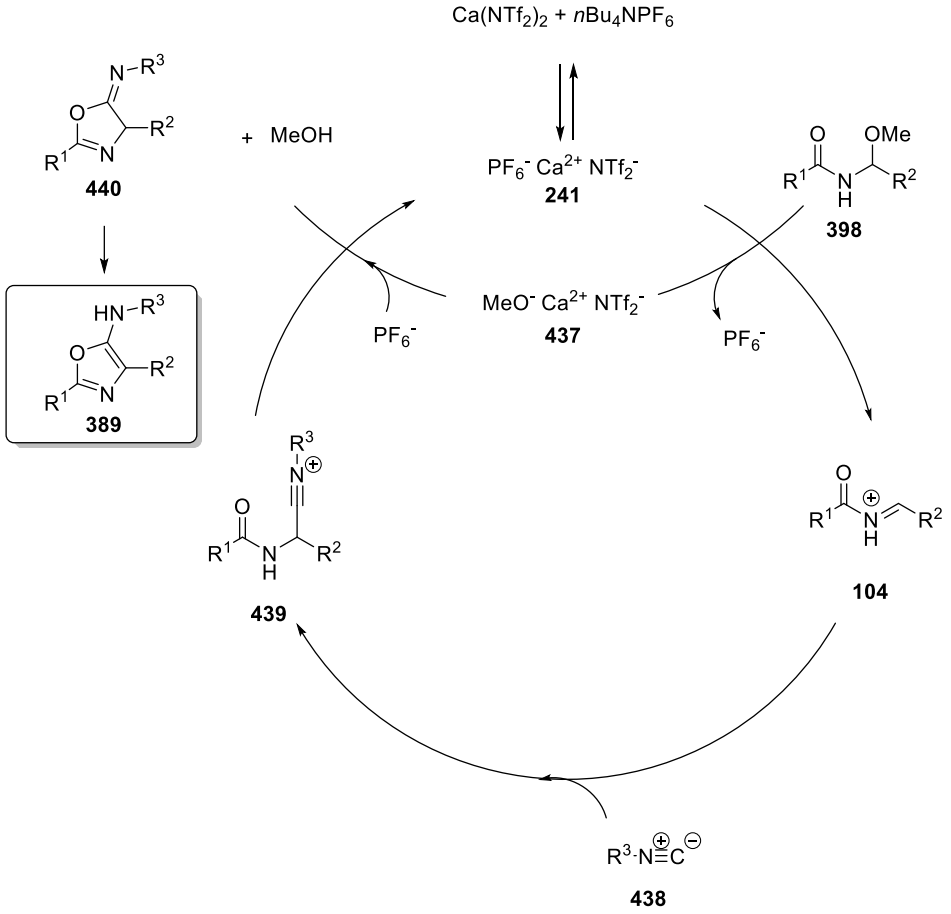


Figure 42. Proposed catalytic cycle for the formation of 5-aminooxazoles

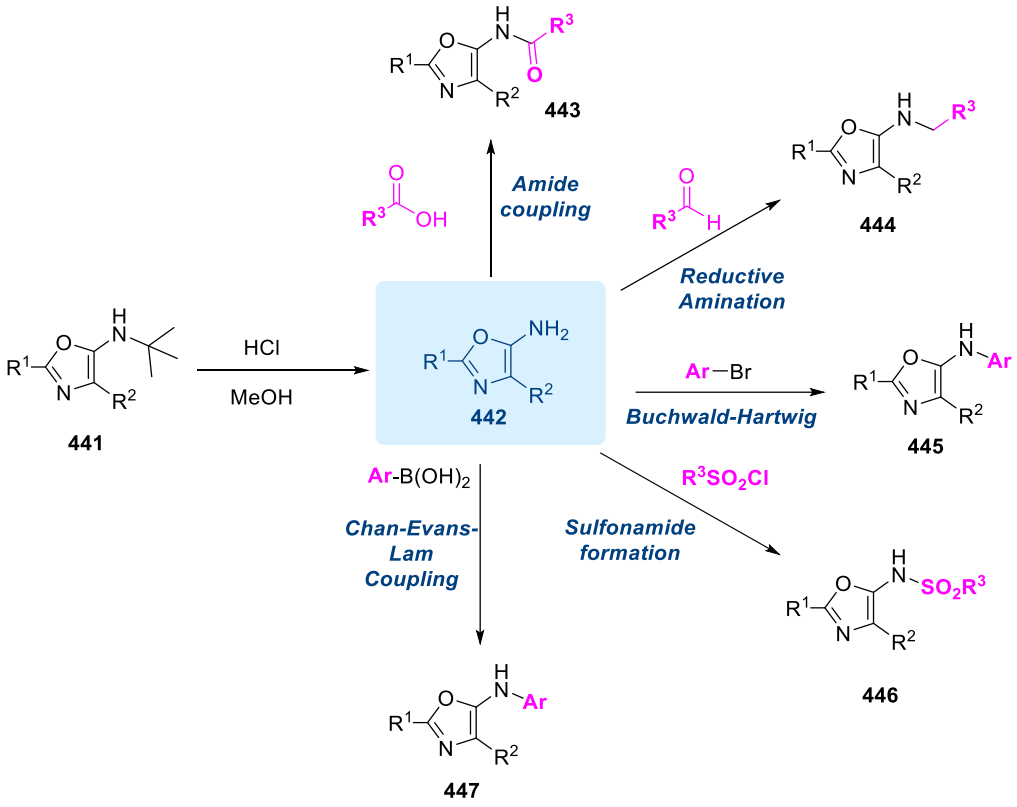
4.4. Conclusions

In summary, a highly modular and sustainable route to access 5-amino-oxazoles and 5-amino-thiazoles has been developed. Calcium has been shown to be an effective catalyst at catalytically generating *N*-acyliminium ions from *N*-acyl-*N,O*-acetals which can be trapped with isocyanides and undergo a subsequent cyclisation to afford 5-aminooxazoles. The mild nature of the reaction, utilising a sustainable catalyst in a benign solvent, results in a high amount of functional group tolerance with all positions of the heterocycle being varied. The methodology has also been extended towards the catalytic generation of *N*-thioacyliminium ions for access to 5-aminothiazole derivatives. Furthermore, the reaction displays a high atom economy, with the sole by-products being innocuous alcohols. Although the catalyst employed is not reusable in the

traditional sense, it has been shown that the calcium catalyst remains fully active for up to three sequential additions of starting materials offering the scope for iterative additions of varying starting materials.

4.5. Future Work

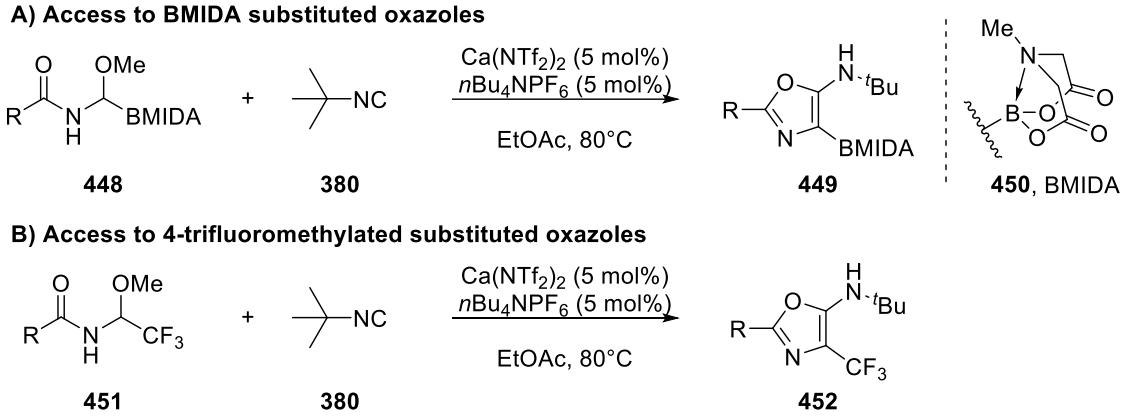
The methodology employed here was designed so the installation of an amine functional handle offers scope for further synthetic manipulation (Scheme 79). A deprotection of the *tert*-butyl group on the amine would provide access un-protected 5-aminooxazole **511** which could be subjected to a wide range of well-known transformations.



Scheme 79. Deprotection of 441 and synthetic maniuplations.

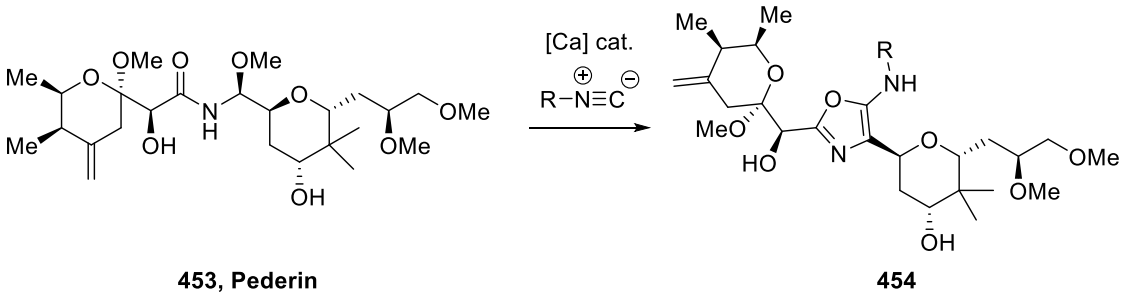
Another avenue for future work on this project could focus on the addition of more desirable groups attached directly to the oxazole ring. Recently, the first formyl MIDA boronate has been synthesised and subjected to a range of nucleophiles.[149] Utilisation of the MIDA aldehyde for the synthesis of a BMIDA-substituted *N*-acyl-*N,O*-acetal **448** and subsequent subjection to the optimised conditions would result in an 5-aminooxazole **449** with a BMIDA **450** handle at the 4-position offering potential for

cross-coupling directly to an oxazole (Scheme 80A). Alternatively, the Lautens group have utilised *N,O*-acetals with a trifluoromethyl moiety **451**.[150] These have potential as precursors for the formation of 4-trifluoromethylated oxazoles **452** under these optimised conditions (Scheme 80B).



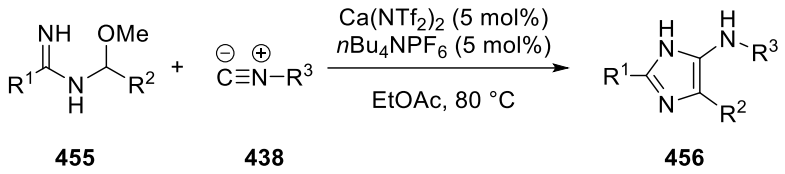
Scheme 80. Proposed access to 4-BMIDA or 4-CF_3 substituted oxazoles.

Due to the mild nature of the methodology developed, this transformation could also be applied to late-stage functionalisation of existing natural products which contain the *N*-acyl-*N,O*-acetal motif. For example, Pederin **453** which is a natural product found in beetles and has shown promising anti-cancer like properties.[151] Subjecting Pederin **453** to the optimised conditions would allow for a mild and direct installation of a 5-aminooxazole in the centre of a natural product core offering a new library of scaffolds such as **454** for screening and medicinal chemistry projects (Scheme 81).



Scheme 81. Postulated late-stage functionalisation of natural products with an *N*-acyl-*N,O*-acetal motif.

Furthermore, having demonstrated access to oxazoles and thiazoles, it is possible that the methodology could also be applied to synthesise 5-amino-imidazoles **456** (Scheme 82). However, there are currently no reported preparations for the synthesis of amidine derived acetals **455** and so preparation of them would first need to be investigated.



455 **438** **456**

Scheme 82. Postulated access to 5-amino-imidazoles.

5. Chapter 5: Intermolecular trapping of *N*-acyliminium Ions with Radicals

5.1. Introduction

5.1.1. 1,2-Diamines

1,2-Diamines **457** are highly versatile compounds with a long-established and wide-ranging use in chemistry (Figure 43). The structural motif features in a range of medicinal agents such as Eloxatin **458** which is an FDA approved anti-cancer drug[152] and Tamiflu **459** which is used to treat influenza A and B.[153] They have also found extensive use in transition metal catalysis and feature in the Jacobsen epoxidation catalyst **460**[154] and in the Grubbs' II catalyst **461**.[155] Furthermore, the 1,2-diamine motif is prevalent in a range of natural products including agelastatin A **462** and balanol **463**.

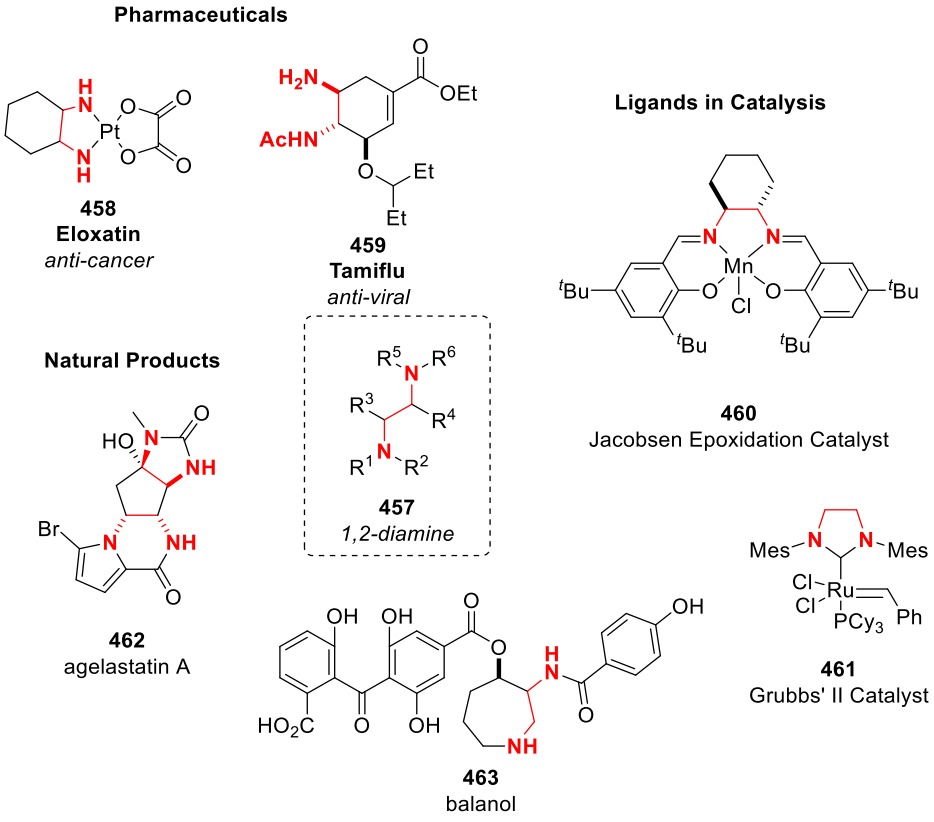
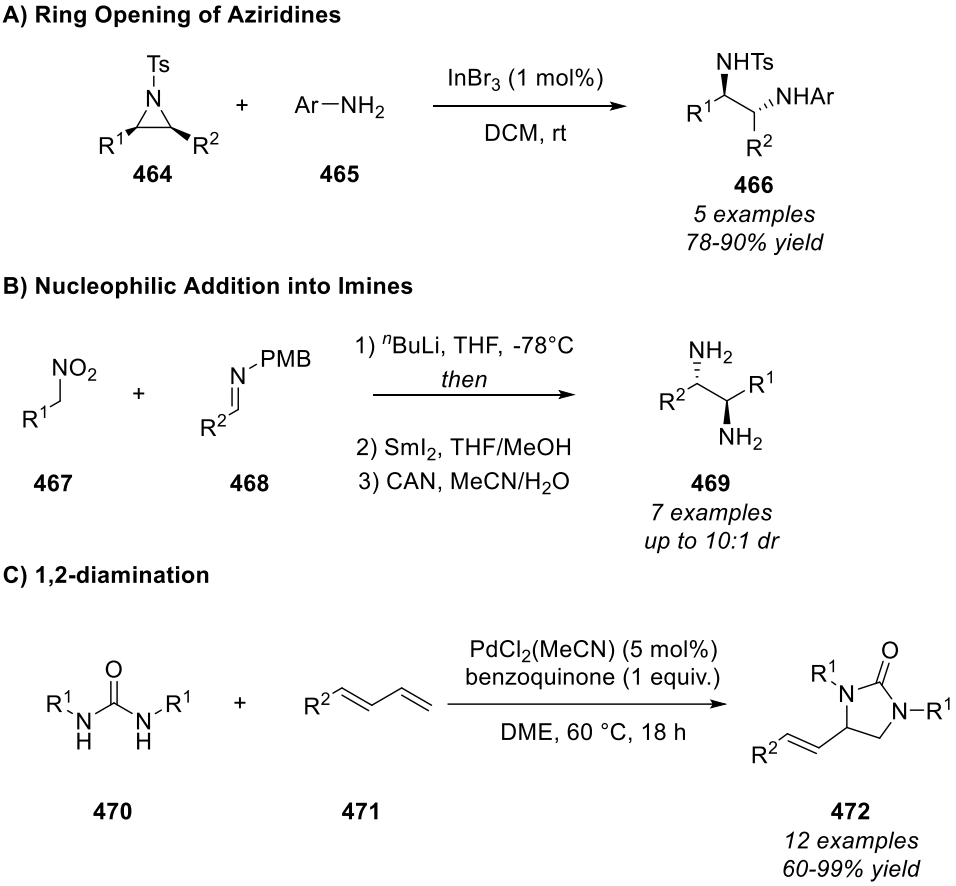


Figure 43. General structure of a 1,2-diamine and it's wide ranging applications.

Despite their wide-ranging occurrence, there are currently limited modular methods for their synthesis. Traditionally they can be assembled *via* several routes (Scheme 83).

Aziridines **464** can be ring opened in the presence of an amine nucleophile **465** and Lewis acid, as demonstrated by Yadav (Scheme 83A).[156] The nucleophilic addition into imines is also an effective way to access 1,2-diamines (Scheme 83B).[157] The Anderson group have reported a diastereoselective addition of alkyl nitronate anions into PMP-protected imines **468** in a nitro-Mannich type reaction. Deprotonation of nitro alkanes **467** using ^{n}BuLi followed by reduction of the nitro group and subsequent PMP-deprotection afforded a range of 1,2-diamines **469** with moderate to good diastereoselectivity, which is driven by H-bonding in the Zimmermann-Traxler transition state. The Booker-Millburn group reported a palladium catalysed 1,2-diamination of conjugated dienes **471** for access to 1,2-diamine type scaffolds (Scheme 83C).[158] The authors proposed the reaction proceeds *via* an amino-palladation of the olefin and amine in the presence of palladium(II) followed by a direct reductive displacement by a second amine to generate the product and palladium(0) which is subsequently reoxidised by the benzoquinone. The methodology provides access to a range of imidazolidinone scaffolds in good to excellent yields.

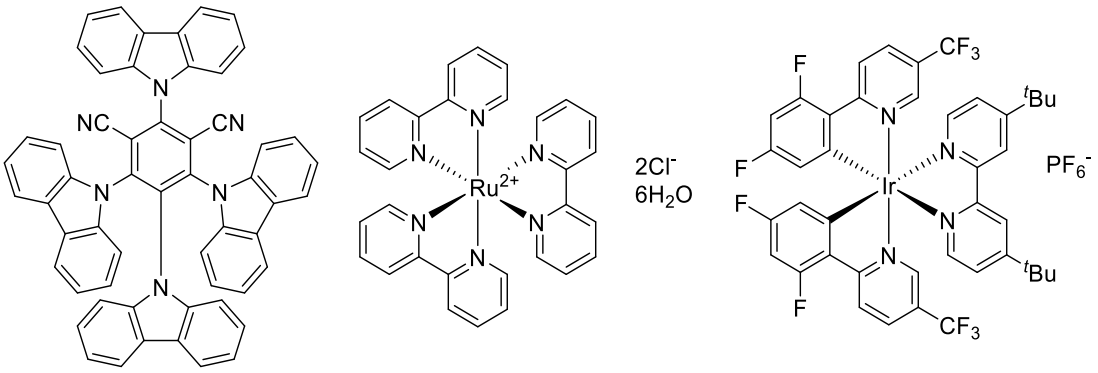


Scheme 83. Synthesis of 1,2-diamines.

While these methods all provide access to 1,2-diamines they have some limitations. For example, the nucleophilic ring opening of aziridines requires access to pre-functionalised aziridines. Also, the nucleophilic addition to imines reported by Anderson, was only tolerant to nitro-alkanes. Additionally, this approach had multiple steps and utilised both stoichiometric reductants and oxidants to access their desired scaffolds. The 1,2-diamination procedure reported by Brooker-Milburn cites a common problem when using transition metals, with the authors disclosing that the choice of the less-nucleophilic urea was selected to prevent direct amine coordination to the metal, and an intramolecular process was devised to limited side reactions. Due to these limitations in the traditional approaches, more streamlined and modular methodology for their assembly is always desirable.

5.1.2. Photoredox Catalysis

Over the past two decades, the development of photoredox catalysis in organic synthesis has been on an exponential trajectory. The field is underpinned by using visible light to excite a photocatalyst which in the excited state can induce an accompanying substrate to participate in a reaction that was unattainable by thermal control. Transition metal of polypyridyl complexes or organic photosensitizers are efficient catalysts to facilitate these transformations (Figure 44).



473
4CzIPN
PC^{-1}/PC E^{red} = *-1.21 V*

474
$Ru(bpy)_3Cl_2$
Ru(I)/Ru(II) E^{red} = *-1.33 V*

475
$[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$
Ir(II)/Ir(III) E^{red} = *-1.45 V*

Figure 44. Common transition metal and organic photoredox catalysts.

When a photoredox transition metal catalyst is subjected to visible light and absorbs a photon, a metal to ligand charge transfer (MLCT) process occurs whereby an electron in the photocatalyst's t_{2g} orbitals is excited to a ligand centred π* orbital (Figure 45). The electron in the singlet state then undergoes a rapid inter-system crossing to the longer-lived triplet state, due to its subsequent decay being spin forbidden. The long-lived triplet state can then either act as an oxidant or reductant. When acting as an oxidant, the triplet state can thereby accept an electron into its partially filled t_{2g} orbital. When acting as a reductant, an electron can be expelled from the high energy triplet state.

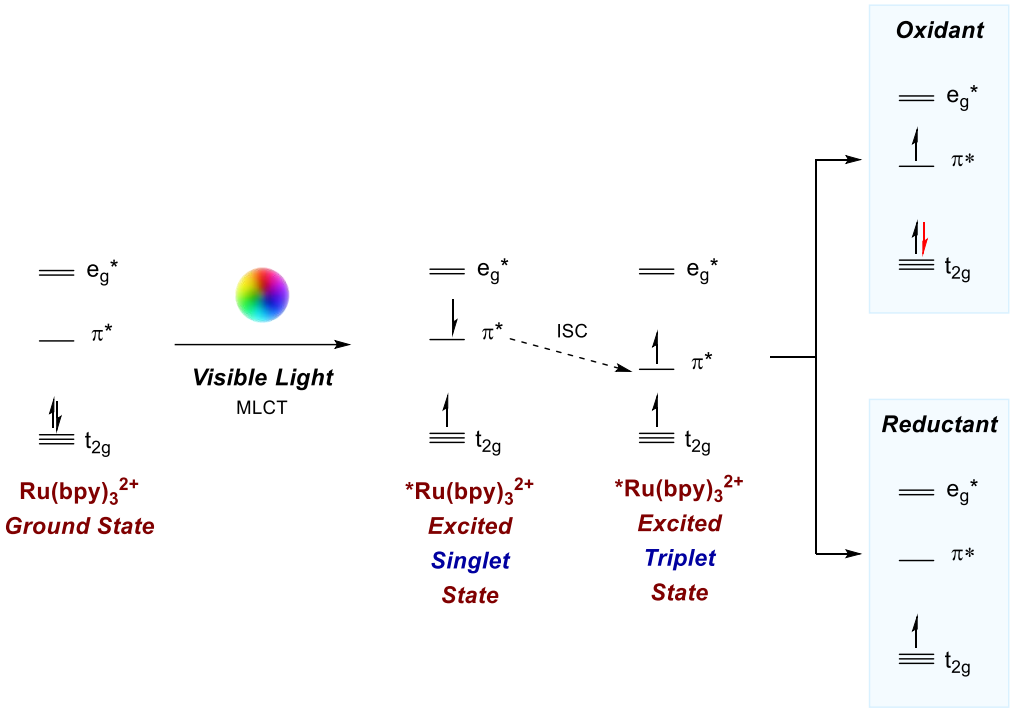


Figure 45. Molecular orbital depiction of the MLCT process of Ru(bpy)$^{2+}$ and it's ability to act as either an oxidant or reductant.

Due to this unique property, photoredox catalysed transformations can either proceed *via* an oxidative or reductive quenching cycle (Figure 46). When an oxidative quenching cycle proceeds, an electron-acceptor (A) accepts the electron from the π* orbital resulting in a radical anion. Regeneration of the catalyst then proceeds *via* oxidation of an electron donor D. When a reductive quenching cycle proceeds, an electron donor reduces the photoexcited $^*Ru(bpy)_3^{2+}$ forming a radical cation. An oxidant then re-oxidises the catalyst back to the ground state $Ru(bpy)_3^{2+}$ forming a radical anion in the process.

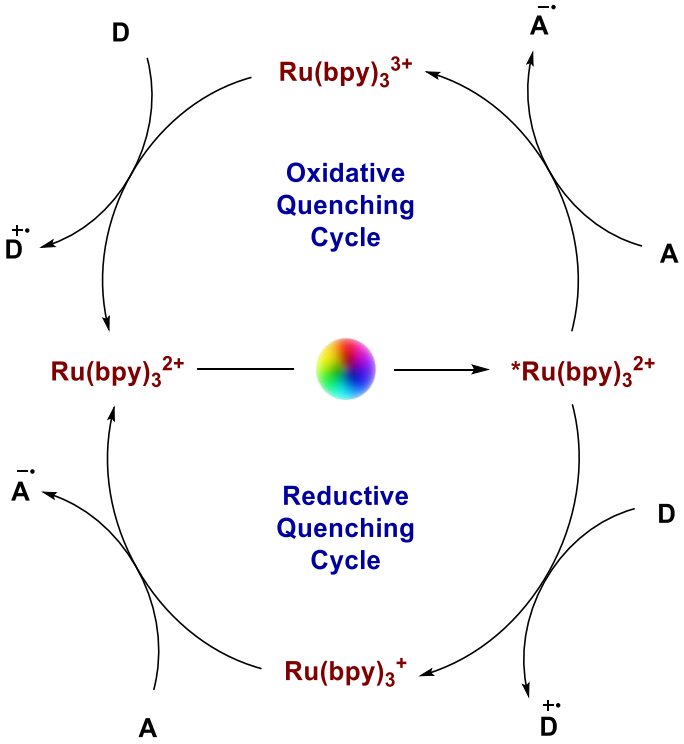
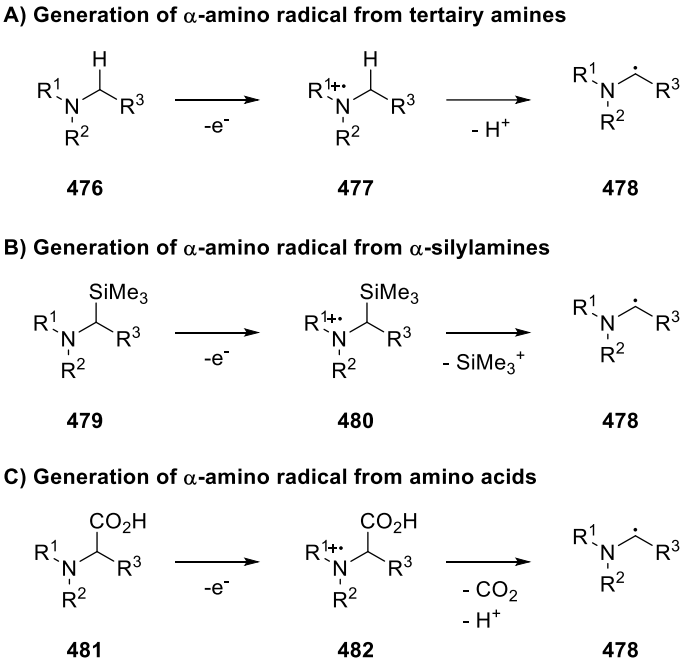


Figure 46. Oxidative and reductive quenching cycle of $Ru(bpy)^{2+}$.

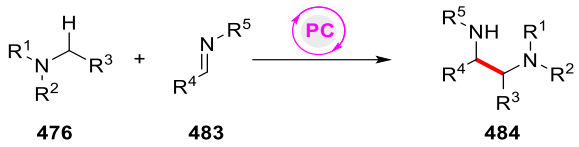
5.1.2.1. α-Amino Radicals

Amines **476** are ideal candidates to undergo single electron oxidation owing to their electron-rich nature. They can be oxidised into a radical cation **477** under photoredox conditions. Once oxidised, the C-H bond adjacent to the nitrogen atom is greatly acidified (pK_a = 8) and deprotonation occurs readily forming an α-Amino radical **478** and a proton (Scheme 84A). α-Amino radicals can also be generated from α-silyl amines **479** and amino acids **481**.



Scheme 84. Generation of α-amino radicals from a range of precursors.

The reactivity of α-amino radicals towards a range of electrophiles has been well studied. Their addition into alkenes, alkynes, aromatic rings and in substitution reactions have all been reported.[159] It is their addition into nitrogen containing electrophiles, particularly imines **483** and their derivatives that is of particular interest, because it gives access to 1,2-diamine derivatives **484** (Scheme 85).



Scheme 85. Overall transformation for addition of α-amino radical into an imine.

When an α-amino radical reacts with an imine under photoredox conditions, there are two possible mechanisms that can take place. The first pathway is *via* a radical-radical coupling between two α-amino radicals **478** and **485** whereby **485** is generated by a single-electron reduction of imine **483** to regenerate the photocatalyst (Figure 47A). The alternative pathway is *via* direct addition of α-amino radical **478** into the imine to generate radical cation **486** (Figure 47B). Reduction of the resulting radical cation reoxidises the photocatalyst.

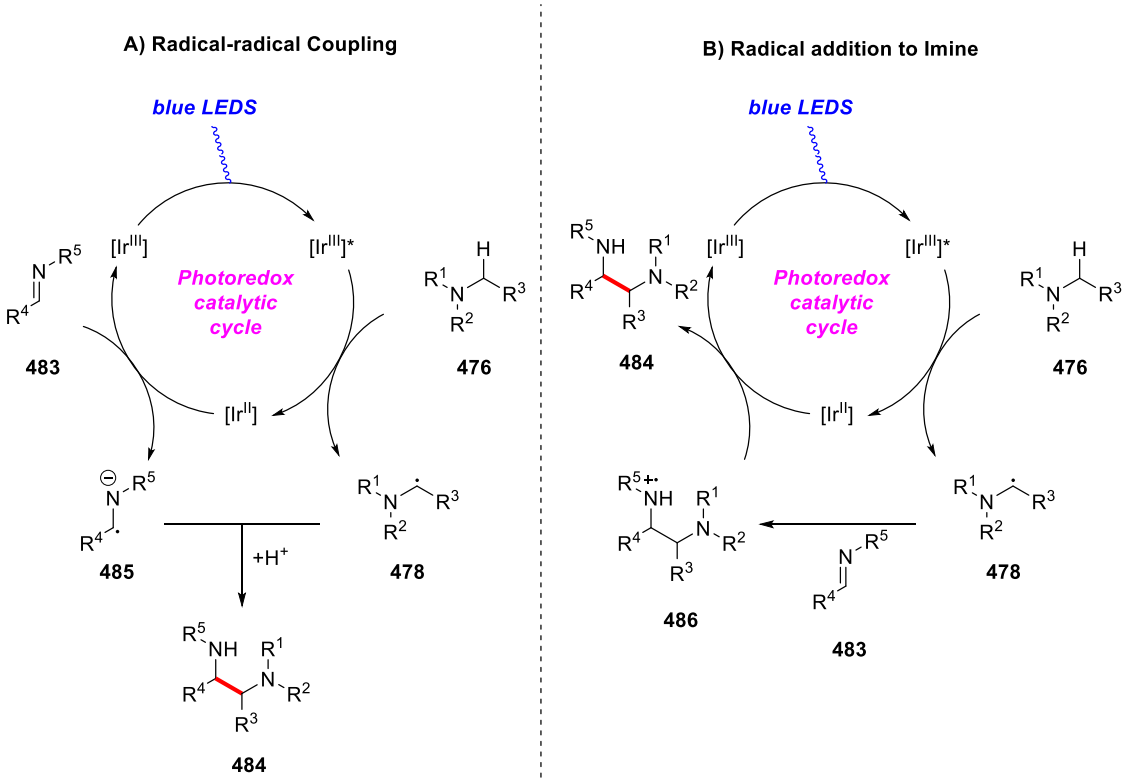
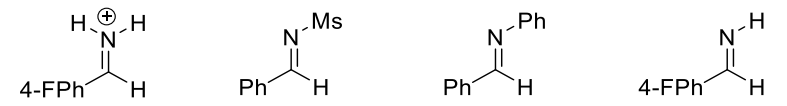


Figure 47. Mechanistic pathways for α-amino radical addition into an imine.

To determine which mechanism dominates, the redox potentials of the imines/iminium salts must be considered **487-490** (Figure 48). *N*-sulfonyl imines **488** are more readily reduced than *N*-aryl imines **489** and even more reducible than *N*-H imines **490**. However, the reduction potentials of **489** and **490** fall out of the range of most photoredox catalysts suggesting that electron-transfer to a neutral imine is thermodynamically unfavourable suggesting a direct radical addition to be more favourable. A phenomenon known as proton-coupled electron transfer (PCET) has shown that by coordination of a Brønsted acid to generate the equivalent iminium ion **487** can significantly increase the reduction potential of an imine (**487** compared to **490**).[160]



487 E^{red} = - 1.10 V

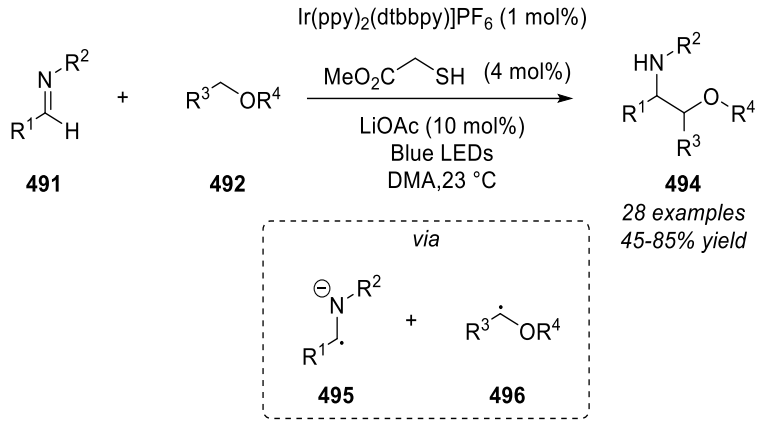
488 E^{red} = -1.45 V

489 E^{red} = -1.91 V

490 E^{red} = - 2.43 V

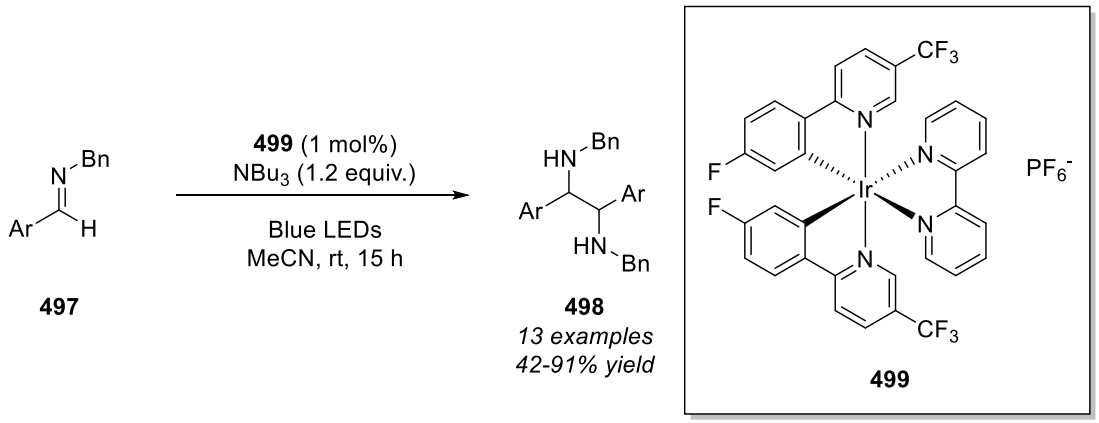
Figure 48. Reduction potentials of imines and iminiums.

The α-functionalisation of amines using this mode of activation was first reported by MacMillan in 2014 when they reported the coupling of benzylic ethers **492** with a range of imines **491** to afford β-amino ethers **494** (Scheme 86).[161] The authors propose the reaction proceeds *via* an α-amino radical **495** and benzylic radical **496** which undergo a radical-radical coupling.



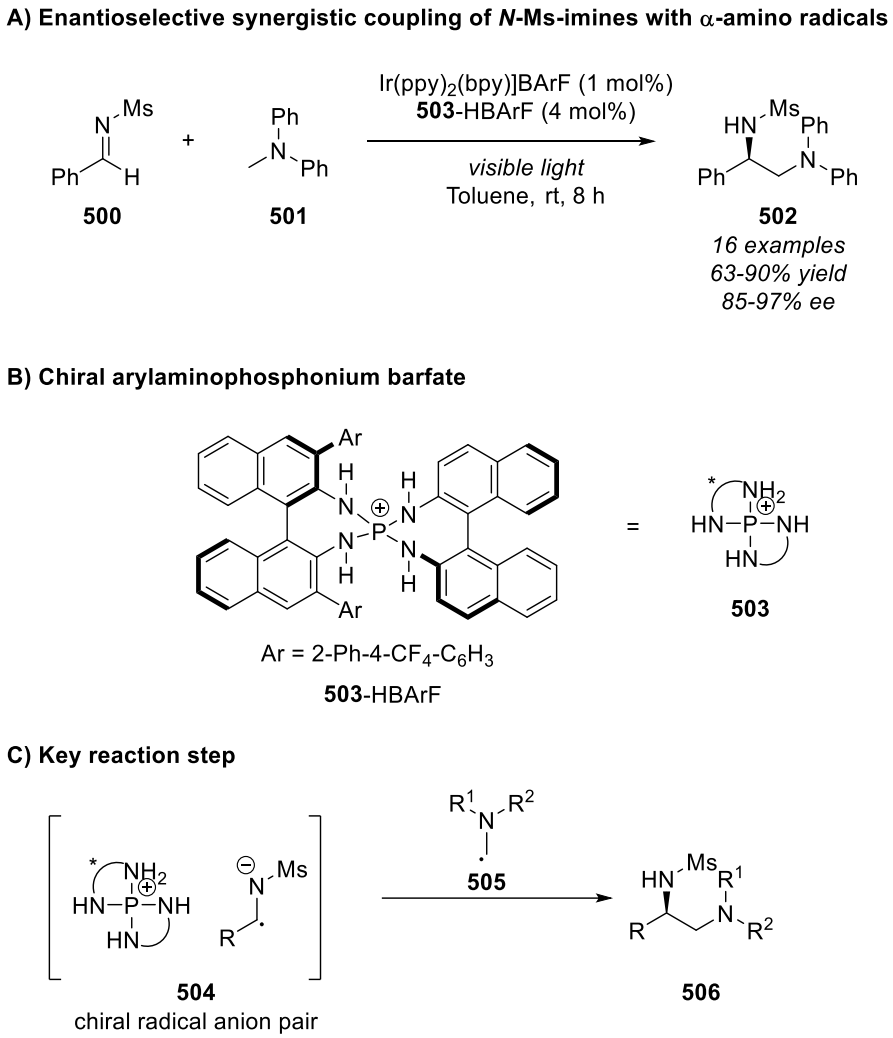
Scheme 86. Photoredox catalysed coupling of benzylic ehters with imines reported by MacMillan.

However, it was the Rueping group who, in 2015 applied this reactivity towards the 1,2-diamine synthesis. They reported a photoredox catalysed reductive pinacol coupling of N-Bn substituted imines **497** to access symmetrical 1,2-diamines **498** (Scheme 87).[162] The authors display how their methodology displays excellent reactivity towards a range of imines with varying electronics and heterocyclic substituted motifs.



Scheme 87. Photoredoex catalysed reductive pinacol coupling of *N*-Bn imines reported by Rueping.[162]

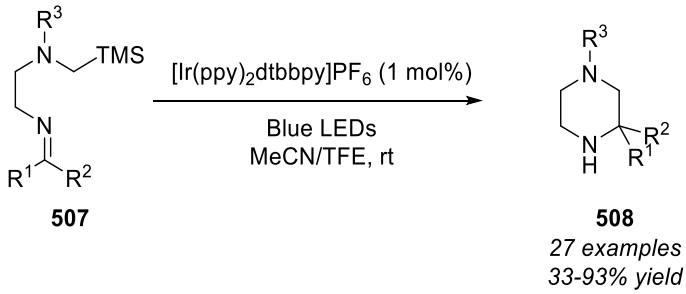
In the same year, the Ooi group then reported a major advancement of Rueping's initial study when they disclosed an enantioselective coupling of *N*-sulfonylimines **500** with α-amino radicals **501** (Scheme 88A).[163] The authors propose the reaction proceeds *via* a radical-radical coupling pathway (Figure 47A) with the enantioselectivity arising from the addition of a chiral arylaminophosphonium barfate **503** (Scheme 88B) which forms a chiral anion pair **504** with the α-amino radical of the reduced *N*-Ms imine (Scheme 88C). A library of chiral 1,2-diamines **502** is reported with enantioselectivities up to 97% *ee*.



Scheme 88. Enantioselective coupling between *N*-arylaminomethanes and *N*-sulfonyl aldimines reported by Ooi.[163]

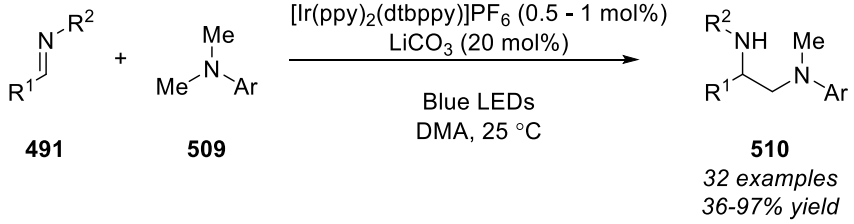
The direct α-amino radical addition to imines under photoredox conditions was first reported by Bode in 2016 (Scheme 89).[164] The authors disclosed the intramolecular

trapping of imines with α-amino radicals to access a range of piperazine derivatives **508**. The cyclisation is tolerant to both aldimines along with both acyclic and cyclic ketimines providing access to substituted, gem-disubstituted and spirocyclic piperazines respectively. The authors propose the reaction proceeds *via* a direct radical addition into the imine (Figure 47B), followed by reduction of the resulting nitrogen radical cation.



Scheme 89. Intramolecular cyclisation of α-amino radicals with imines for access to piperazines.[164]

In the same year, the Rueping group reported a reductive coupling of aldimines **491** and *N,N*-dimethylanilines **509** which built upon their earlier[162] pinacol coupling study (Scheme 90).[165] The authors propose the reaction proceeds *via* a radical-radical coupling mechanism and provides access to a wide range of 1,2-diamine derivatives **510**.

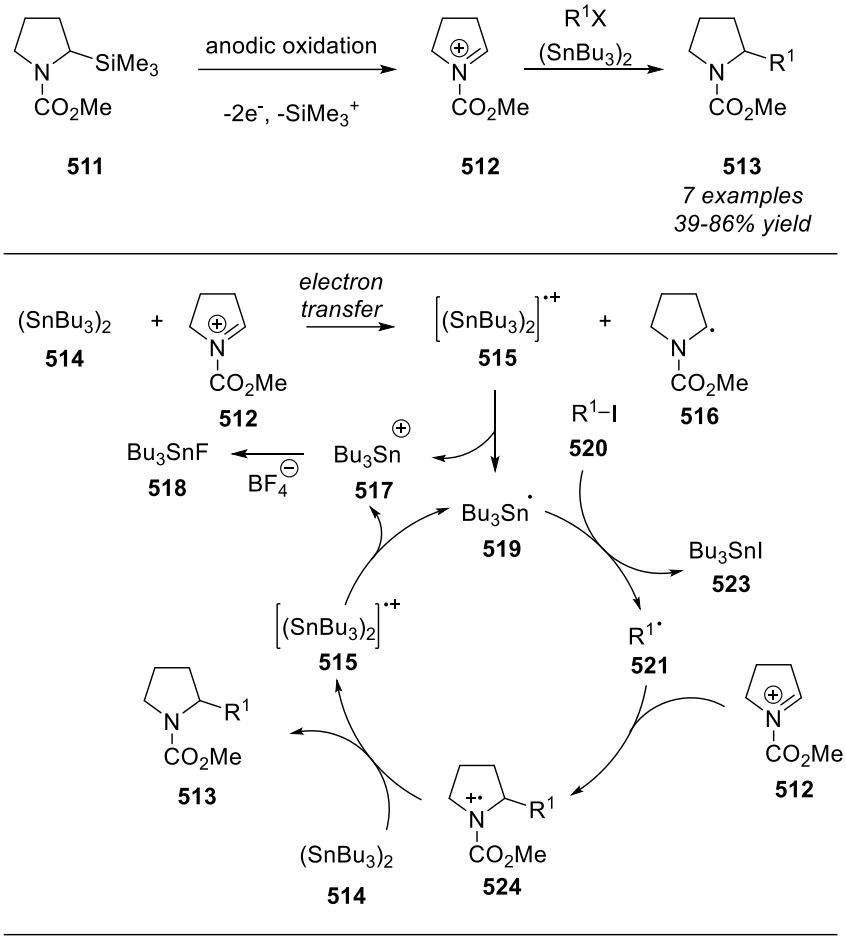


Scheme 90. Reductive coupling of aldimines and *N,N*-dimethylaniline derivatives reported by Rueping.[165]

5.1.3. Radical addition to *N*-acyliminium Ions

The addition of radicals into *N*-acyliminium ions has been reported sparingly within the literature. The only reports that exist have been reported by the Yoshida group. They first reported an electro-chemical anodic oxidation of **511** to generate bulk *N*-acyliminium ion **512**.[166] The group then reported alkyl radical addition generated from alkyl halides **520** and hexabutylditin **514** (Scheme 91).[167, 168] The authors propose an

initial single electron transfer between **512** and **514** to generate radical cation **515** and radical **516**. The radical cation cleaves to form stannyl cation **517** which reacts with the tetrafluoroborate in the electrolyte to give **518** and stannyl radical **519** which abstracts the halide from the alkyl halide **520** to generate alkyl radical **521** and Bu_3SnI by-product **523**. The alkyl radical then adds into the *N*-acyliminium ion to generate radical cation intermediate **524** which is reduced to the product **513** by another equivalent of **514** and thereby regenerating radical cation **515**.



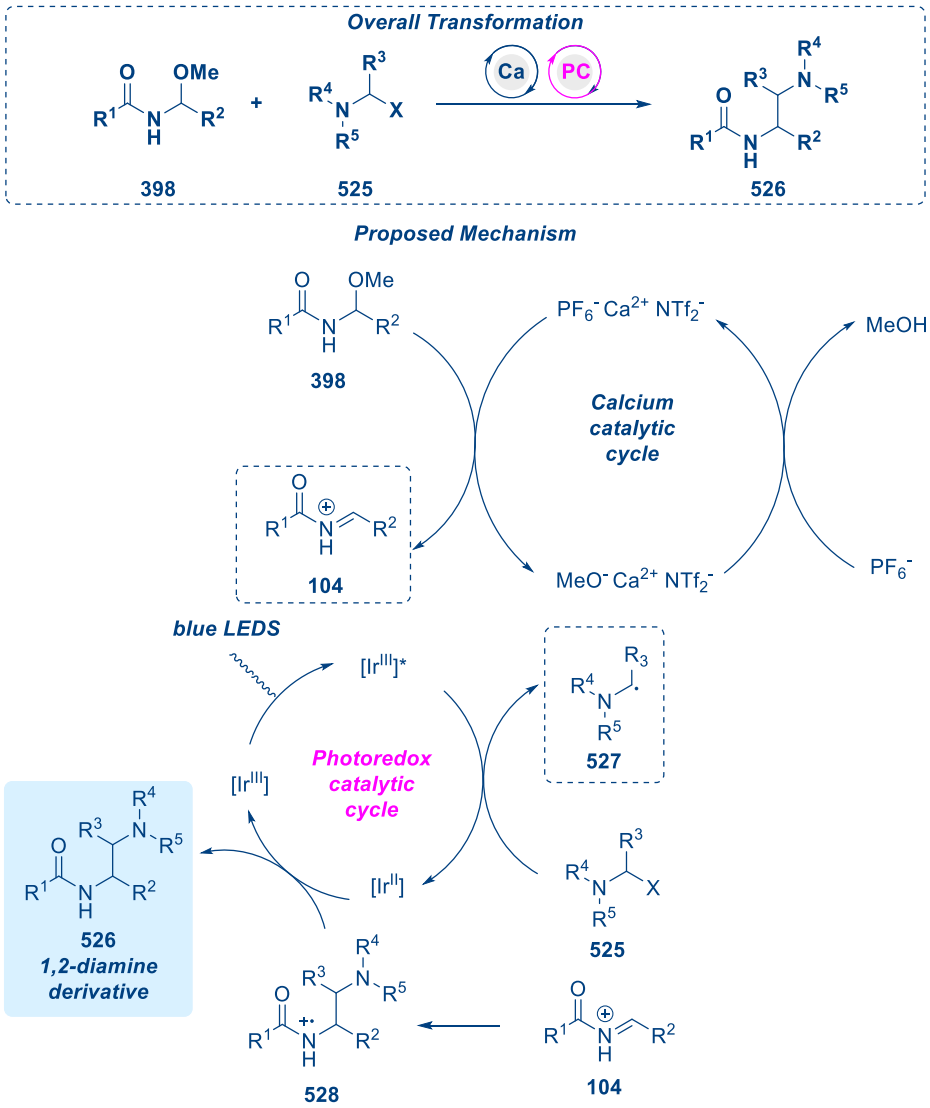
Scheme 91. Alkyl radical addition into electrochemically generated *N*-acyliminium ions.

While the transformations described above all provide access to highly substituted and versatile medicinally relevant building blocks, they all require preformation of the imine or *N*-acyliminium ion precursor. Furthermore, radical addition into *N*-acyliminium ions has only been demonstrated under electrochemical conditions using stoichiometric quantities of *N*-acyliminium ion which requires access to specialist equipment.

5.2. Aims

Chapters 2,3 and 4 each discussed the calcium catalysed generation of *N*-acyliminium ions and their subsequent trapping with "traditional" stoichiometric quantities of nucleophiles. In this chapter, the reactivity of catalytically generated *N*-acyliminium ions **104** towards radicals **527** and, whether these radicals can also be catalytically generated *in-situ* will be investigated.

The aim is to explore whether radicals do add into *N*-acyliminium ions under non-electrochemical conditions. In doing so, the goal is to develop a synergistic calcium/photoredox catalysed addition of α-amino radicals to *N*-acyliminium ions to provide access to highly substituted 1,2-diamine derivatives **526** (Scheme 92). The hypothesis is that the reaction proceeds *via* the previously reported calcium catalysed generation of *N*-acyliminium ion **104** in synergy with a photoredox catalytic cycle whereby single-electron oxidation of **525** results in the formation of α-amino radical **527** which combines with the *N*-acyliminium ion to give radical cation intermediate **528**. Reduction of radical cation **528** results in product **526** and reoxidises the photocatalyst.

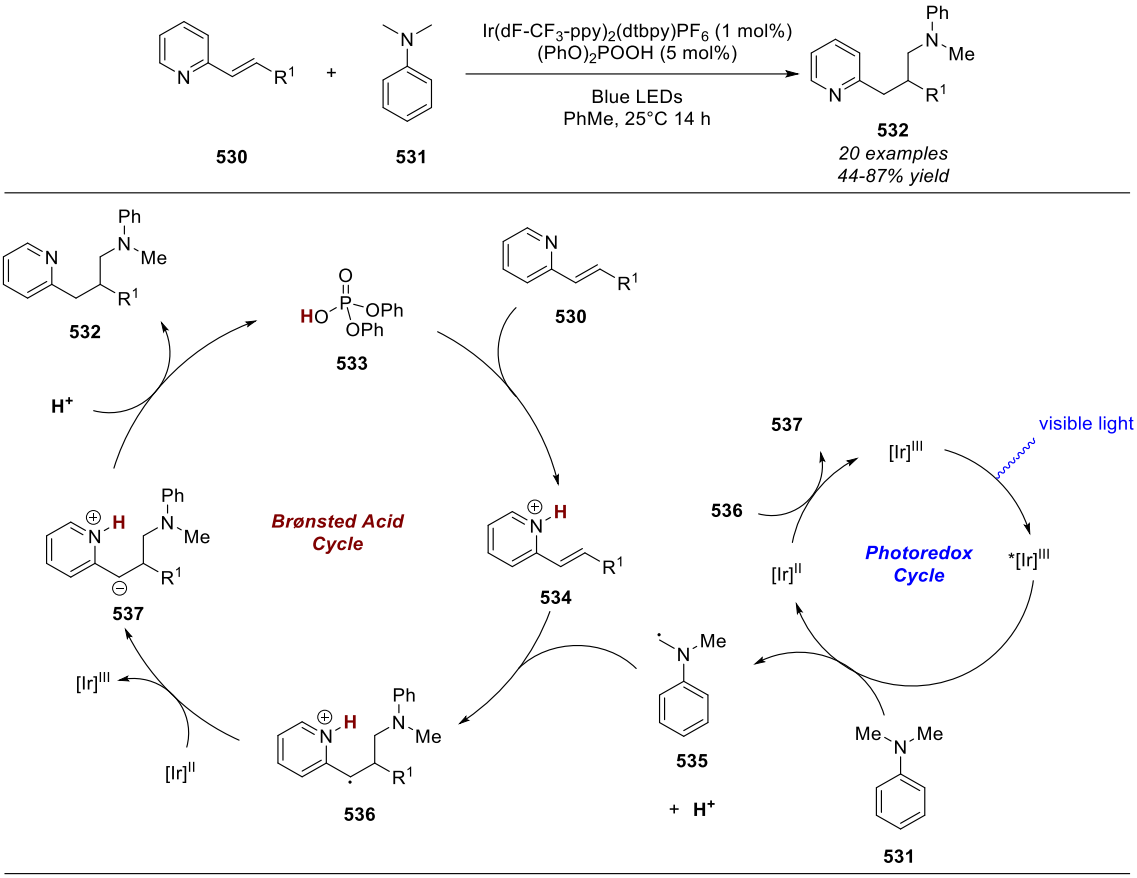


Scheme 92. Proposed overall transformation and synergistic mechanism for access to 1,2-diamine derivatives *via N*-acyliminium ions and photoredox catalysis.

5.3. Results & Discussion

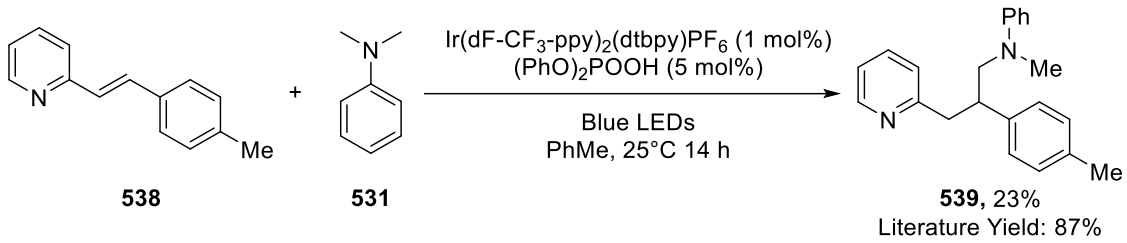
Due to the capricious nature of photoredox catalysed transformations, firstly, it was important to ensure that α-amino-radicals could be generated using the experimental set-up devised. To do this two closely related literature procedures which generated α-amino radicals from di-methylanilines and α-silyl-amines were identified.

The first, by Melchiorre, reported a synergistic Brønsted acid/Photoredox catalysed conjugate addition of α-amino radicals into pseudo iminium ions (Scheme 93).[169] The authors propose the reaction proceeds by protonation of the pyridine to generate pyridinium **534**. Simultaneously, irradiation of the photoredox catalyst forms an excited iridium(III)* species which generates α-amino radical **535** by single-electron oxidation followed by deprotonation. Radical conjugate addition into the pyridinium results in intermediate **536** which undergoes single-electron reduction with the reduced iridium(II) species to re-oxidise and regenerate the catalyst. The resulting anion **537** is then protonated to generate product **532**.



Scheme 93. Synergistic Bronsted acid/photoredox catalysed conjugate addition reported by Melchiorre.[169]

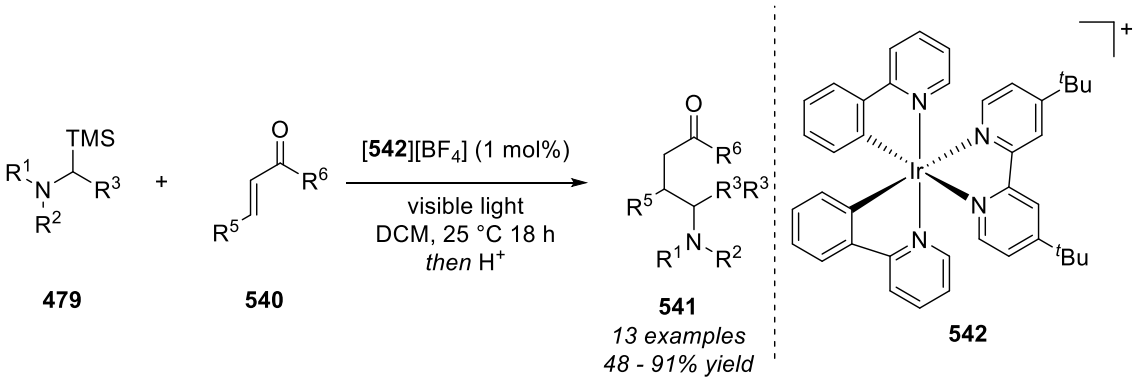
This methodology was ideal, as it is closely related to the overall aims of this chapter. This transformation was repeated, and upon reaction of olefin **538** and dimethylaniline **531** under their optimised conditions, product **539** was accessed in 23% yield (Scheme 94).

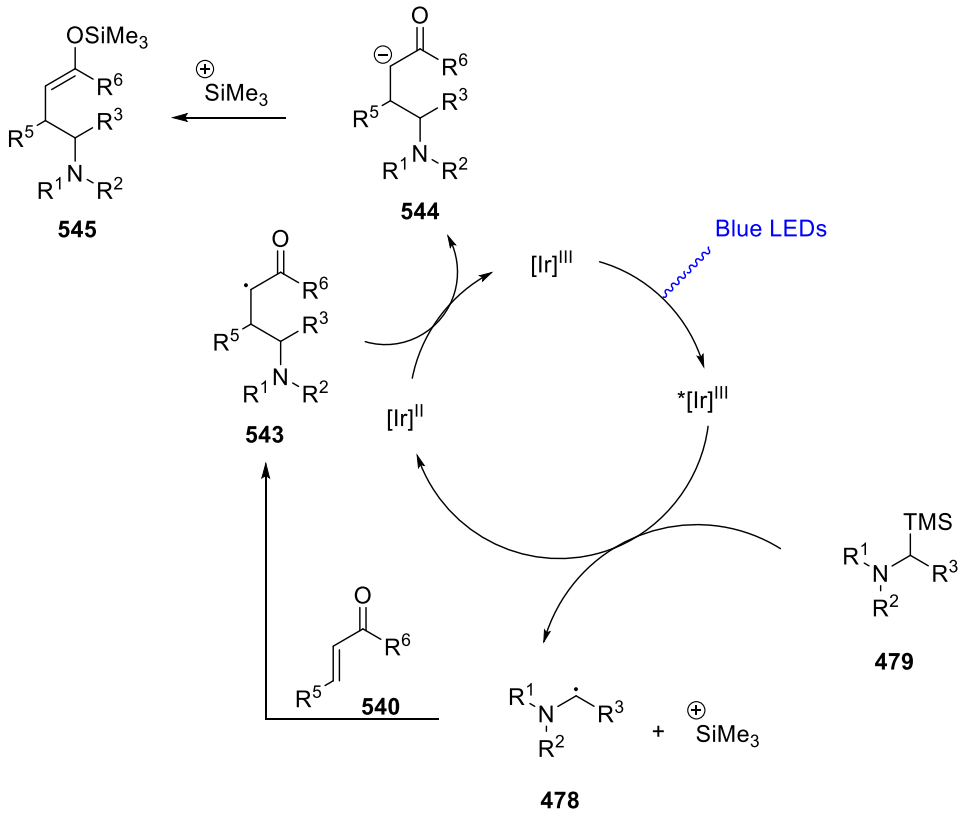


Scheme 94. Repeating the methodology reported by Melchiorre.

The second example identified was a report by Nishibayashi who disclosed a photoredox catalysed conjugate addition of α-amino radicals into α,β-unsaturated carbonyl compounds **540** (Scheme 95).[170] The authors propose the reaction proceeds *via* an initial

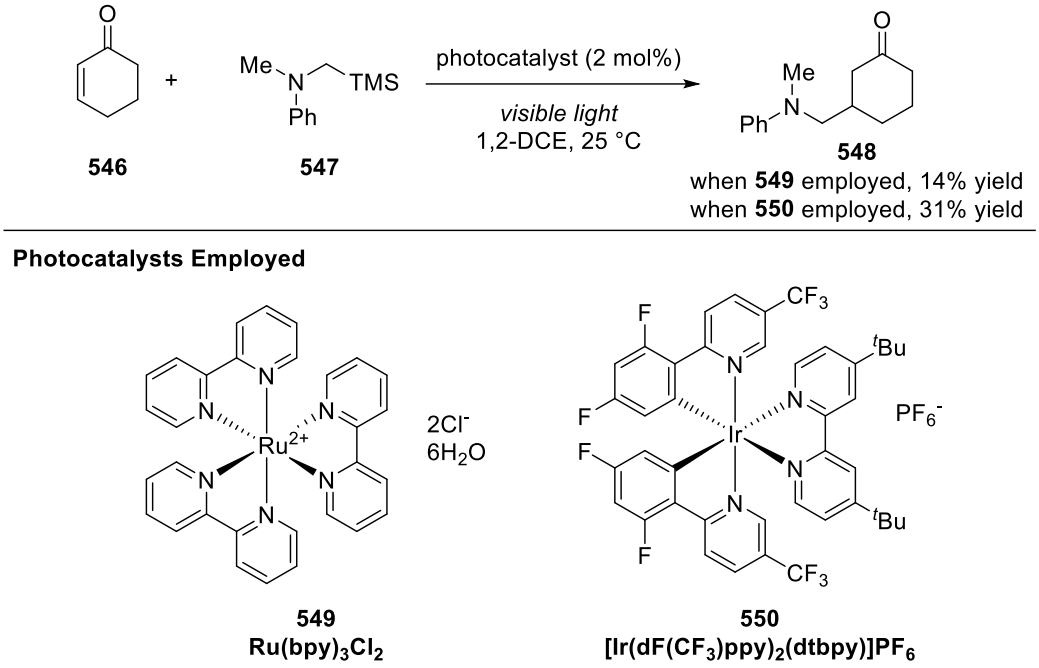
photoexcitation of the photoredox catalyst followed by single electron oxidation of α-silyl amine **479** which generates α-amino radical **478** by desilylation. Subsequent conjugate addition into **540** affords α-keto radical intermediate **543** which is then reduced to anion **544** by the reduced form of the photocatalyst, subsequently regenerating the ground state photoredox catalyst. The product then exists as silyl-enol ether **545** until acidic work up.





Scheme 95. Addition of α-amio radicals from α-silylamines into α,β-unsaturated carbonyl compounds reported by Nishibayashi.[170]

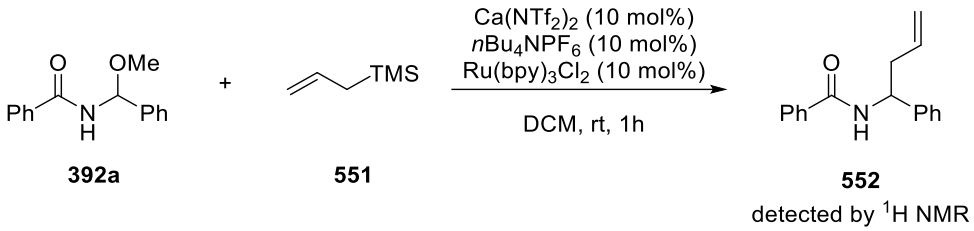
Repeating this methodology was then attempted with **546** and **547**, using the photoredox catalysts available within the laboratory. When the ruthenium photoredox catalyst **549** was subjected to the optimised conditions, **548** was isolated in 14% yield (Scheme 96).[170] Using the iridium photoredox catalyst **550** afforded the product in 31% yield. These were comparable to the yields reported within their initial optimisation.



Scheme 96. Repeating the methodology reported by Nishibayashi.

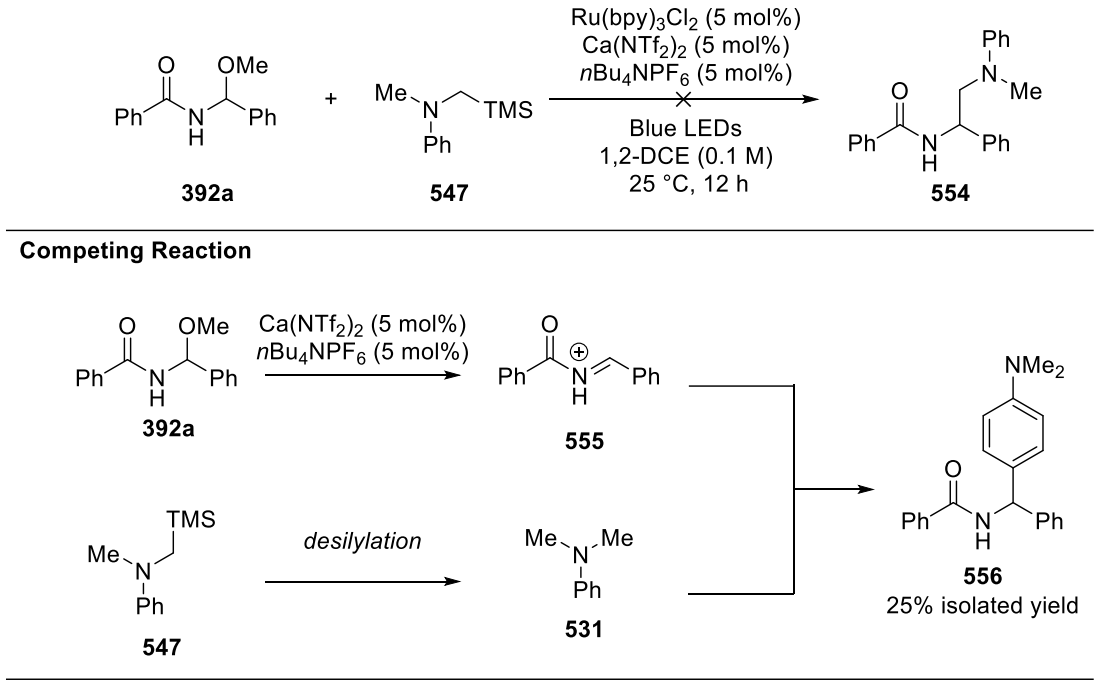
Satisfied that α-amino radicals could be generated from both *N,N*-dimethylanilines and α-silyl amines, we planned to merge this concept with the previously developed calcium catalysed generation of *N*-acyliminium ions began.

A control reaction was first performed to ensure the calcium catalyst remains active in the presence of the transition metal photoredox catalyst (Scheme 97). Subjecting **392a** and allyltrimethyl silane **551** to 10 mol% $Ca(NTf_2)_2$/*n*Bu_4NPF_6 in the presence of 2.5% $Ru(bpy)_3Cl_2$ afforded allyl amide **552** which was detected by ^1H NMR of the crude reaction mixture. This indicates that the $Ca(NTf_2)_2$/*n*Bu_4NPF_6 catalyst system remains active in the presence of photoredox catalysts.



Scheme 97. Control reaction in the presence of photoredox catalyst.

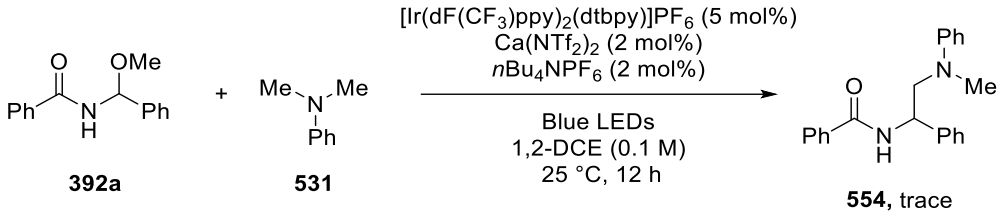
Optimisation of the photoredox catalysed reaction then began by subjecting α-silyl amine **547** and **392a** to 5 mol% of calcium and photoredox catalyst (Scheme 98). However, no product **554** was detected in the ^{1}H NMR of the crude reaction mixture, and side-product **556** was isolated in 25% yield. It was reasoned that a desilylation reaction was taking place followed by an aza-Friedel-Crafts type reaction into the *N*-acyliminium ion to afford product **556**.



Scheme 98. Initial attempt of dual calcium/Photoredox catalysis and competing aza-Friedel-Crafts reaction.

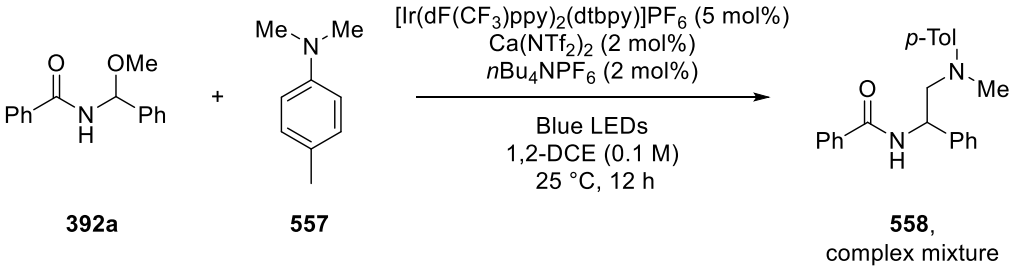
As the α-silyl amine was proven to be unstable under the conditions employed, the α-amino radical precursor was changed to *N,N*-dimethylaniline **531**. To ensure there was sufficient quantity of α-amino radical present to combine with the *N*-acyliminium ion, the amount of photocatalyst relative to calcium was increased. Furthermore, in an

attempt to prevent by-product **556** forming, a more reducing iridium photocatalyst **550** (-0.81 V vs -0.89 V) was used (Scheme 99). However, side-product **556** again appeared to form in a low 7% yield, but upon isolation and ^{1}H NMR analysis, desired product **554** appeared to be present in trace quantities. Further isolation and characterisation of this was unsuccessful.



Scheme 99. Further optimisation with trace quantities of 554 detetcted.

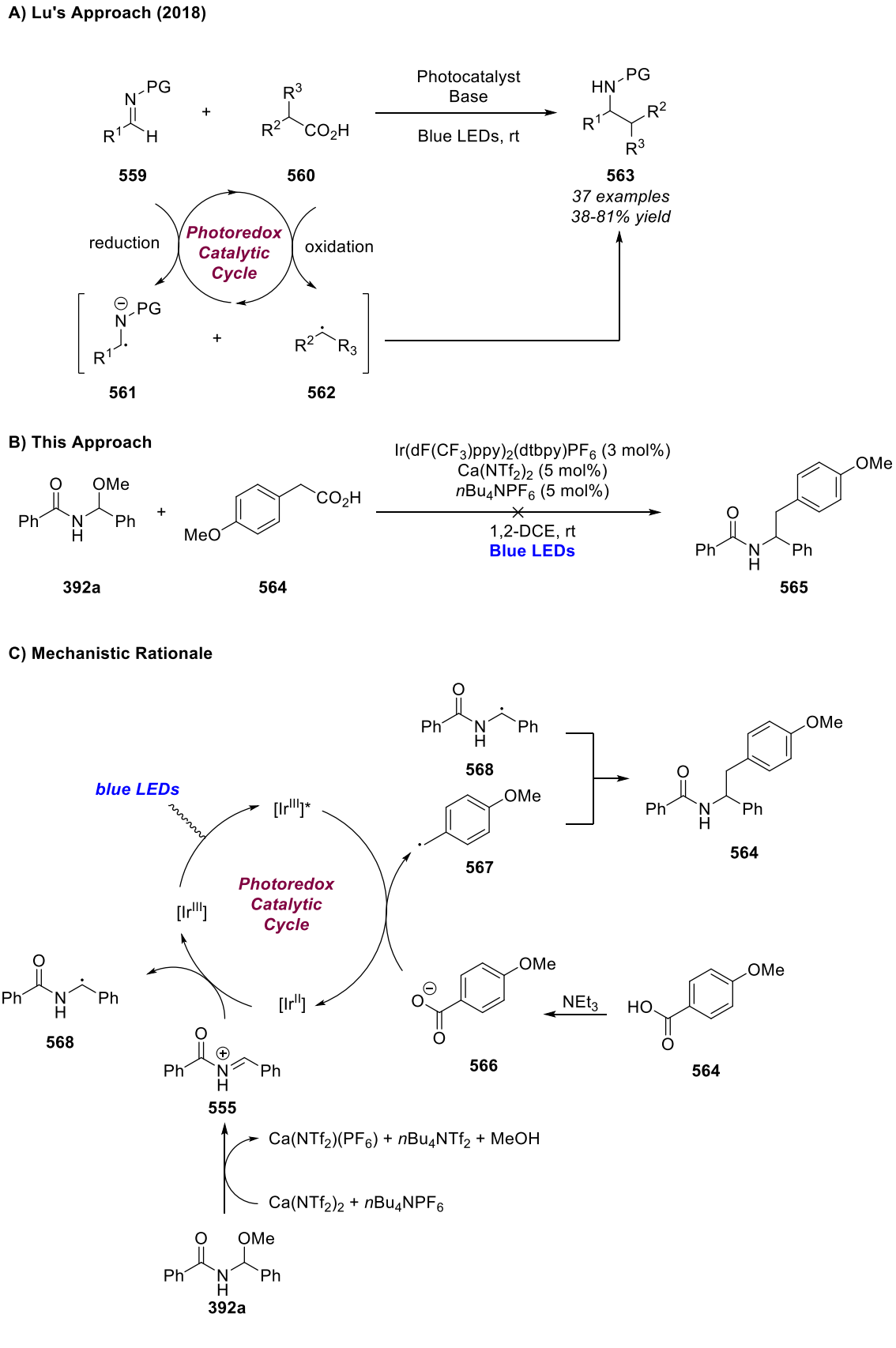
To prevent the aza-Friedel-Crafts side-product forming, the reaction conditions used above were repeated, however using *N,N*-Dimethyl-p-toluidine **557** instead of *N,N*-dimethylaniline (Scheme 100). However, no reaction took place, and a ^{1}H NMR of the crude reaction mixture indicated a mixture of **392a** and **557**. The reaction was then heated to 80°C which then resulted in a rapid degradation profile and a complex mixture of products. This same reaction was also attempted in toluene in which a complex mixture of products was obtained after 12 h at room temperature.



Scheme 100. Reaction using *N,N*-Dimethyl-p-toluidine 557.

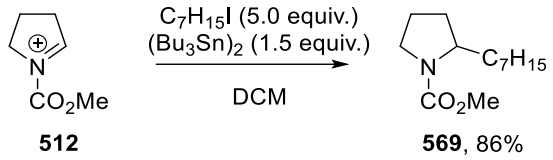
As the side reaction was unable to be prevented, alternative radical sources were then studied. Carboxylic acids were identified as a source of radical precursors and thus we envisioned a photocatalysed decarboxylative radical addition into *N*-acyliminium ions. Inspired by Lu and co-worker's study on the decarboxylative radical addition into imines (Scheme 101A), [171] it was reasoned a similar approach could be applied to *N*-acyliminium ions (Scheme 101B). The mechanistic rationale began with irradiation of the iridium

photocatalyst to the generated photoexcited species (Scheme 101). Deprotonation of acid **564** followed by decarboxylative oxidation results in the formation of benzylic radical **567**. Simultaneously, catalytic generation of *N*-acyliminium ion **555** from **392a** with calcium and a subsequent reduction of **555** generates radical species **568** while reoxidising the catalyst. Radical-radical coupling of **567** and **568** would generate product **565**. However, when the reaction in Scheme 101B was carried out, no reaction took place, with unreacted starting material re-isolated. The reaction was then repeated without the super stoichiometric quantities of NEt_3, with the reasoning that the liberated methoxide would deprotonate the acid, without success. Lastly, the reaction was attempted without $Ca(NTf_2)_2$ and $n Bu_4NPF_6$ with the possibility that the acid would subsequently protonate **392a** and catalyse the formation of *N*-acyliminium ion **555** and subsequently generate carboxylate **566**. However, this resulted in decomposition of **392a** to benzamide and benzaldehyde due to stoichiometric quantities of *N*-acyliminium ion being generated.



Scheme 101. Decaboxylative radical generation inspired by Lu's work.[171]

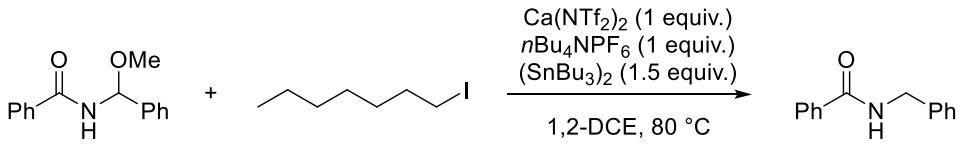
As shown in previous chapters, there is very little that can be changed with regards to the calcium catalysed generation of *N*-acyliminium ions. These reactions typically require chlorinated solvents and temperatures around 80°C. On the contrary, photoredox catalysed generation of radicals typically requires lower temperatures and are tolerant to a wider range of reaction conditions and solvents. It was therefore decided to study whether catalytically generated *N*-acyliminium ions could be trapped out with stoichiometric radicals. As previously mentioned, there is also very little literature precedent for radical addition into *N*-acyliminium ions and identified the distannane/alkyl halide mediated approach for alkyl radical formation reported by Yoshida as the starting point (Scheme 102).



512 **569**, 86%

Scheme 102. Literature precedent for alkyl radical generation in the presence of *N*-acyliminium ions.

The study began by investigating the reactivity using a stoichiometric quantity of calcium catalyst to closely mimic the reaction described above (Scheme 103). However, when **392a** was subjected to the reaction conditions, reduction of the *N*-acyliminium ion was taking place, with N-benzyl benzamide **571** isolated in excellent yield with a co-eluting tin by-product. Furthermore, unreacted alkyl halide **570** was also reisolated from the reaction mixture suggesting the alkyl radical was not forming. This indicates that *N*-acyliminium ion and subsequent reduction with tributyltin hydride is faster than radical generation.

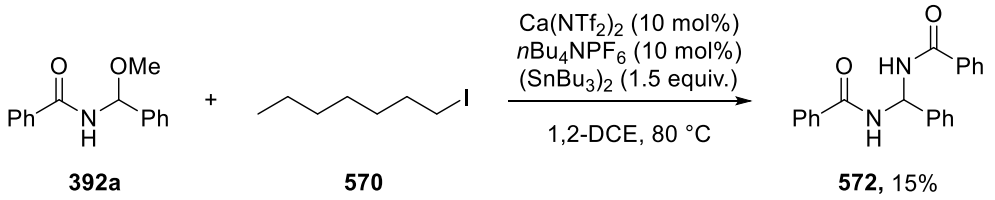


392a **570** **571**, 98%

Scheme 103. Stoichionmetric reaction resulting in *N*-acyliminium ion reduction.

As generating stoichiometric quantities of *N*-acyliminium ion using these conditions resulted in a rapid reduction, the reaction was repeated using 10 mol% of calcium

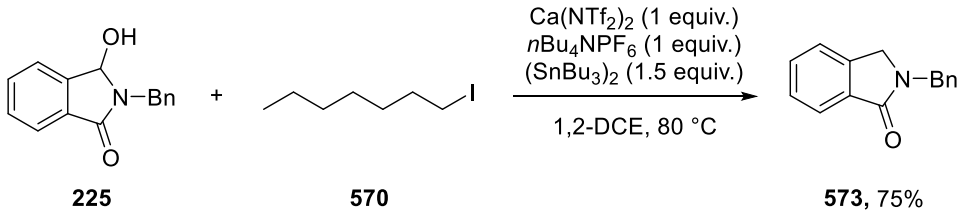
catalyst to hopefully introduce more control into the reaction by allowing time for alkyl radical formation (Scheme 104). Under these conditions, the reaction proceeded much slower, with bis-amide product **572** isolated in a low yield with the remaining mass balance being unreacted starting material. The differing reactivity suggests that calcium is not catalytically active in the presence of hexabutylditin.



Scheme 104. Reaction carried out using catalytic calcium.

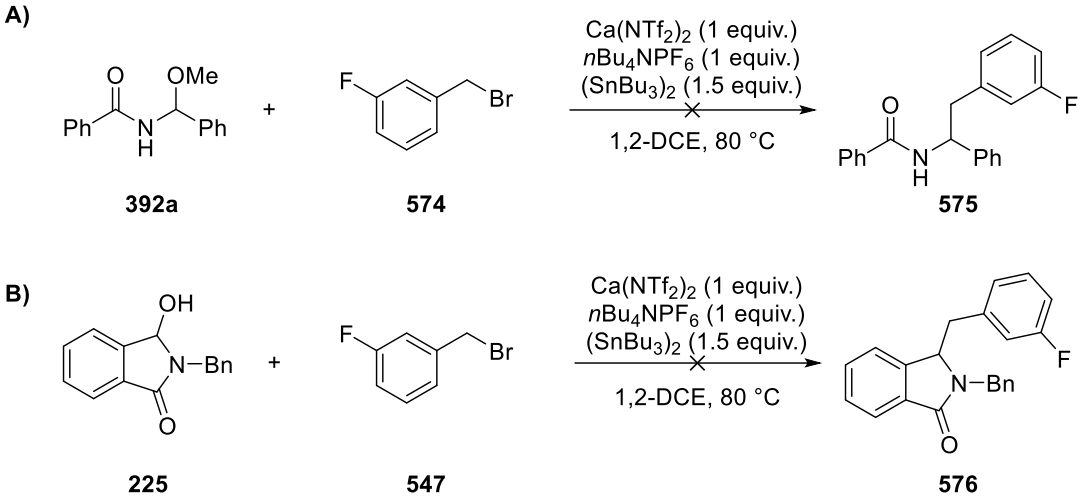
To allow time for radical formation, the reaction in Scheme 94 was repeated but first stirring $(SnBu_3)_2$ and iodoheptane **570** separately for 30 mins prior to adding the calcium catalyst and **392a**. However, this did not change the outcome of the reaction with small quantities of bis-amide **572** detected along with unreacted starting material **392a**.

A similar trend was observed when applying this towards 3-hydroxyisoindolinone **225**. Using stoichiometric quantities of Lewis acid under identical conditions, the reduced lactam product **573** was isolated in 75% yield (Scheme 105). Furthermore, when applying the same conditions using catalytic Lewis acid, no reaction took place.



Scheme 105. Reduction of isoindolinone derived *N*-acyliminium ion in the presence of stoichiometric Lewis acid.

As any radical addition was not being detected in the crude, attention was turned to studying whether a more stable benzylic radical from **574** could be generated under identical conditions. However, in both cases, no product **575 or 576** were detected within the ^{1}H NMR with unreacted halide **574** reisolated (Scheme 106).



Scheme 106. Attempted reaction of *N*-acyl-*N,O*-acetal (A) and 3-hydroxyisoindolinone (B) derived *N*-acyliminium ions with benzylic radicals.

5.4. Conclusions

In summary, both photoredox and stoichiometric radical addition into *N*-acyliminium ions has been studied. The addition of α-amino radicals resulted in the aza-Friedel-Crafts product forming and when substituents were introduced to prevent this, decomposition occurred. However, this undesired side-product does show that the Lewis acid catalyst employed does retain activity in the presence of transition metal photocatalysts. A photoredox mediated decarboxylative route to access radicals also proved unsuccessful with

Addition of stoichiometric radicals generated from hexabutyl-di-tin also proved to be unsuccessful providing only the reduced *N*-acyliminium ion in good yield.

5.5. Future Work

Synergistic catalysis is the combining of two reactive intermediates which have been activated by two different catalysts (Figure 49). For a successful synergistic catalytic cycle, both catalysts must not react with each other and retain activity within each other's presence, which has been demonstrated.[172] Furthermore, both catalysts (cat-1 and cat-2) must activate the desired reagents, which has also been demonstrated.[172] Furthermore, when the catalysts react, they must do so with comparable and compatible activation rates (k_1 and k_2). It is postulated that one of the issues arising

within this chapter, is due to the rate of formation of the *N*-acyliminium ion being significantly faster than the rate of formation of the desired radical. Offsetting the ratio of calcium to photoredox catalyst further could circumvent this however this equally runs the risk of large quantities of highly reactive radicals being present. Alternatively, tuning the strength of the calcium Lewis acid could also synergise the rates. This can be achieved by using a more coordinating weakly coordinating anion such as tetrafluoroborate.

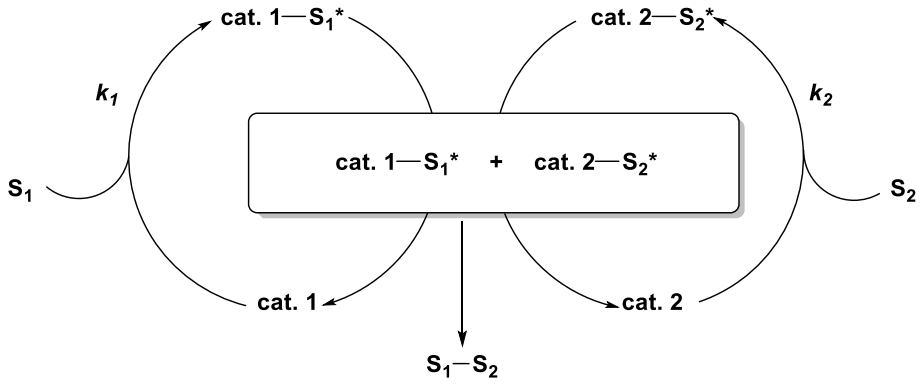


Figure 49. Synergistic catalysis schematic.

A synergistic Lewis acid/photoredox catalysed transformation of *N*-acyliminium ions and radicals remains un-reported within the literature.

6. Chapter 6: Intermolecular Trapping of *N*-acyliminium ions with anilines as C4-nucleophiles; access to Friedel-Crafts products

6.1. Introduction

Medicinal chemists continually require access to novel building block which are structurally diverse and can be assembled readily. However, few reactions still dominate this field when adding to the medicinal chemistry toolbox (Figure 50).[173] The reason for such dominance of these reactions is because they are considered "robust", by the synthetic community. For methods to be defined as robust, they must meet the following requirements: (1) no special equipment (e.g. glovebox), (2) operate at moderate temperatures, (3) be high yielding with limited by products, (4) have compelling literature precedence, (5) broad applicability (e.g. include polar substrates) and functional group tolerance, (6) broad availability of starting materials and reagents, (7) low-risk reagents, (8) short reaction times.[174]

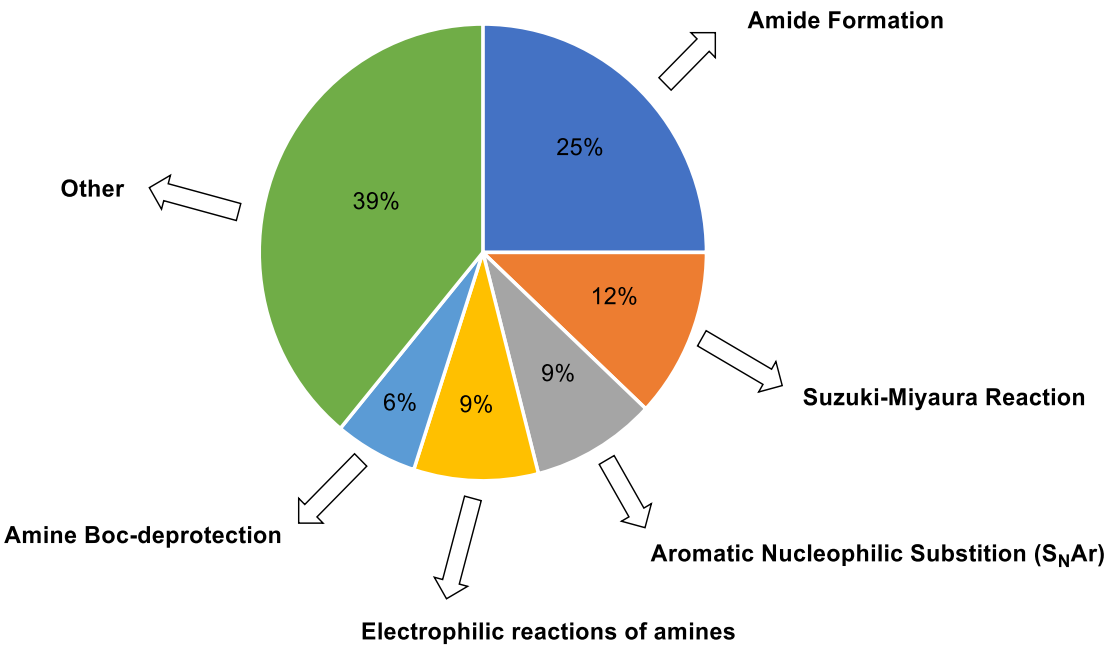
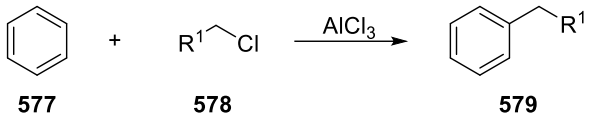


Figure 50. Most common reactions in the medicinal chemistry toolbox.

Friedel-Crafts reactions are an important set of reactions for the installation of substituents on an aromatic ring (Scheme 107). Traditionally, the reaction proceeds *via*

the activation of a carbon-halogen bond, by a Lewis acid to generate either a carbocation or acylium ion which reacts with an electron-rich arene **577** to give alkylated **579** or an acylated product respectively.

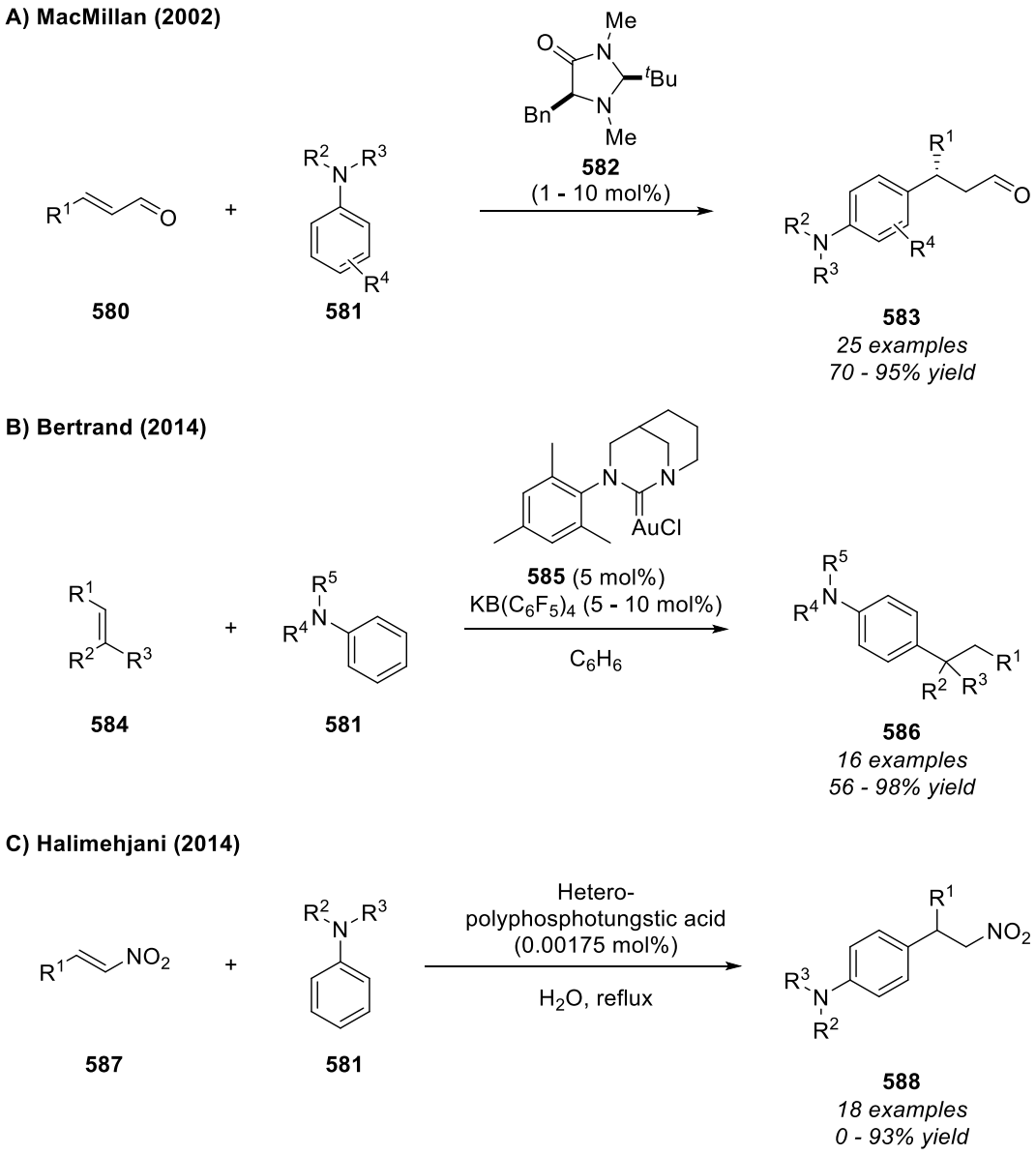


577 **578** **579**

Scheme 107. General General Friedel Crafts alkylation reaction.

Due to the presence of these highly reactive Lewis acids, Friedel-Crafts reactions are not particularly robust and the utilisation of any Lewis basic functionalities, such as amines, is futile. To circumvent this, alternative modes of electrophilic activation must be considered should anilines be used as nucleophiles in an aza-Friedel-Crafts alkylation.

There are, however, few examples of the use of anilines as C4-nucleophiles in aza-Friedel Craft type reactions in the literature. This is due to the limited number of catalysts that are tolerant to the Lewis basic amines. In 2002, MacMillan reported the first organocatalytic aza-Friedel Crafts reaction for the addition of di-substituted anilines **581** into α,β-unsaturated carbonyls **580** (Scheme 108A).[175] This afforded a range of stereodefined aldehydes **583**, with the reaction proceeding *via* a catalytically generated iminium ion. Gold(I) carbene complex **585** has been shown to promote the hydroarylation of alkenes **584** with di-substituted anilines **581**, as reported by Bertrand (Scheme 108B).[176] A range of Markovnikov addition products were synthesised with high *para*-regioselectivity. The reaction scope could also be extended towards enones. Nitroalkenes **587** have also been shown to be effective electrophiles towards the addition of di-substituted anilines **581** using a heteropolyphosphotungstic acid catalyst to afford a range of nitro alkane anilines **588** (Scheme 108C).[177] These examples show how di-methylanilines are effective nucleophiles in aza-Friedel crafts reactions towards a range of electrophiles. However, they require either expensive or non-commercially available catalysts and any reactivity towards more reactive electrophiles including *N*-acyliminium ions has not been explored.



Scheme 108. Addition of anilines into various electrophiles.

Owing to its robustness, the use of calcium as a Lewis acid in catalytic transformations is something that can be exploited by medicinal chemists to generate robust reactions that are otherwise highly capricious. It is therefore reasoned that the trapping of *N*-acyliminium ions with *N,N*-disubstituted anilines would give access to versatile building blocks **589**. Furthermore, these compounds also have shown promising biological activity with **590** displaying anti-malarial activity and **591** as a CB2 inverse agonist (Figure 51).[178, 179]

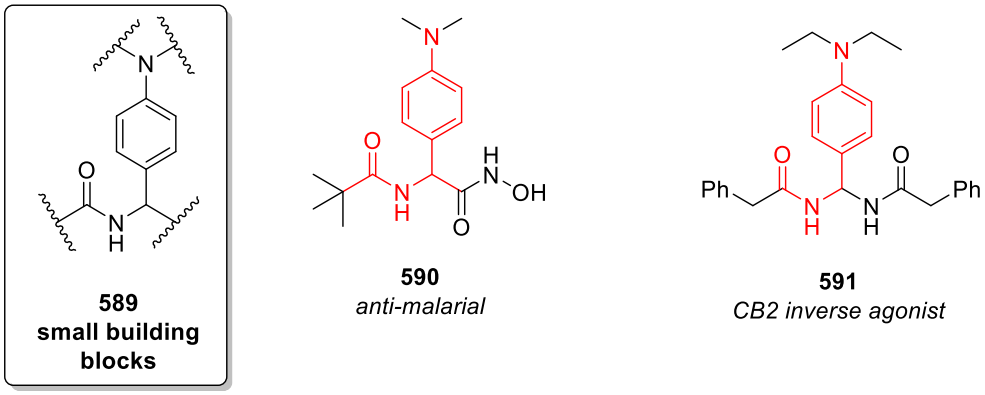


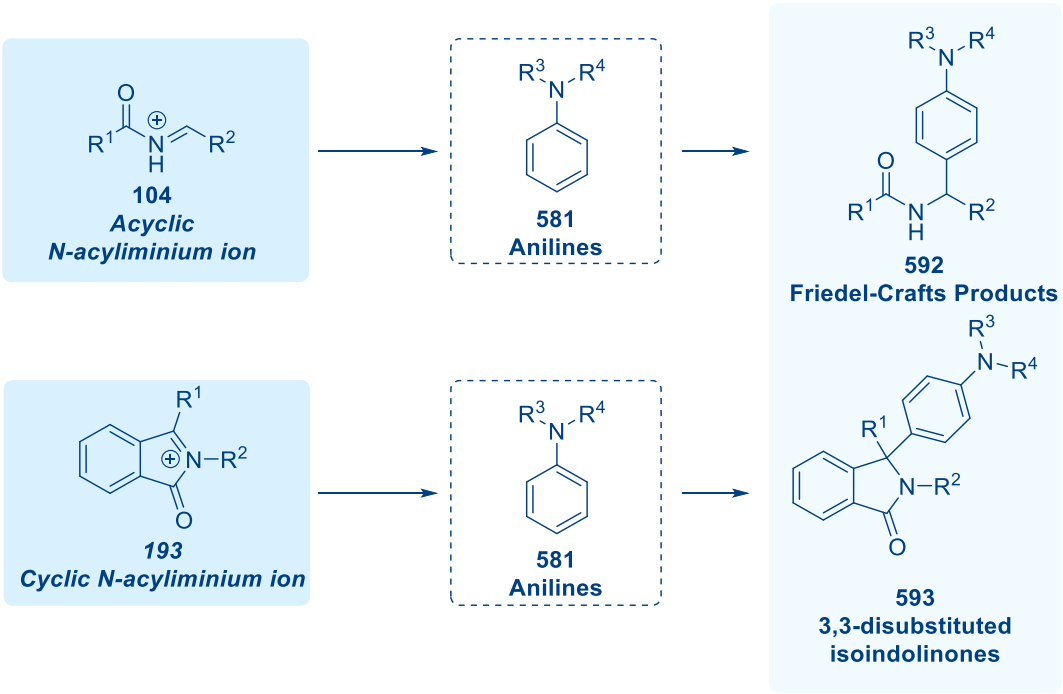
Figure 51. Biological activity of target products.

6.2. Aims

It is rather surprising that the use of anilines in this type of transformation has been underexplored, especially since the incorporation of amines into building blocks and medicinally relevant scaffolds is so important to medicinal chemists.

Preliminary data reported in 5.3 has shown that di-methylanilines do indeed add to *N*-acyliminium ions, and seek to optimise this side reaction towards and explore the reactivity further.

In doing so the aim is to develop a simple and "robust" approach to access highly versatile amide building blocks by developing a calcium catalysed aza-Friedel-Crafts reaction between catalytically generated *N*-acyliminium ions and di-substituted anilines (Scheme 109).



Scheme 109. Addition of aniline derivatives as C4-nucleophiles into *N*-acyliminium ions.

6.3. Results & Discussion

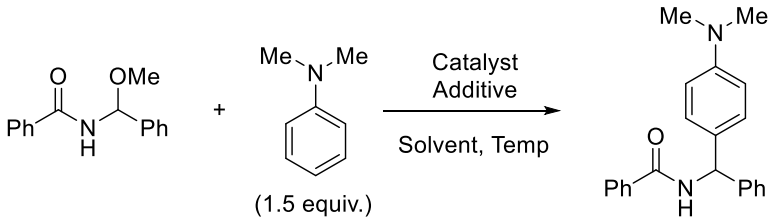
The work described in this section has been published:[180]

A. J. Basson and M. G. McLaughlin, *Cell. Rep. Phys. Sci.,* 2023, **4**, 101234.

6.3.1. Optimisation Studies

The optimisation began by subjecting *N*-acyl-*N,O*-acetal **392a** and dimethylaniline **531** to 10 mol% of catalyst, in 1,2-DCE at 80 °C which afforded product **601a** in excellent yield (entry 1, Table 49). Lowering the catalyst loading to 5 mol% had no effect on yield (entry 2). Further reducing the catalyst loading had a slight effect on yield forming **601a** in 73% yield (entry 3). Due to this diminished yield, 5 mol% was chosen to be optimal loading. A range of solvents were then screened, without success, which resulted in the decomposition of **392a** to benzamide and benzaldehyde in all cases (entries 4-6) and deemed 1,2-DCE to be the solvent of choice. Lowering the temperature of the reaction resulted in no reaction taking place (entry 7). Furthermore, no reaction took place without either the presence of the additive (entry 8) or catalyst (entry 9) respectively, supporting the necessary formation of a highly Lewis acidic $Ca(NTf_2)(PF_6)$ species.

Table 49. Optimisation of aza-Friedel Crafts reaction.



392a **531** **601a**

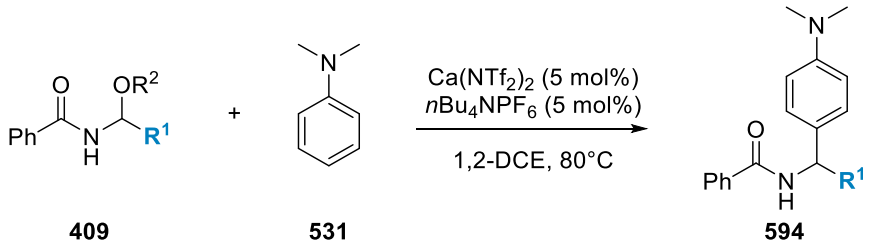
Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield [a]
1	$Ca(NTf_2)_2$	nBu$_4$NPF$_6$	10 mol%	80ºC	1,2-DCE	2 h	83%
2	$Ca(NTf_2)_2$	nBu$_4$NPF$_6$	5 mol%	80°C	1,2-DCE	2 h	82%
3	$Ca(NTF_2)_2$	nBu$_4$NPF$_6$	1 mol%	80°C	1,2-DCE	12 h	73%
4	$Ca(NTF_2)_2$	nBu$_4$NPF$_6$	5 mol%	80°C	EtOAc	2 h	decomp.
5	$Ca(NTF_2)_2$	nBu$_4$NPF$_6$	5 mol%	80°C	HFIP	2 h	decomp.
6	$Ca(NTF_2)_2$	nBu$_4$NPF$_6$	5 mol%	80°C	Toluene	2 h	decomp.
7	$Ca(NTF_2)_2$	nBu$_4$NPF$_6$	5 mol%	40°C	1,2-DCE	2 h	n.r
8	$Ca(NTF_2)_2$	-	5 mol%	80°C	1,2-DCE	2 h	n.r
9	-	nBu$_4$NPF$_6$	5 mol%	80°C	1,2-DCE	2 h	n.r

[a] Isolated yields
n.r = no reaction
decomp. = decomposition

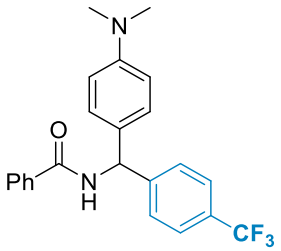
6.3.2. Development of Substrate Scope

With the reaction optimised the substrate scope based on a range of *N*-acyl-*N,O*-acetals which had previously been synthesised was then probed. First, the reactivity with respect to the aldehyde derived component of the acetal was studied (Table 50). The reaction was tolerant to electron-deficient acetals, affording **594a** in excellent yield. The reaction also proved tolerant to scaffolds with groups useful for further diversification. Halo-substituted and nitro-substituted products **594b** and **594c** were synthesised in excellent yields respectively. Differentially substituted cyano-groups worked well affording *para*- and *meta*-substituted products **594d** and **594e** in excellent yields. Furthermore, heterocycles were also well tolerated with thiophene product **594f** synthesised in good yield.

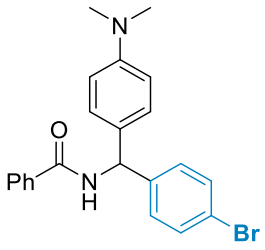
Table 50. Functionalised Friedel-Crafts Products – Aldehyde Component.



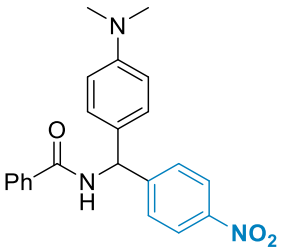
409 **531** **594**



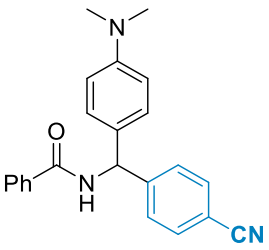
594a, 87%



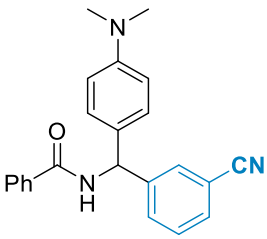
594b, 88%



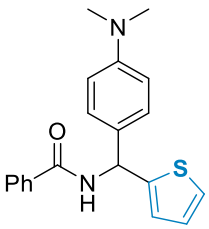
594c, 83%



594d, 83%



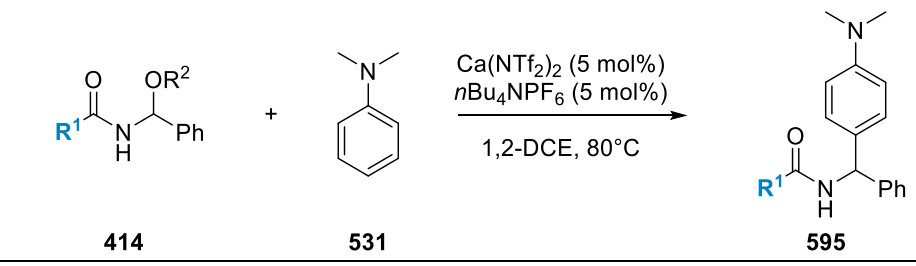
594e, 87%



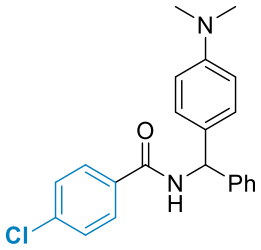
594f, 64%

The reactivity with respect to the amide component was then studied (Table 51). Halo-substituted amides were well tolerated afforded chloro- and bromo- substituted products **595a** and **595b** in excellent yield. Electron-deficient amides could also be accessed with trifluoromethyl product **595c** synthesised in excellent yield. Electron-rich and *meta*-substituted amide were also well tolerated affording **595d** and **595e** respectively in high yield. Heterocycles were again tolerated with furan derivative **595f** isolated in good yield.

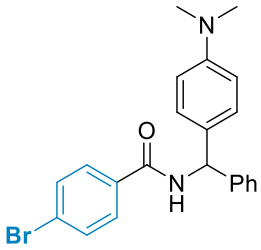
Table 51. Functionalised Friedel-Crafts Products – Amide Component.



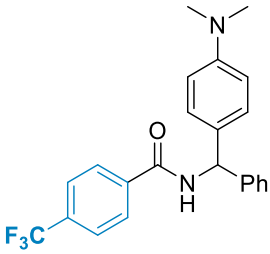
414 **531** **595**



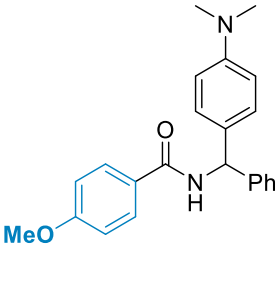
595a, 86%



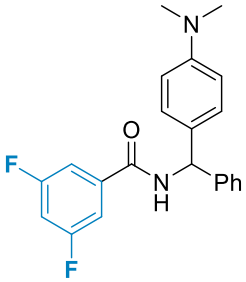
595b, 85%



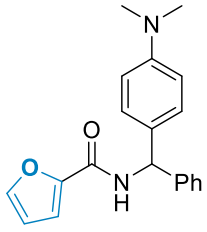
595c, 90%



595d, 86%



595e, 89%

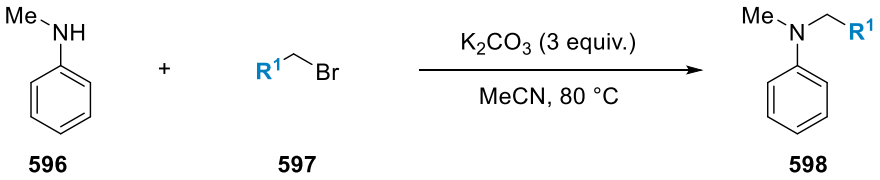


595f, 67%

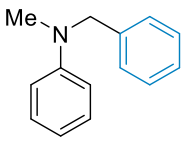
The range of anilines that could be accessed using this chemistry was then studied. Therefore access to a library of aniline derivatives with varying substitution patterns was required. These were accessed by either *N*-alkylation of reductive amination chemistry.

A range of *N*-substituted anilines *via N*-alkylation were first synthesised by reacting N-methyl-aniline **596** and an alkyl bromide **597** in the presence of K_2CO_3 (Table 52). In addition to *N*-benzyl derivative **598a**, *meta*-substituted benzyl anilines **598b** and **598c** were synthesised in excellent yields along with electron-deficient benzyl anilines **598d** and **598e**.

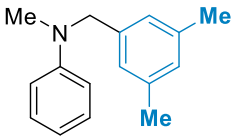
Table 52. *N*-substituted anilines synthesis *via N*-alkylation.



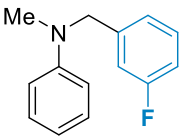
596 **597** **598**



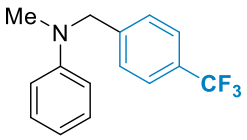
598a, 38%



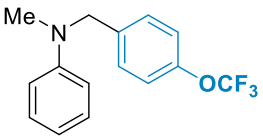
598b, 89%



598c, 95%



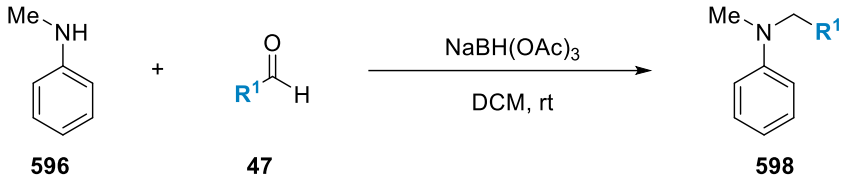
598d, 94%



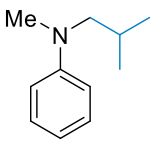
598e, 95%

The library of aniline derivatives was extended further by performing a reductive amination of *N*-methyl-aniline **596** with a range of aldehydes (Table 53). Alkyl substituted anilines **598f** and **598g** were synthesised in excellent yield along with thio-ether product **598h**. Heterocyclic derivatives also worked well affording thiophene and pyridine substituted amines **598i** and **598j** in good yield.

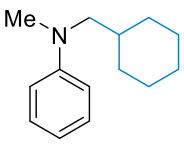
Table 53. *N*-substituted anilines synthesis *via* reductvie amination.



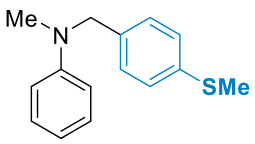
596 **47** **598**



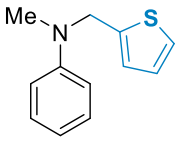
598f, 93%



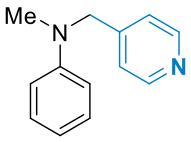
598g, 93%



598h, 84%



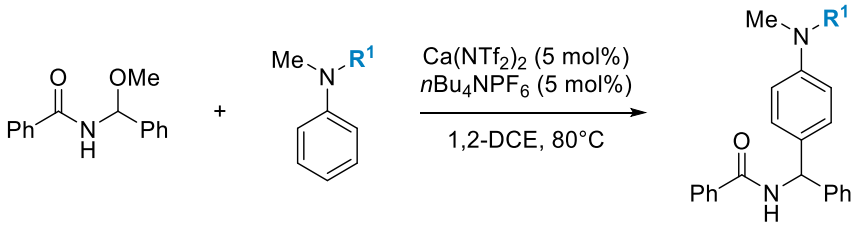
598i, 86%



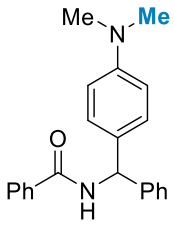
598j, 75%

With a library of substituted anilines accessed, they were then subjected to the optimised conditions (Table 54). In addition to *N,N*-dimethyl-aniline affording **601a** and *N*-benzyl-substituted product **601b**, *N*-benyl-substituted anilines with electron deficient **601c, 601d** and electron-rich **601e** and **601f** substituents also worked in good yields. Alkyl substituted anilines were also well tolerated affording **601g** and **601h** in good yield. Additionally, heterocyclic aniline derivatives were tolerant affording thiophene substituted product **601i** in good yield.

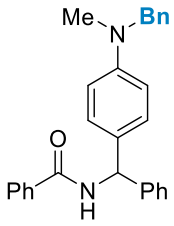
Table 54. Functionalised Friedel-Crafts Products – Amine Component.



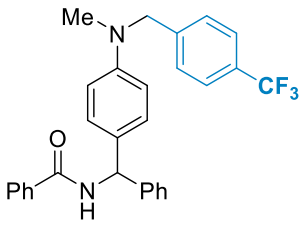
392a **598** **601**



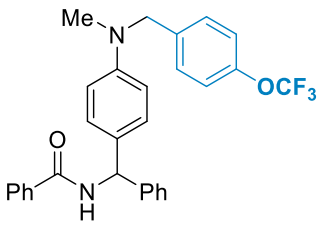
601a, 82%



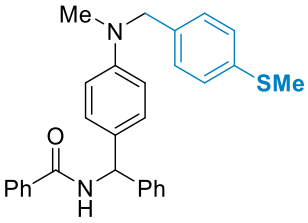
601b, 85%



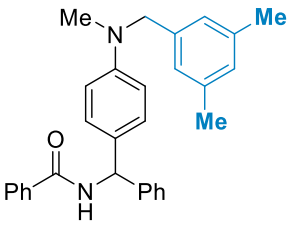
601c, 77%



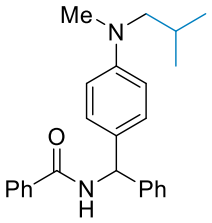
601d, 76%



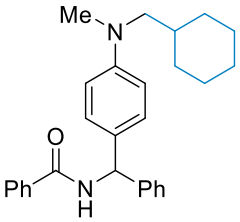
601e, 81%



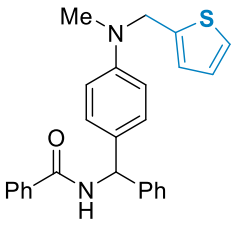
601f, 91%



601g, 83%

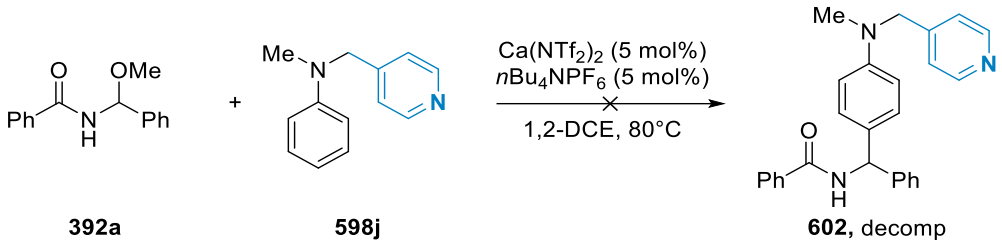


601h, 87%



601i, 81%

When pyridyl-substituted aniline **598j** was subjected to the optimised conditions, decomposition of the starting material **392a** was observed, possibly due to the pyridine deprotonating the *N*-acyliminium ion (Scheme 110).

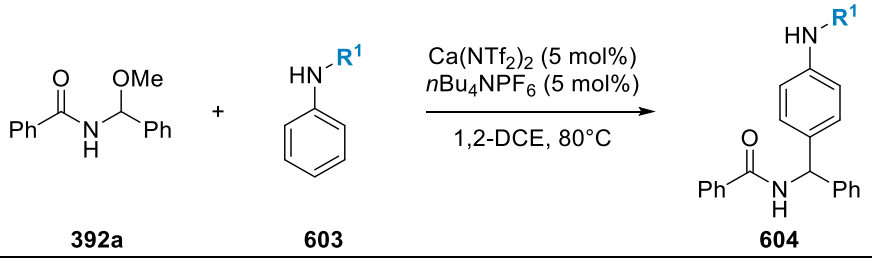


392a **598j** **602,** decomp

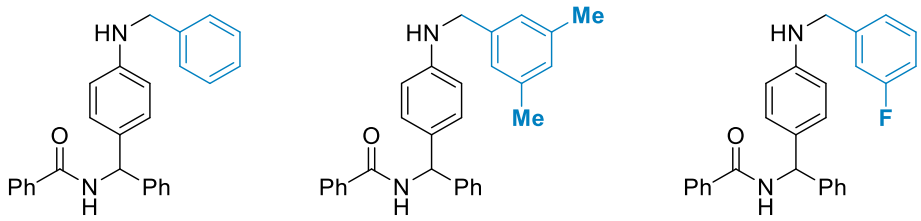
Scheme 110. Unsuccessful reaction utilising pyridine-substituted aniline 682.

The reactivity towards secondary aniline derivatives **603** was then studied (Table 55). N-benzyl aniline worked well affording product **604a** in good yield, however the reaction was much less clean with trace amounts of by-products being observed. This was unsurprising as secondary substituted anilines are much less nucleophile. This becomes more apparent when extended to other *N*-benzyl anilines with varying substitution. The reactions became more sluggish affording **604b** in moderate yield while attempting to synthesise **604c** resulted in a decomposition of the starting material. This suggests that fine tuning of the electronics of the systems results in the aniline coupling partner having a decreased nucleophilicity making it not nucleophilic enough to add into the *N*-acyliminium ion.

Table 55. Functionalised Friedel-Crafts Products - Secondary Anilines.



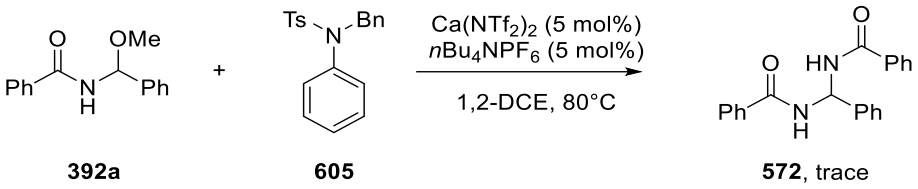
392a **603** **604**



604a, 73% **604b,** 53% **604c,** decomp

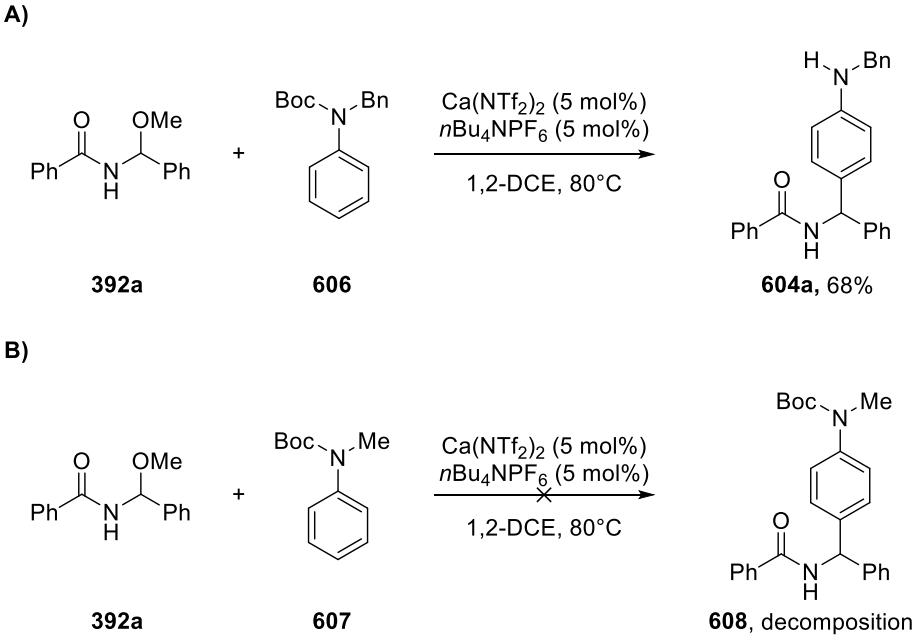
Next, the effect of *N*-substitution on the reaction outcome by introduction of carbamate and sulfonamide *N*-protected anilines was probed. When the *N*-tosyl-protected aniline derivative **605** was subjected to the optimised conditions, decomposition of **392a** into

benzaldehyde and benzamide was observed, with no product detected by ^{1}H NMR. Instead, trace amounts of bis-amide derivative **572** was isolated.



Scheme 111. Attempted addition of *N*-tosyl-protected aniline.

It was reasoned that the tosyl group was having a detrimental effect on the nucleophilicity of the aniline and attention was turned to *N*-Boc protected anilines. When *N*-benzyl derivative **606** was subjected to the optimised conditions, *N*-Boc deprotected Friedel-Crafts product **604a** was isolated in good yield (Scheme 112A). This indicates that the *N*-Boc deprotection is taking place, probably *via* a thermal Lewis acid mediated process. The reaction using *N*-methyl derivative **607** was also studied in which full decomposition of **392a** was observed (Scheme 112B).



Scheme 112. Reaction with *N*-Boc protected aniline derivatives.

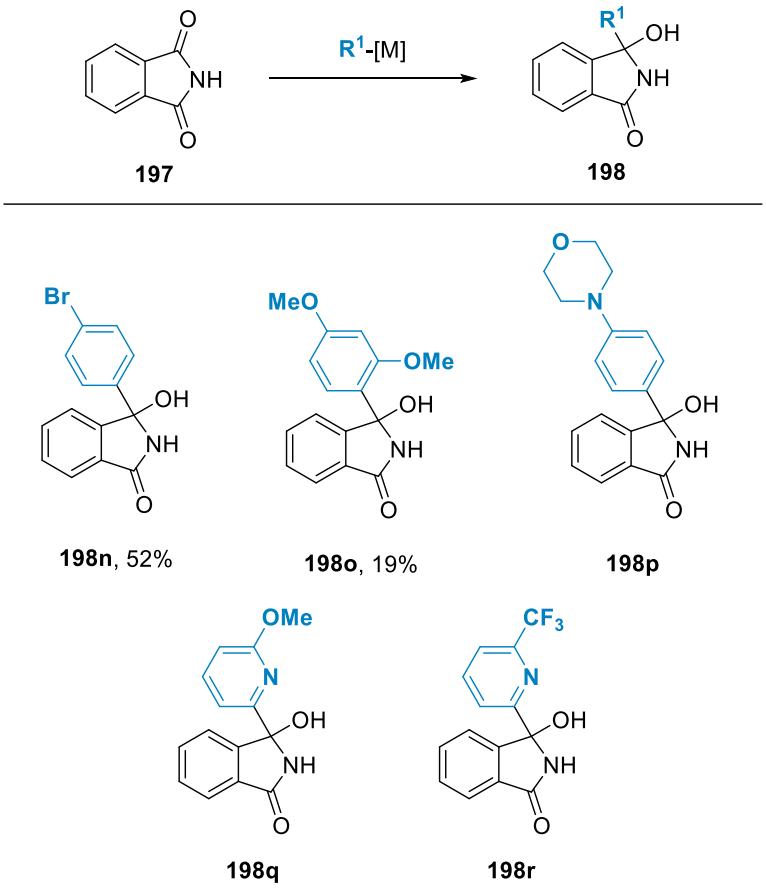
Based on the findings above it is clear that the reaction is incredibly sensitive towards to nucleophilicity of the aniline and is heavily influenced by the electronics of the substituents of the amine. There is a clear trend in which electron-deficient tertiary

anilines have a slightly reduced yield, while secondary anilines have a detrimental effect on yield. This is further supported by the study of tosyl and carbamate substituted anilines in which the *N*-tosyl or *N*-Boc substituted Friedel-Crafts products could not be accessed using this methodology.

6.3.3. Application towards isoindolinones

Due to the unprecedented reactivity displayed by *N,N*-disubstituted anilines as nucleophiles towards *N*-acyliminium ions, it was reasoned that this same methodology could be applied towards isoindolinones to access 3,3,-disubstituted products with an amino-functional handle. Firstly, the library of 3-hydroxyisoindolinone precursors synthesised in Table 3 and Table 5 was expanded to include compounds **198n** and **198o** while compounds **198p-198r** were obtained from the in-house library (Table 56).

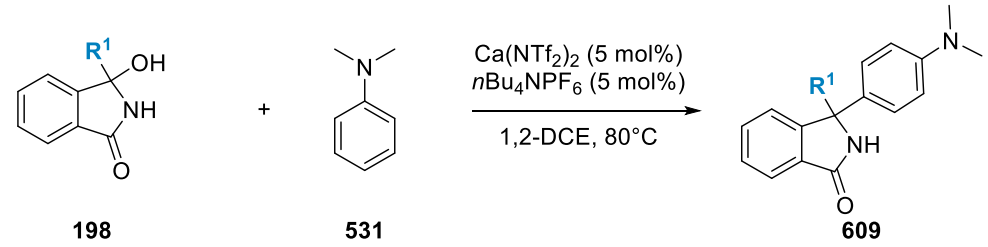
Table 56. Library of 3-hydroxyisoindolinones synthesised.



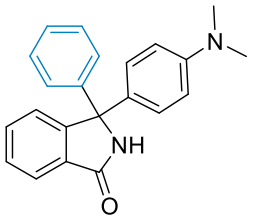
With a diverse library of 3-hydroxyisoindolinones in hand, the substrate scope was then probed using *N,N*-dimethyl aniline as the coupling partner (Table 57). When **198a** was

subjected to the optimised conditions, **609a** was isolated in excellent yield. Electron-rich, and halo-substituted isoindolinones were tolerant affording products **609b** and **609c** in almost quantitative yields. Sterically hindered ortho-substituted product **609d** also formed in high yield. A range of heterocycles were subjected to the optimised conditions, with great success. Acetal-protected and furan substituted products **609e** and **609f** formed in excellent yield as did thiophene substituted product **609g**. Furthermore, pyridyl substituted products **609h** and **609i**, each with varying Lewis basicity formed in good to excellent yield. Additionally, saturated *N*-heterocycles were also tolerated with morpholine substituted isoindolinone **609j** forming in excellent yield. However, when **609k** and **609l** were subjected to the optimised conditions, no reaction took place, with unreacted starting material re-isolated in both cases.

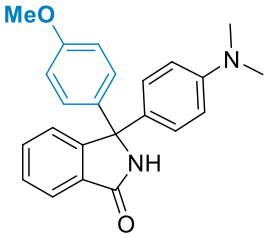
Table 57. Functionalised Friedel-Crafts scaffolds - isoindolinone variation.



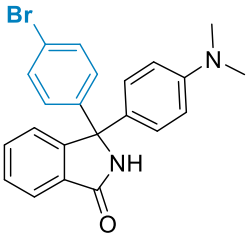
198 **531** **609**



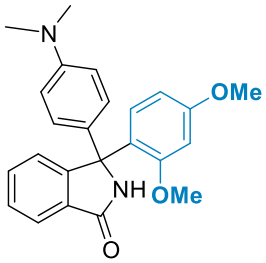
609a, 92%



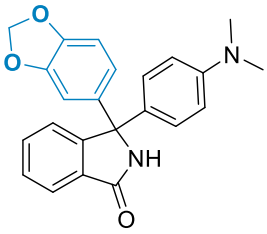
609b, 95%



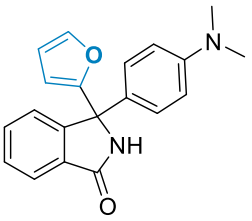
609c, 96%



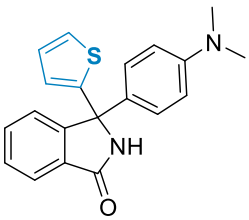
609d, 91%



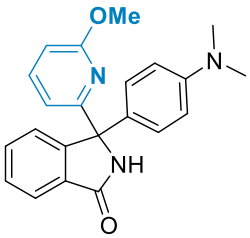
609e, 90%



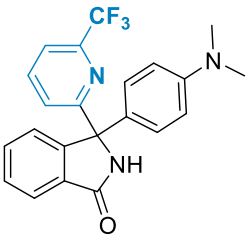
609f, 93%



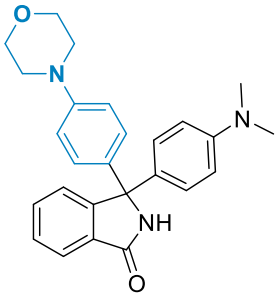
609g, 89%



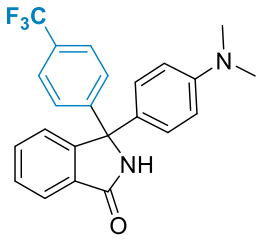
609h, 96%



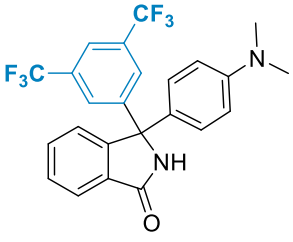
609i, 70%



609j, 94%



609k, trace

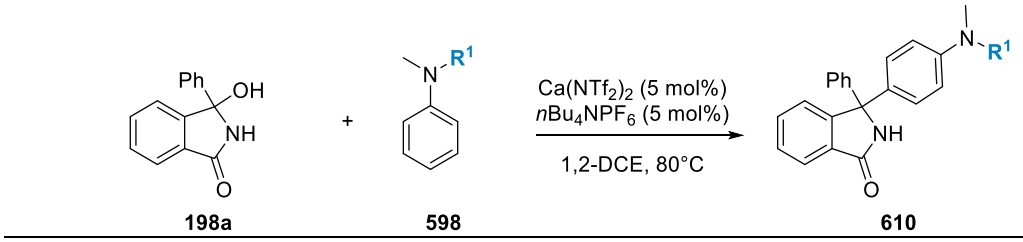


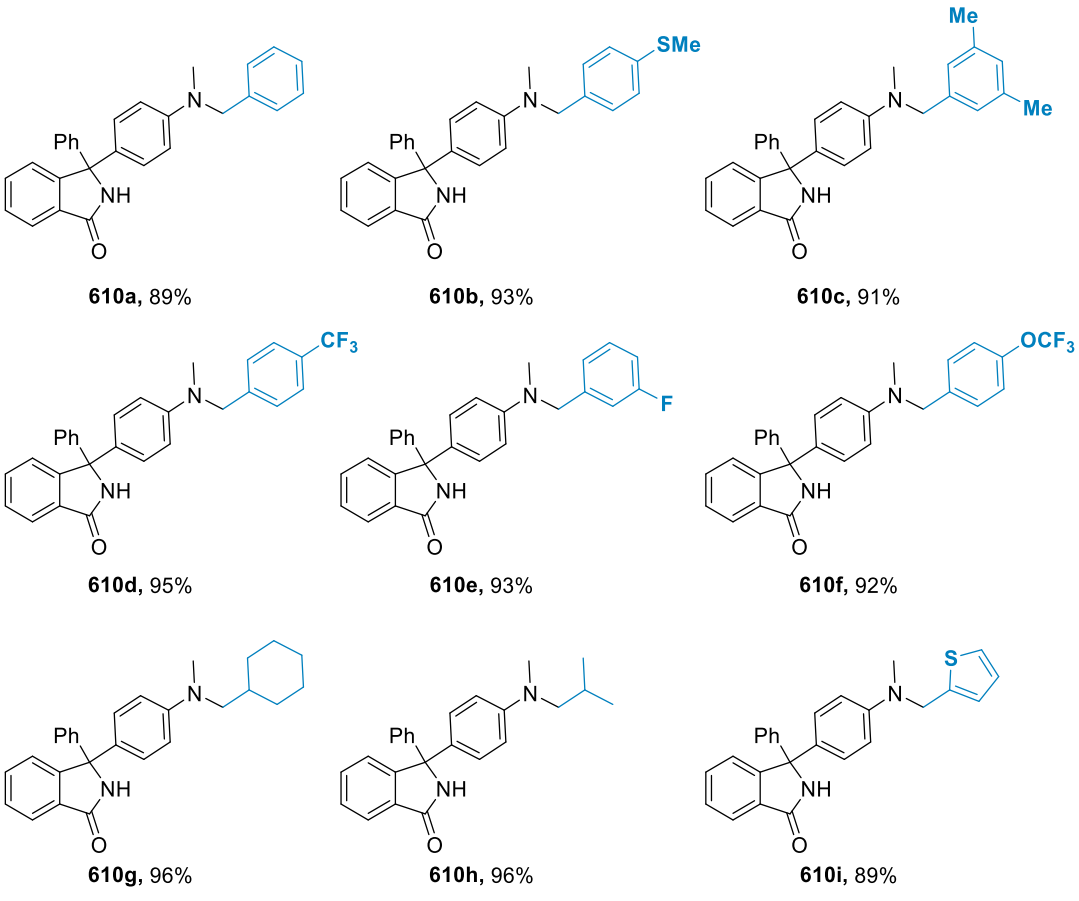
609l, trace

The range of amines that could be added into the isoindolinone derived *N*-acyliminium ions was then probed (Table 58). Benzyl-substituted and electron-rich anilines worked

well forming products **610a-610c** in excellent yield. Electron-deficient anilines were also well tolerated forming **610d-610f** again in excellent yield. Cyclohexyl and isopropyl-substituted anilines were well tolerated affording **610g** and **610h** respectively. Finally, thiophene substituted product **610i** was synthesised in excellent yield, again showing tolerance towards heterocycles.

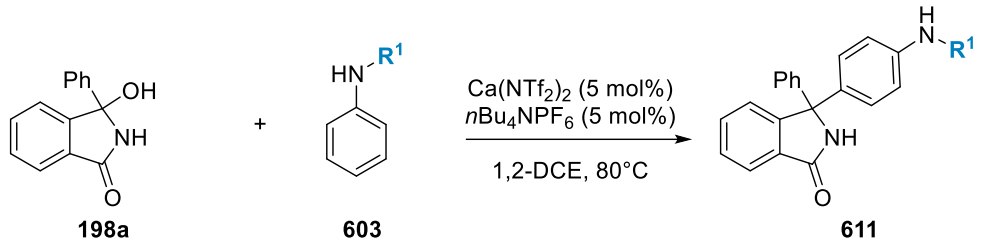
Table 58. Functionalised isoindolinone Friedel-Crafts scaffolds - Amine Variation.

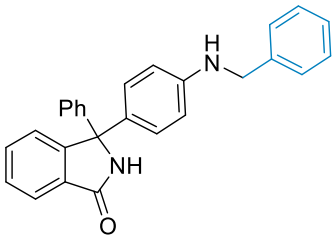




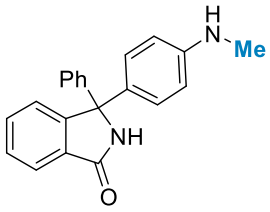
As with the *N*-acyl-*N,O*-acetals, whether secondary anilines were tolerant towards isoindolinone derived *N*-acyliminium ions was also explored (Table 59). This was successful with *N*-benzyl and *N*-methyl aniline proving effective coupling partners affording products **611a** and **611b** in excellent yields.

Table 59. Addition of secondary anilines to isoindolinones.





611a, 94%



611b, 92%

6.4. Plausible Mechanism

The proposed mechanism is expected to proceed as previously reported[39] (Figure 52). The active catalyst **241** is formed by anion metathesis which catalytically generates *N*-acyliminium ion **104** and intermediate **437**. Addition of the aniline derivative **531** into **104** results in iminium intermediate **612** which aromatises to form product **613**, facilitated by the methoxide anion and re-entry of PF_6^- to regenerate the active catalyst.

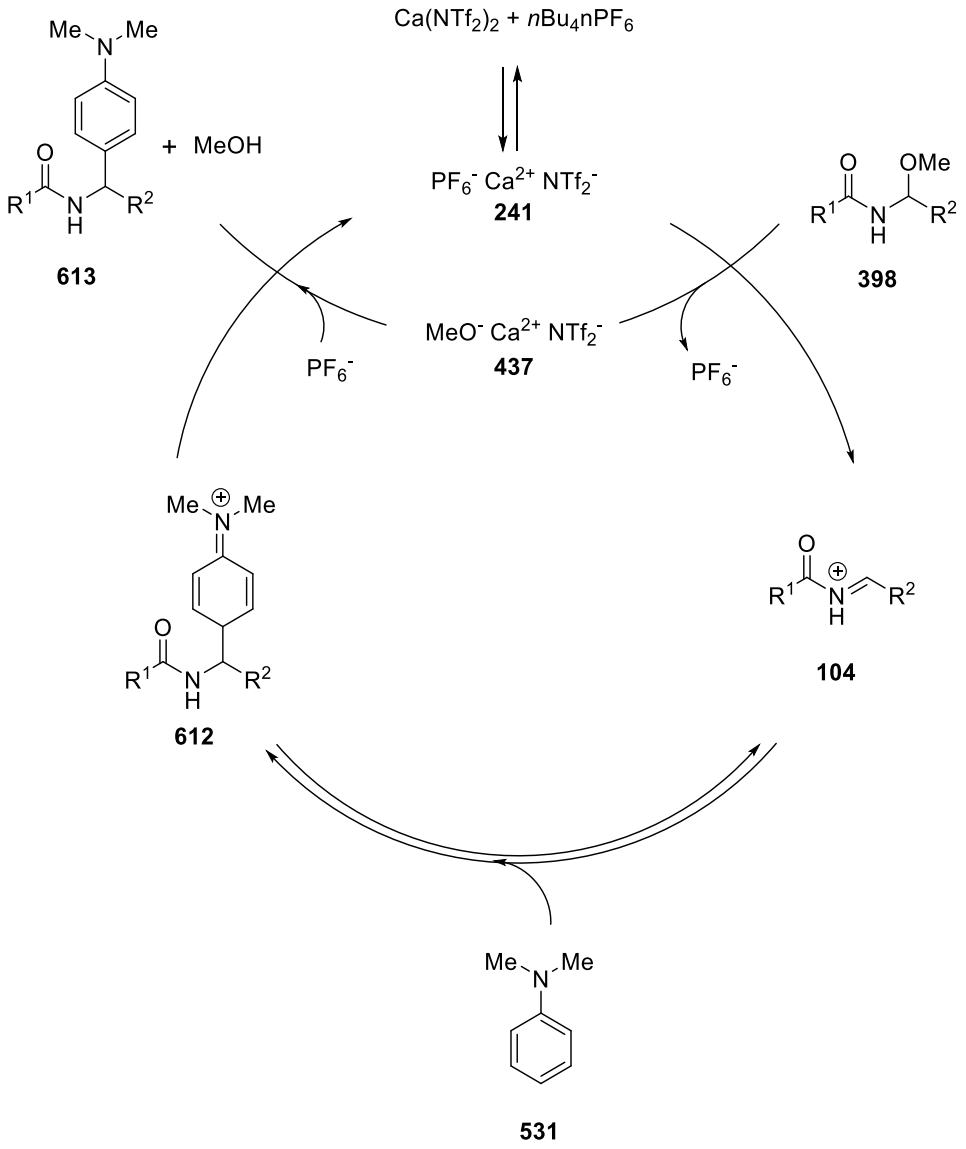


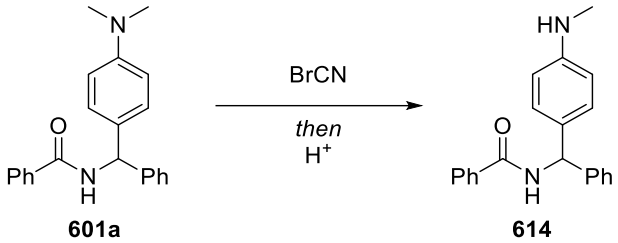
Figure 52. Proposed catalytic cycle.

6.5. Conclusions

In summary, it has been shown how secondary and tertiary substituted anilines are high effective C4-nucleophiles for addition into *N*-acyliminium ions. Calcium has been shown to be an effective catalyst in catalytically generating *N*-acyliminium ions in the presence of Lewis basic tertiary amines. The reaction is tolerant to a range of *N*-acyliminium ions, derived from both *N*-acyl-*N,O*-acetals and 3-hydroxyisoindolinones and tolerant to a range of aniline derivatives. The electronics of the aniline derivatives however is crucial in the outcome of the reaction, with more electron-deficient protecting groups proving inefficient.

6.6. Future Work

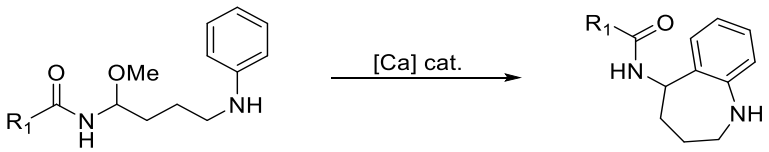
The modular assembly of the compounds synthesised in this chapter offer scope for further diversification. *N*-demethylation of **601a**, in the presence of cyanogen bromide and subsequent hydrolysis would provide access to the secondary amine **614** which can be subjected to further transformations as desired (Scheme 113).[181]



601a **614**

Scheme 113. *N*-demethylation of 601a *via* the van Braun reaction.

Additionally, an intra-molecular variant of this transformation would prove useful to medicinal chemists. By reacting an *N*-acyl-*N,O*-acetal **615** containing a tethered aniline under the optimised conditions described above could undergo an intra-molecular aza-Friedel Crafts cyclisation to provide access to C-5 substituted benzazepines **616** (Scheme 114).



615 **616**

Scheme 114. Intramolecular aza-Friedel-Crafts with a tethered aniline.

7. Chapter 7: Intermolecular Trapping of *N*-acyliminium ions with cyanide sources; access to α-amido-nitriles

7.1. Introduction

7.1.1. Synthesis of α-amino-nitriles

α-amino nitriles have a profound use as small building blocks and as structural motifs in medicinally relevant scaffolds. The motif features in a range of naturally occurring, biologically active compounds including Anagliptin **617**, which is a anti-hyperglycaemic used in the treatment of type 2 diabetes,[182] and Phthalascidin **618** which is an anti-tumour antibiotic (Figure 53).[183]

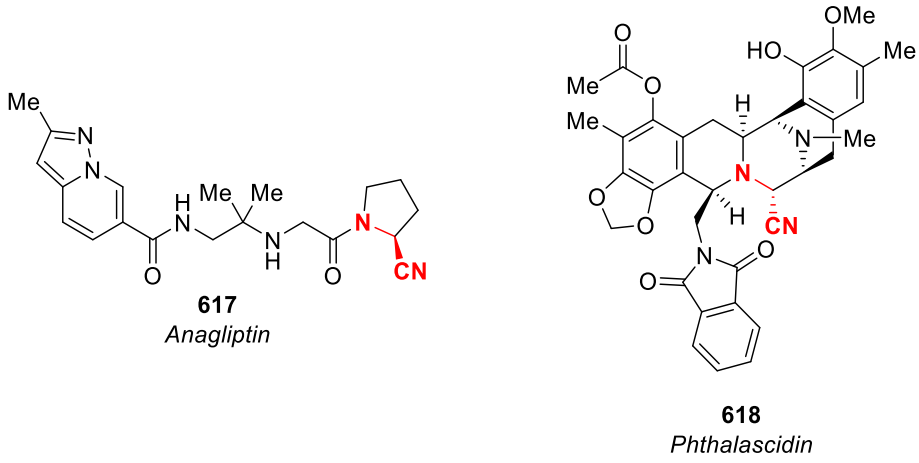


Figure 53. Medicinally relevant α-amino nitriles.

Their versatility as building blocks is due to the presence of both a nitrile and amine being attached to the same carbon which can be selectively transformed into mono- and bi-functional scaffolds (Figure 54). Acidic hydrolysis provides access to amino acids **620**, while reduction of the nitrile allows access to 1,2-diamines **621** and α-amino aldehydes **622**. Addition of an organometallic such as a Grignard reagent provides α-amino ketones **623**. Furthermore, the properties of the amino group are rather intrinsic with the ability to act as a hydrogen bond donor, while the electron-withdrawing nature of the nitrile also makes the nitrogen atom an excellent hydrogen bond acceptor.

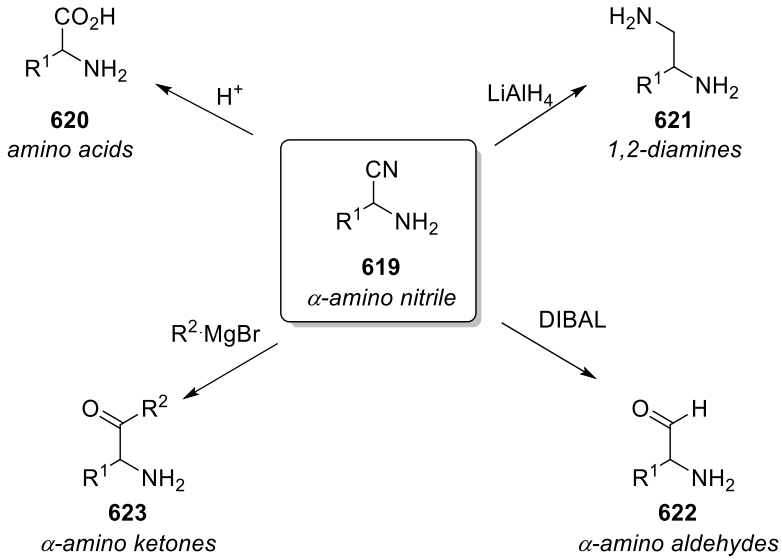
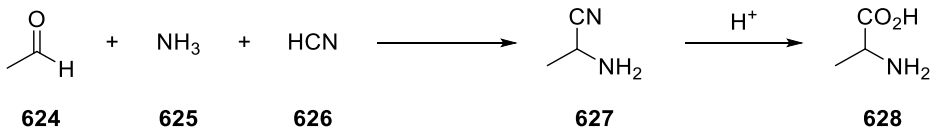


Figure 54. Synthetic versatility of α-amino nitriles towards a range of applications.

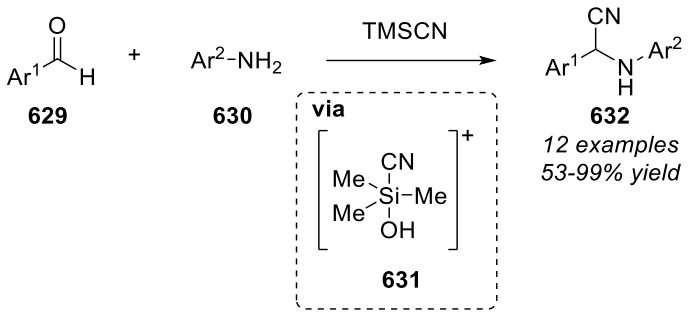
Due to this versatility, they have attracted considerable interest from synthetic chemists. The earliest report for the synthesis of an α-amino nitrile was in 1850 by Adolph Strecker. Treatment of acetaldehyde **624** in aqueous ammonia **625** and hydrogen cyanide **626** afforded α-amino nitrile product **627**, which upon acidic hydrolysis afforded racemic alanine **628**.[184]



Scheme 115. Strecker synthesis of α-amino nitrile.

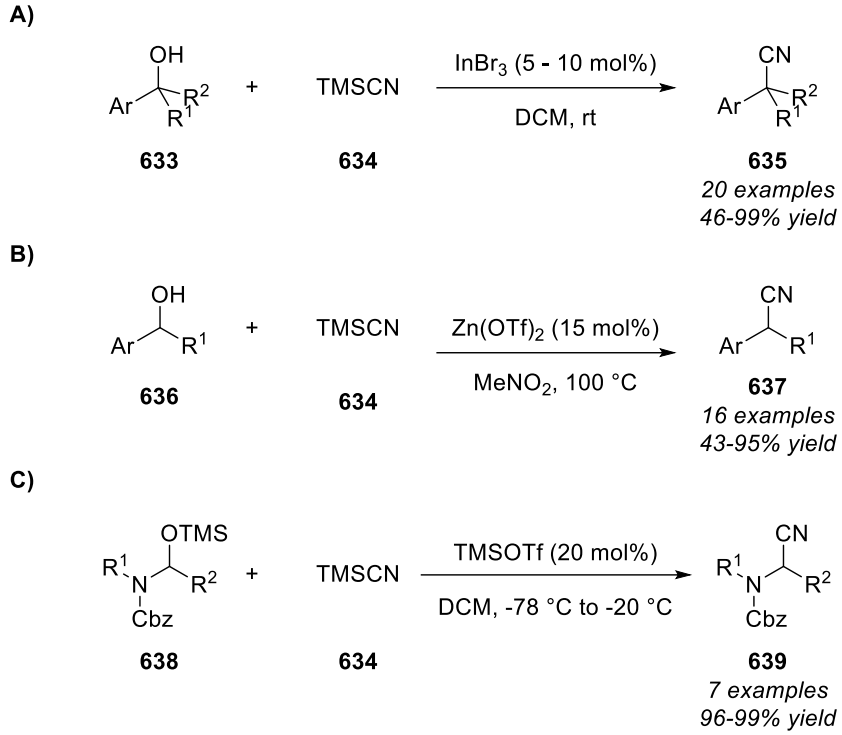
A significant limitation in the classical Strecker reaction is the use of the gaseous and highly toxic hydrogen cyanide. Alkaline metal cyanides such as KCN and NaCN have also been used, however these are highly basic which therefore limits functional groups that can be used. To overcome this, several safer and milder cyanating agents have been developed. Reagents including tributyl tin cyanide,[185] diethyl aluminium cyanaide[186] and potassium hexacyanoferrate(II) ($K_4[Fe(CN)_6]$)[187] have all been utilised as sources of the cyanide ion which can add in to imines and iminium ions. However, by far the most widely used cyanating agent is trimethylsilyl cyanide (TMSCN) owing to its increased solubility in organic solvents.

Strecker reactions involving aldehydes **629** and amines **630** utilisng TMSCN have been shown to take place without the presence of a catalyst, with the Yus group proposing that such reactions proceed *via* the formation of more nucleophilic cyanide source, pentavalent siliconate intermediate **631** (Scheme 116).[188]



Scheme 116. Catalyst free Strecker synthesis *via* the formation of a pentavalent siliconate intermediate.

However, to carry out a Strecker like cyanation reaction on less reactive substrates, a catalyst is required to activate the desired electrophile. This can be achieved by activation of a leaving group to generate an electrophilic reactive intermediate. Lewis acids have been shown to be fruitful in catalysing this process. The dehydration of benzylic alcohols **633** in the presence of catalytic $InBr_3$ and TMSCN afforded a range of nitriles in moderate to excellent yields **635** (Scheme 117A).[189] $Zn(OTf)_2$ has also been shown to be effective in catalysing a similar transformation (**636** to **637**) (Scheme 117B).[190] The catalytic generation of *N*-acyliminium ions has been far less explored in which the Suh group reported addition of TMSCN to *N*-acyliminium ions using catalytic TMSOTf (Scheme 117C).[191] However, the authors report a limited substrate scope of **639** with only alkyl *N,O*-acetal derivatives being tolerated.



Scheme 117. Catalytic dehydrative cyanations.

Therefore it's reasoned that calcium can be utilised as a Lewis acid to catalytically generate *N*-acyliminium ions to then undergo cyanation in the presence of TMSCN and subsequently offer much more control.

7.2. Aims

In this chapter, the aim is to develop a calcium catalysed Strecker type reaction for the addition of nitriles into *N*-acyliminium ions **104** (Figure 55). The work within this thesis has already shown calcium to be effective in catalytically generating *N*-acyliminium ions, and the intention now is to extend this study into the addition of nitriles to access useful building blocks **640** which can be subjected to a plethora of transformations **641**-**643**.

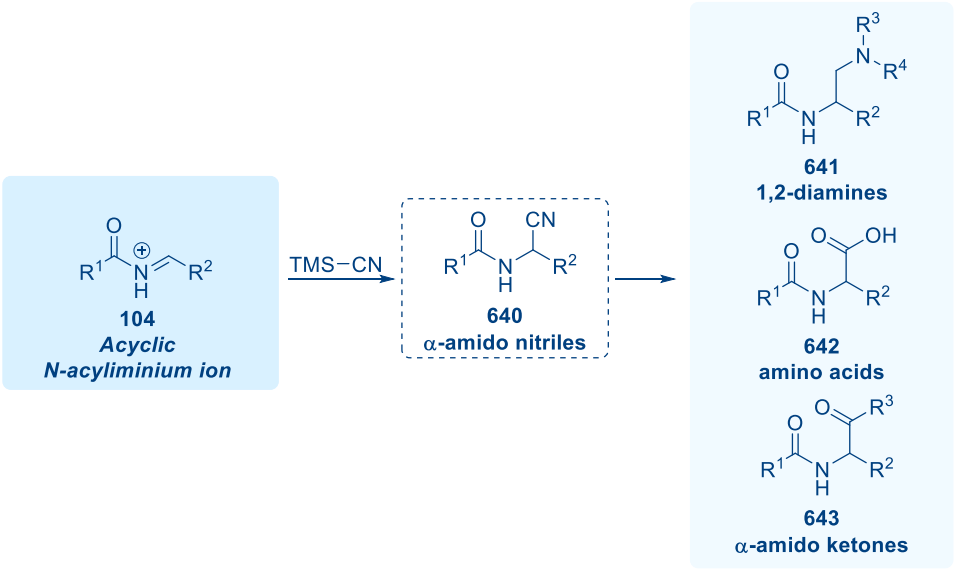


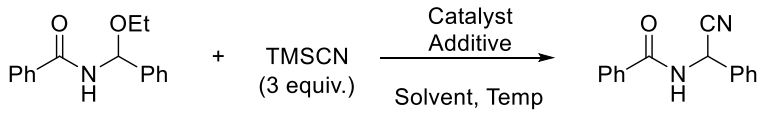
Figure 55. Proposed TMSCN addition into catalytically generated *N*-acyliminium ions to access versatile a-amido nitriles.

7.3. Results & Discussion

7.3.1. Reaction Optimisation

The optimisation began by subjecting **644a** and TMSCN **634** to 5 mol% of catalyst in DCM at 25 °C in which desired product **645a** formed in a low 22% yield (entry 1, Table 60). It should be noted here that utilising the ethoxy acetal versus methoxy- or isopropoxy-variants is not important in the reactivity and the ethoxy derivative was used due to ease of preparation. Increasing the temperature to 40 °C saw only a slight increase in yield (entry 2). Using a large excess of TMSCN (10 equiv.) resulted in a decrease in yield (entry 3). Changing the additive to the BF_4^- adduct had a negative effect on yield (entry 4), while increasing the catalyst loading had only a slight effect on yield (entry 5).

Table 60. Initial Reaction Screening.



644a **634** **645a**

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time	Yield[a]
1	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	25°C	DCM	12 h	22%
2[b]	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	40°C	DCM	12 h	29%
3[b]	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	40°C	DCM	12 h	8%
4	$Ca(NTf_2)_2$	nBu_4NBF_4	5 mol%	40°C	DCM	12 h	12%
5	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40°C	DCM	12 h	34%

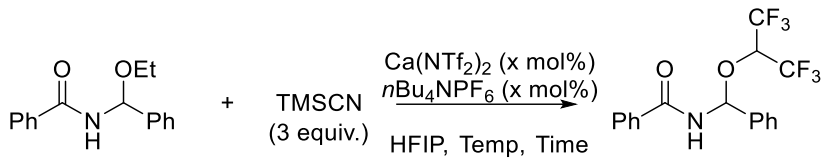
[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard
[b] 10 equiv of TMSCN
n.r = no reaction

In all cases the reaction did not go to completion and there were multiple side reactions taking place.

To circumvent these side reactions taking place, the use of HFIP as a solvent was then studied. Lebeouf and co-workers have recently reported how the formation of *N*-acyliminium ions in HFIP generates a more stable HFIP-hemiaminal reservoir which results in a cleaner, higher yielding reaction.[192] Therefore, an initial screening with HFIP as solvent was carried out (Table 61). When **644a** was reacted with TMSCN using 5 mol% catalyst in HFIP at 40 °C the reaction proved much cleaner with full consumption of starting material observed. However, the major product was HFIP-hemiaminal **646** with no desired α-amido-nitrile present after 12 h (entry 1). To gain more insight into the

hemiaminal formation, the reaction was studied over 1 h and 4 h in which the reaction appeared to plateau after 4 h with an increase in by-products (entries 2 and 3). To circumvent by-product formation, the catalyst loading was lowered which saw a more sluggish reaction and subsequent decrease in yield (entry 4). To ascertain if the temperature was contributing to the by-product formation, the temperature of the reaction was reduced which saw a slight increase in the formation of **646** (entries 5 and 6). Lowering the catalyst loading at the reduced temperature had little effect and was comparable to entry 4 (entry 7). The conclusion from varying these conditions was that the reaction was incredibly sensitive towards hemiaminal formation and degradation with no clear trend observed. Lower temperatures and catalyst loadings made the reactions slower yet cleaner, and higher temperatures and catalyst loadings resulted in full consumption of starting materials with increased by-products.

Table 61. Initial Screening with HFIP as solvent.



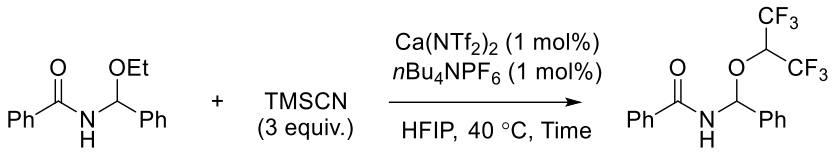
644a **634** **646**

Entry	Loading	Temp	Time	Yield[a]
1	5 mol%	40°C	12 h	46%
2	5 mol%	40°C	1 h	32%
3	5 mol%	40°C	4 h	48%
4	**1 mol%**	**40°C**	**1 h**	**23%**
5	5 mol%	25°C	1 h	44%
6	5 mol%	25°C	4 h	58%
7	1 mol%	25°C	1 h	25%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Given entry 4 resulted in the cleanest reaction profile, these conditions were used as model conditions to optimise further to see if this could be extended towards forming the desired α-amido-nitrile product. Firstly, this reaction was studied over longer reaction times (Table 62). After 1 h hemiaminal **646** had formed in 62% yield with some unreacted starting material remaining (entry 1). Leaving the reaction for a longer period then resulted in increasing formation of by-products and a decrease in hemiaminal **646** with the amount of hemiaminal appearing to plateau (entries 2-5).

Table 62. Reaction monitoring over 5 hours.

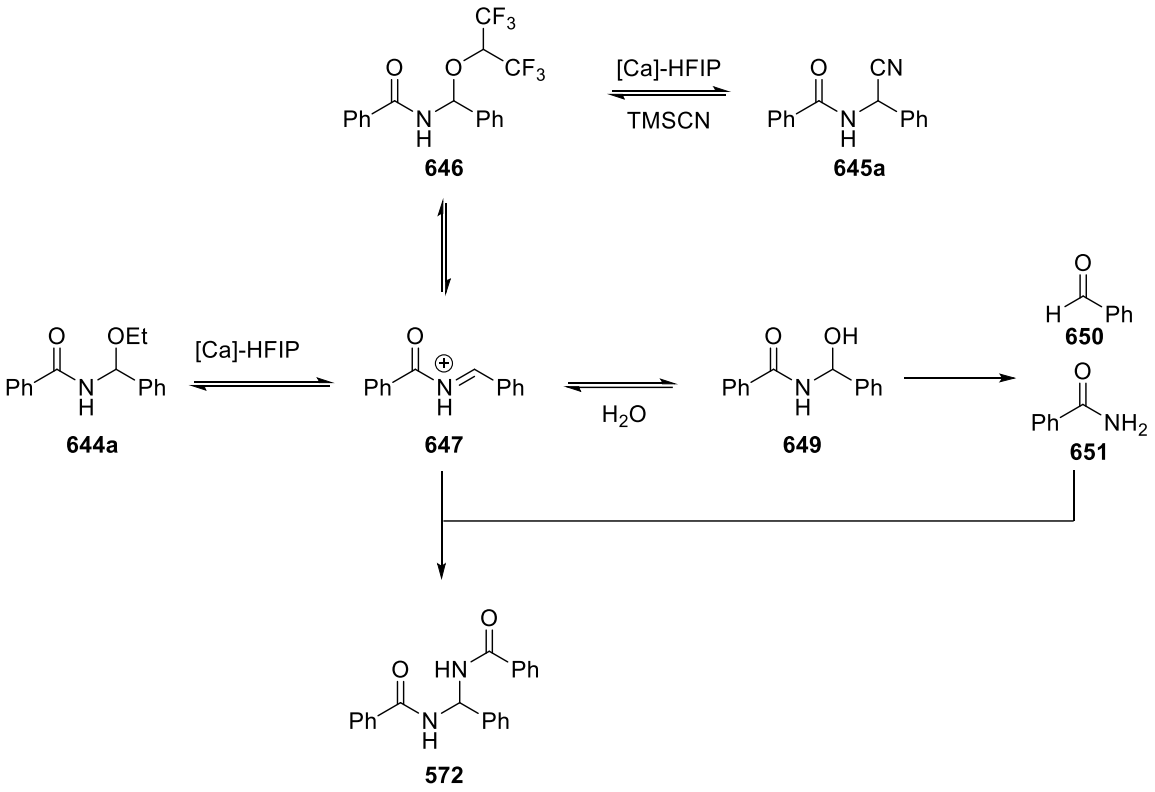


644a **634** **646**

Entry	Time	Yield[a]
1	1h	62%
2	2h	54%
3	3h	56%
4	4h	54%
5	5h	54%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

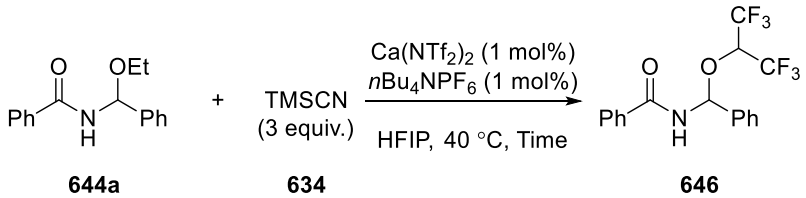
Based on this screening, it was reasoned that the products formed when performing the reaction in HFIP could be potentially unstable and degrading, along with numerous side reactions. The *N*-acyliminium ion **647** formed by the calcium-HFIP complex could react in several ways (Scheme 118). It could react in the desired way by being initially trapped out with HFIP to generate a reservoir pool of hemiaminal **646** which is then further activated by the [Ca]-HFIP complex to generate another *N*-acyliminium ion which is trapped out with TMSCN to give desired product **645a**. Alternatively, trace water could trap out *N*-acyliminium ion **647** to generate hemiaminal **649** which then decomposes to benzaldehyde **650** and benzamide **651**. The formation of benzaldehyde can be observed by ^{1}H NMR. The benzamide formed could trap out **647** generating bis-amide **572**. Despite this, the reaction proved to be much cleaner when carried out in HFIP and a range of conditions in HFIP were then screened.



Scheme 118. Possible side reactions when HFIP is used as the solvent.

The degradation of the products forming within the reaction could be more closely observed when monitoring the reaction over 1 hour, at 15-minute intervals (Table 63). There is a rapid initial formation of **646** after 15 mins (entry 1) which increases more slowly after 30 and 45 minutes (entries 2 and 3). However, after 1 hour there is a decrease in yield of **646** and no α-amido-nitrile product is detected indicating that the *N*-acyliminium ion is preferentially either being trapped out by the solvent or decomposing.

Table 63. Reaction Monitoring up to 1 hour at 15 minute intervals.

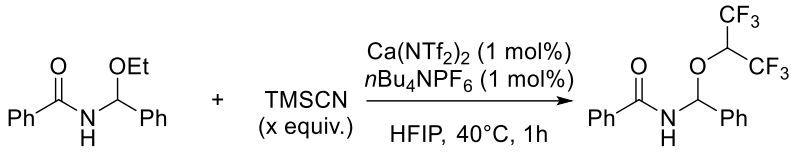


Entry	Time	Yield[a]
1	15 min	41%
2	30 min	51%
3	45 min	52%
4	60 min	46%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Whether the equivalents of TMSCN influenced the reaction outcome was then studied (Table 64). Decreasing the equivalents resulted in an increase in formation of hemiaminal **646** (entry 1) with an increase in by-product formation. Increasing the equivalents saw a slight decrease in yield but a cleaner reaction (entry 2 and 3). Using a large excess of TMSCN saw an increase in hemiaminal formation but with a larger quantity of by-products (entry 4). Due to the cleaner reaction profile, 6 equivalents of TMSCN were deemed optimal.

Table 64. Varying the equivalents of TMSCN.



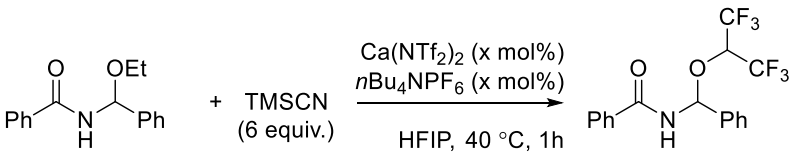
644a **634** **646**

Entry	TMSCN (equiv.)	Yield [a]
1	1.50	58%
2	3.00	48%
3	6.00	53%
4	12.00	58%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Moving forward, utilising 6 equivalents of TMSCN, whether higher catalyst loadings would catalyse the generation of the α-amido-nitrile product from hemiaminal **646** was then studied (Table 65). While no α-amido-nitrile product was observed in any of the reactions, 1 mol% catalyst loading resulted in the cleanest reaction.

Table 65. Effect of catalyst loading.



644a **634** **646**

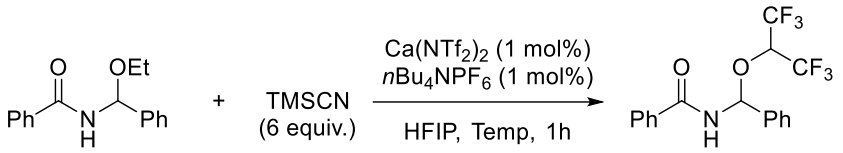
Entry	Loading	Yield [a]
1	1 mol%	59%
2	2 mol%	65%
3	5 mol%	66%
4	10 mol%	49%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

As it has been shown that utilising 1 mol% of catalyst with 6 equivalents of TMSCN results in the cleanest formation of **646**, these conditions were then studied at various

temperatures (Table 66). Increasing the temperature to 50 °C had little effect on yield (entry 1) while increasing the reaction further to 60 °C saw an increase in yield (entry 2).

Table 66. Varying the temperature.



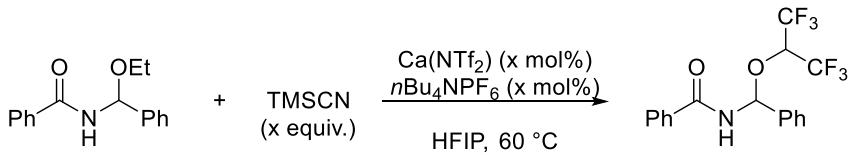
644a **634** **646**

Entry	Temp	Solvent	Yield[a]
1	50°C	HFIP	48%
2	60°C	HFIP	61%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

In this context, a range of catalyst loadings and equivalents of TMSCN were then screened at this new temperature (Table 67). Utilising 1 mol% catalyst and 6 equivalents of TMSCN afforded **646** in excellent yield however no α-amido-nitrile product was detected (entry 1). Increasing the catalyst loading and decreasing the equivalents of TMSCN had a detrimental effect on yield (entry 2). Utilising 2 mol% catalyst and 6 equivalents of TMSCN afforded **646** in excellent yield with full consumption of **644a** now being observed (entry 3), and a comparable yield was observed after 30 mins (entry 4). With full conversion to the HFIP-*N*-acyliminium ion pool, the reaction was left running to see if there would now be conversion to the α-amido-nitrile. However, this resulted in **646** beginning to degrade and therefore the yield decrease (entry 5).

Table 67. Reoptimisation at 60 °C



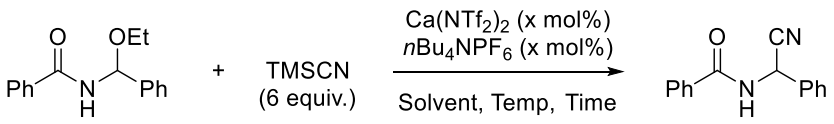
644a **634** **646**

Entry	Loading	TMSCN (equiv.)	Time	Yield[a]
1	1 mol%	6.00	1h	80%
2	5 mol%	3.00	1h	52%
3	2 mol%	6.00	1h	76%
4	**2 mol%**	**6.00**	**30 min**	**78%**
5	2 mol%	6.00	3h	67%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Full consumption of starting material was now being observed under these conditions, however there was still no conversion of **646**into **645a**. Higher catalyst loadings resulted in increasing by-product formation, while lower temperatures and equivalents of TMSCN was resulting in more sluggish reactions. Therefore the conditions used in Table 60 were revisited to see if these could be optimised further (Table 68). This began by subjecting **644a** and **634** to 1 mol% of catalyst at 40 °C in DCM, in which no reaction took place (entry 1). Increasing the temperature to 80 °C resulted in a low yield after 1h (entry 2). Increasing the catalyst loading over the same time period resulted in respective increases in yield (entries 3 and 4). The reaction was then studied over 4 h at 1 and 5 mol% catalyst loadings (entries 5-10). Unsurprisingly, the reaction at 1 mol% is much slower, while higher catalyst loadings resulted in the rapid formation of **645a** in good yield, which then began to degrade. The reaction was then studied overnight at various catalyst loadings to see whether the slower reaction would proceed to completion. Using 2 mol% catalyst, product **645a** formed in excellent yield after 12 h (entry 11). Increasing the catalyst loading saw a decrease in yield (entry 12). Therefore entry 11 was deemed optimal conditions.

Table 68. Reoptimisation in chlorinated solvents.



644a **634** **645a**

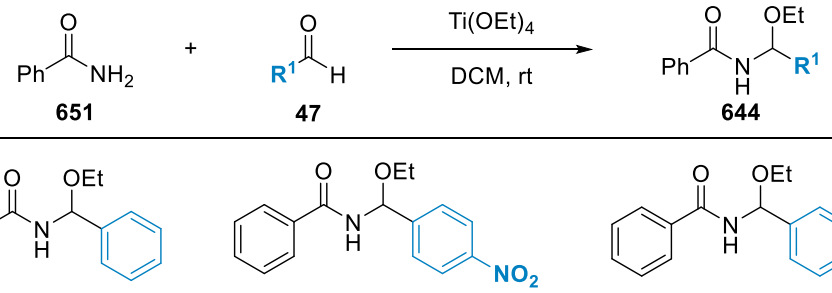
Entry	Loading	Temp	Solvent	Time	Yield[a]
1	1 mol%	40°C	DCM	1h	0%
2	1 mol%	80°C	1,2-DCE	1h	8%
3	2 mol%	80°C	1,2-DCE	1h	11%
4	5 mol%	80°C	1,2-DCE	1h	24%
5	1 mol%	80°C	1,2-DCE	2h	35%
6	1 mol%	80°C	1,2-DCE	3h	35%
7	1 mol%	80°C	1,2-DCE	4h	38%
8	5 mol%	80°C	1,2-DCE	2h	76%
9	5 mol%	80°C	1,2-DCE	3h	71%
10	5 mol%	80°C	1,2-DCE	4h	30%
11	**2 mol%**	**80°C**	**1,2-DCE**	**12 h**	**86%**
12	5 mol%	80°C	1,2-DCE	12 h	21%

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard

7.3.2. Preparation of Starting Materials

With the reaction optimised, a library of *N*-acyl-*N,O*-acetals was synthesised using the method reported by Wen and Huang with varying aldehydes (Table 69).[143] These compounds were added to the library and used in conjunction with those synthesised in 4.3.2. In addition to phenyl-substituted product **644a**, electron-withdrawing **644b** and electron-donating **644c** aldehydes were tolerated. Various substitution patterns on the aromatic ring were also well tolerated with 2-substituted and 2,3-disubstituted products **644d** and **644e** synthesised in good to synthetically useful yields. Furthermore, heterocycles and alkyl-substituted aldehydes were also tolerated affording thiophene-substituted product **644f** and iso-propyl-substituted product **644g** respectively.

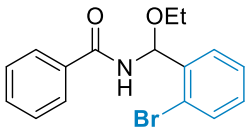
Table 69. Synthesis of *N*-acyl-*N,O*-acetals using procedure reported by Wen & Huang.[143]



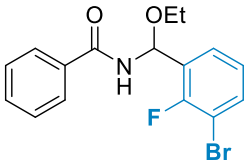
644a, 78%

644b, 45%

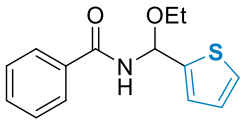
644c, 61%



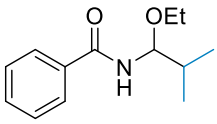
644d, 87%



644e, 19%

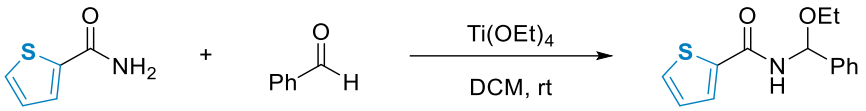


644f, 53%



644g, 70%

Compound **654** was also added to the starting material library which was synthesised from **653** and **407** using the same procedure (Scheme 119).



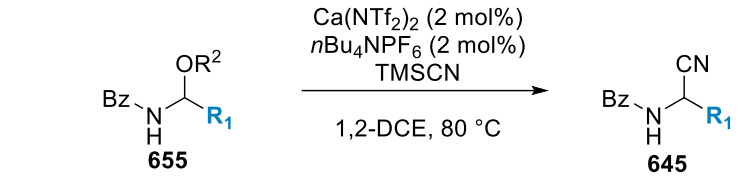
653 **406** **654,** 19%

Scheme 119. Synthesis of 654 using procedure reported by Wen & Huang.[143]

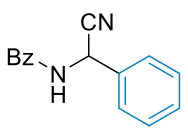
7.3.3. Development of Substrate Scope

With the optimised conditions and a library of *N*-acyl-*N,O*-acetal derivatives synthesised, the substrate scope was probed by first studying the reactivity arising from the aldehyde component (Table 70). In addition to phenyl-substituted product **645a**, electron-deficient *N,O*-acetals were tolerated affording **645b** and **645c** in good yield. Electron-donating groups in the form of a thioether were also tolerated affording **645d** in good yield. The substituted patterns of the aromatic group were then studied. The reaction proceeded unhindered by 2-substituted, 3-substituted and 2,3-disubstituted electron-deficient aromatics affording **645e**, **645f** and **645g** in good to excellent yield. Furthermore, heterocyclic and alkyl substituted group were also well tolerated affording **645h** and **645i** in excellent yields.

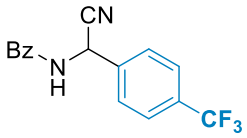
Table 70. Synthesis of α-amido-nitriles – Aldehyde variation.



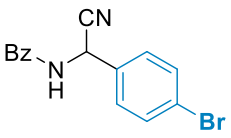
655 → **645**



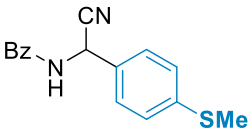
645a, 86%



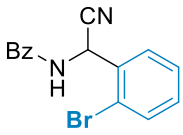
645b, 71%



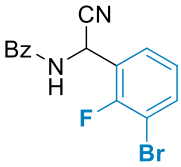
645c, 77%



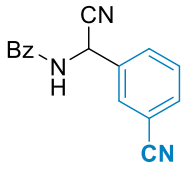
645d, 77%



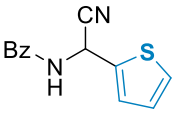
645e, 83%



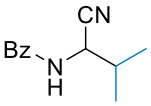
645f, 61%



645g, 92%



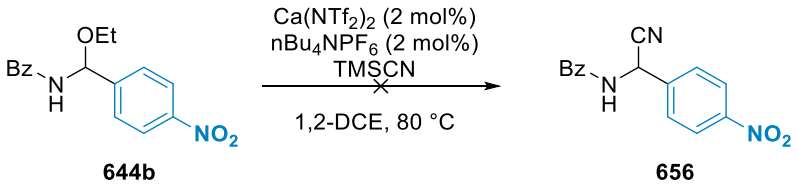
645h, 87%



645i, 88%

R^2 = Me for 645b, 645c, 645g
R^2 = Et for 645a, 645d, 645e, 645f, 645h, 645i

While a diverse library of benzoyl protected α-amino-nitriles have been prepared, the reaction did have some limitations. When more electron-deficient aromatics **644b** were subjected to the optimised conditions, unreacted starting material was re-isolated (Scheme 120).



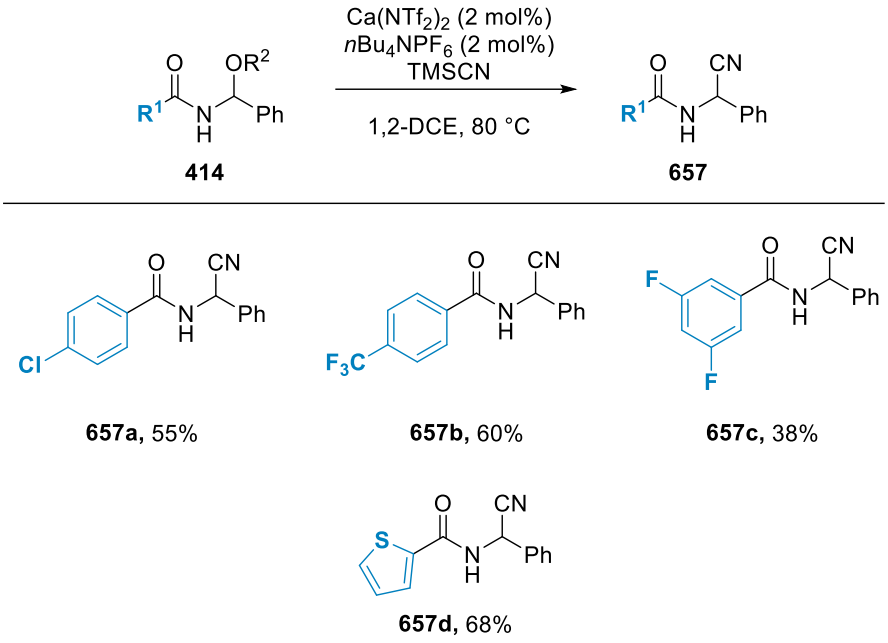
644b → **656**

Scheme 120. Unsuccuessful reaction of 746 when subjected to the optimised conditions.

The reactivity with respect to the amide variation of the *N*-acyl-*N,O*-acetal was then studied (Table 71). Halo-substituted and electron-deficient aromatics worked in

moderate yield affording **657a** and **657b** respectively. *Meta* substituted product **657c** was also synthesised in a synthetically useful yield and heterocycles were again tolerated affording thiophene-substituted product **657d** in good yield.

Table 71. Synthesis of α-amido-nitriles – Amide variation.

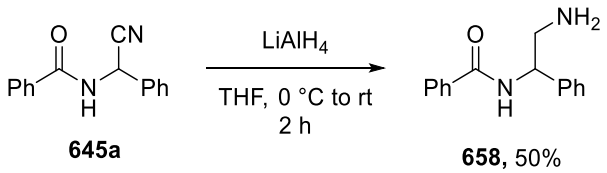


R^2 = Et for 656b, 657d
R^2 = ^{i}Pr for 657a, 657c

7.3.4. Applications of Products

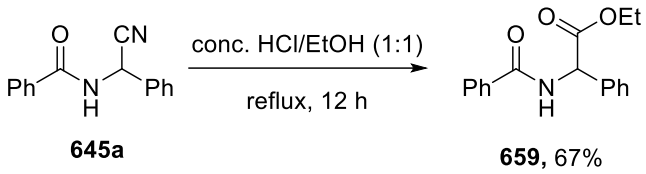
Due to the wide number of applications that the nitrile group possesses, whether the products could be functionalised, to access useful small building blocks was next studied.

Reduction of the nitrile was first studied (Scheme 121). Treatment of **645a** with 10 equivalents of $LiAlH_4$ chemoselectively afforded 1,2-amido-amine **658** in a moderate yield.



Scheme 121. Chemoselective reduction of 645a in the presence of $LiAlH_4$.

It was then reasoned that α-amido-nitriles **645a** are useful precursors for α-amido-esters which are amino-acid derivatives. Subjecting **645a** to a 1:1 mixture of conc. HCl and ethanol successfully hydrolysed nitrile **645a** and afforded α-amido-ester **659** in good yield (Scheme 122).

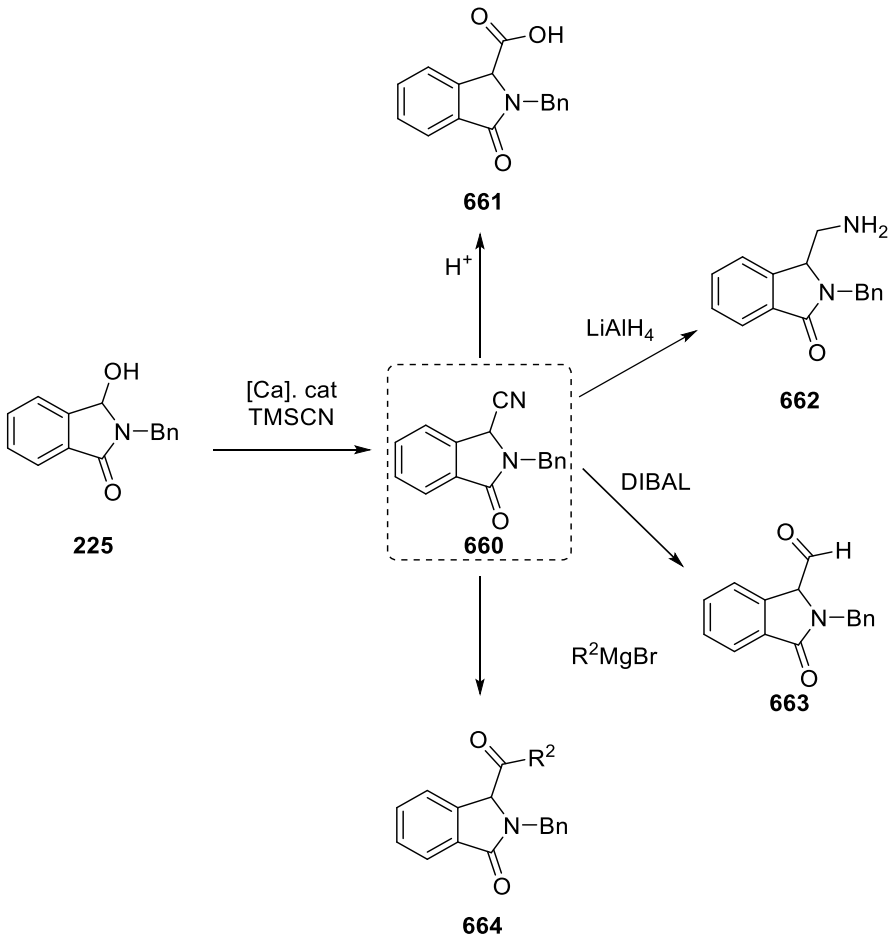


645a **659,** 67%

Scheme 122. Hydrolysis of 645a to access α-amido ester 659.

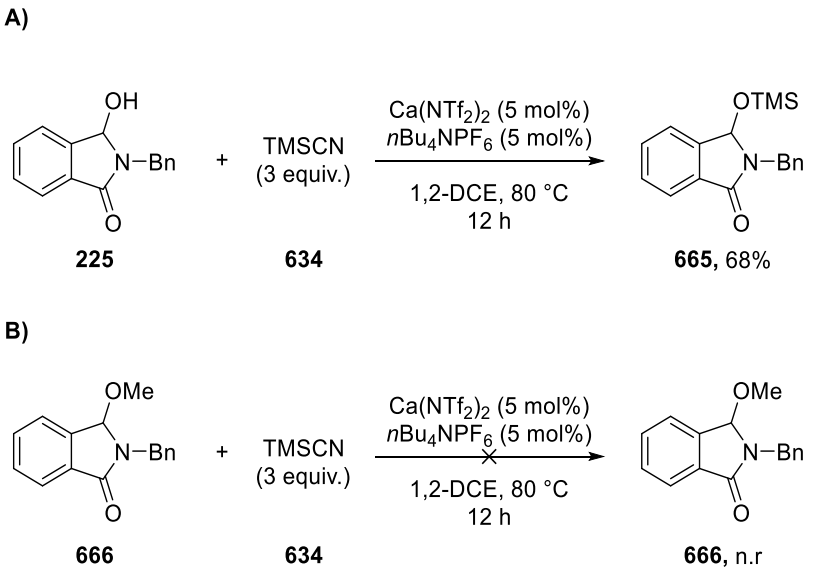
7.3.5. Application towards Isoindolinones

Whether this methodology could be applied towards 3-hydroxyisoindolinones was then explored. If successful, this would provide access to a highly versatile synthetic nitrile intermediate **660** which can be manipulated into products **661**-**664**.



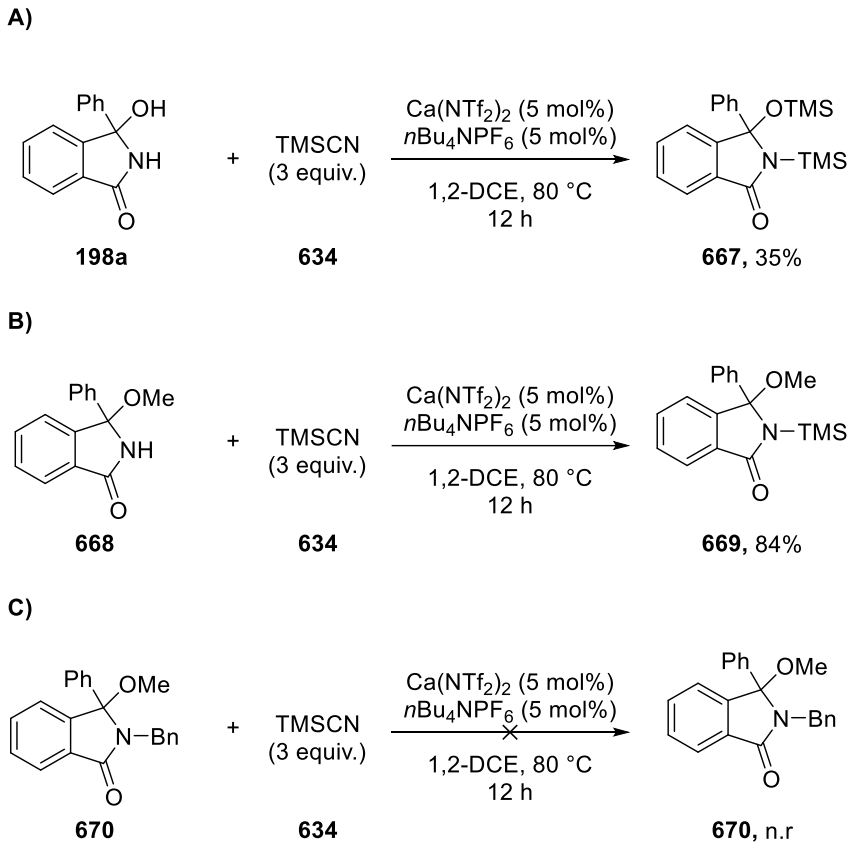
Scheme 123. Desired transformations in the application towards 3-hydroxyisoindolinones.

This began by reacting 3-hydroxyisoindolinone **225** and TMSCN **634** under optimised conditions in which the catalytically inert TMS-protected product **665** was isolated in 68% yield (Scheme 124A). To circumvent this, the alcohol was methylated to afford **666** which was subjected to the optimised conditions. However, no reaction took place and unreacted starting material was isolated (Scheme 124B). This can be attributed to *N*-substituted *N*-acyliminium ions being much less reactive and the increasing steric demand arising from the methyl group of the methoxy, thereby making the calcium Lewis acid less accessible.



Scheme 124. Initial study of α-amido cyanation of 3-hydroxyisoindolinones.

As this could not be developed further, whether 3,3,-disubstituted isoindolinones react in a similar way was then studied. Subjecting **198a** to the optimised conditions resulted in TMS-protected product **667** being isolated in which the amide and alcohol both react with the TMSCN (Scheme 125A). To prevent this from occurring the alcohol was methylated, however this resulted in the *N*-TMS protected product **669** being isolated in 84% yield (Scheme 125B). To prevent TMS-protection taking place, the *N*-Bn methylated compound **670** was synthesised and subjected to the optimised conditions. However, unsurprisingly, no reaction took place and unreacted starting material was re-isolated (Scheme 125C).



Scheme 125. Attempted synthesis of 3,3,-disubstituted isoindolinones with a nitrile functional handle.

To prevent TMS-protection occurring, both the nitrogen and oxygen atoms required protecting which results in a decrease in reactivity towards *N*-acyliminium ion formation, along with lowering the electrophilicity of a resulting *N*-acyliminium that does form. Therefore, it was reasoned that these scaffolds cannot be accessed *via* this methodology.

7.3.6. Proposed Mechanism

Based on previous reports, the following mechanism is proposed. The active catalyst **241** is formed by anion metathesis, which catalytically generates *N*-acyliminium ion **104** and intermediate **437** by loss of PF_6^-. Re-entry of PF_6^- to the cycle along with TMSCN **634** results in the regeneration of the active catalyst and pentavalent siliconate **671** which adds to the *N*-acyliminium ion to give the desired product **640** and TMS-OMe **672**.

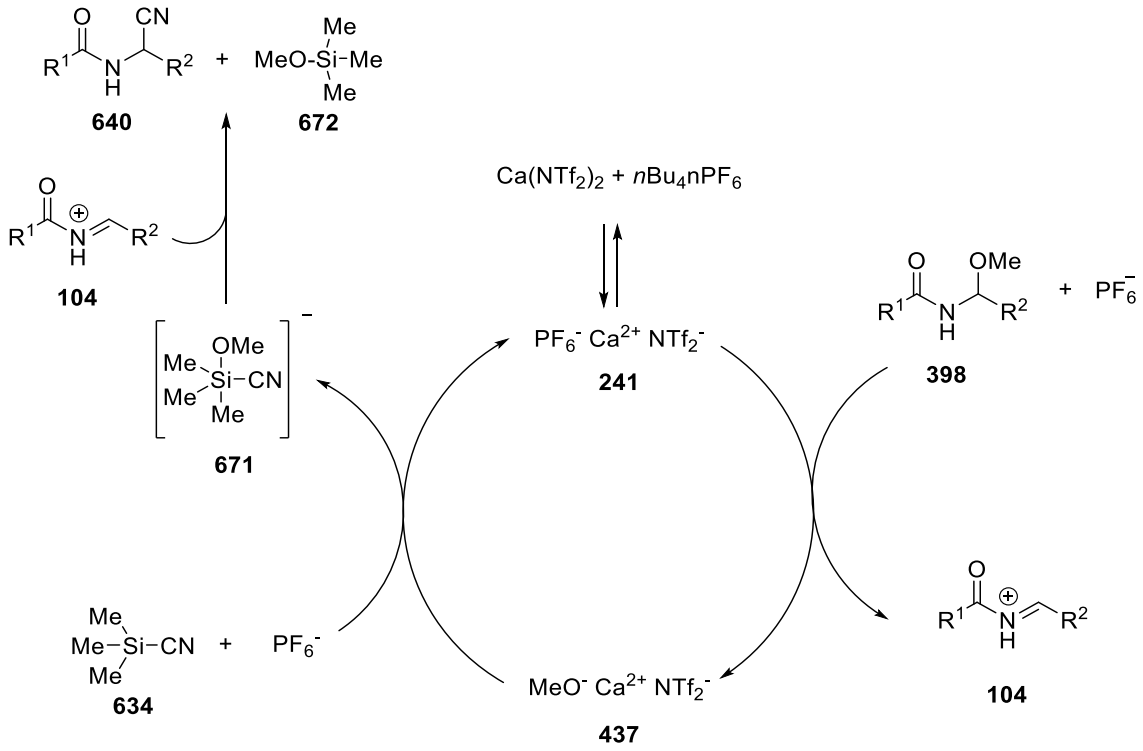


Figure 56. Proposed catalytic cycle.

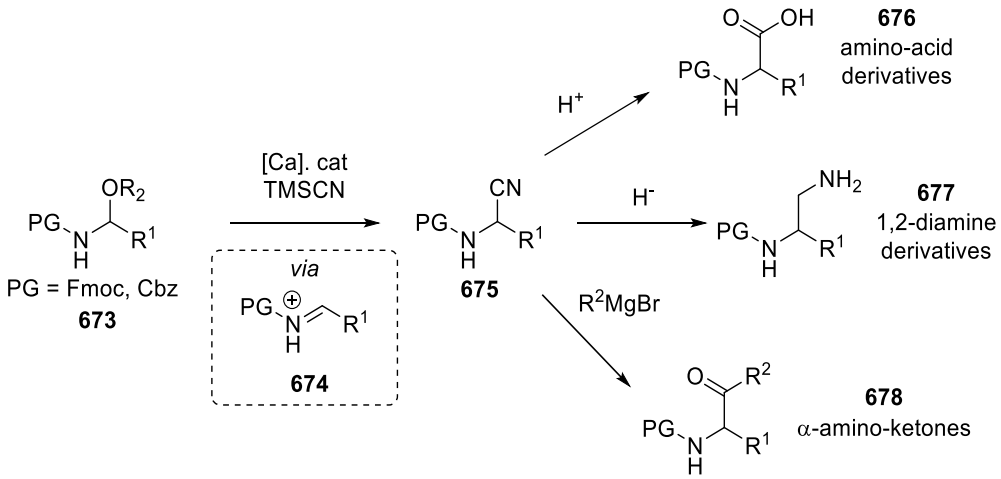
7.4. Conclusions

In summary, a mild and modular approach to access highly versatile α-amido nitrile building blocks has been developed. The reaction took a considerable amount of optimisation and is incredibly sensitive towards varying quantities of catalyst and TMSCN. The optimised conditions were found to be 2 mol% of catalyst with 6 equivalents of TMSCN in which the side reactions and by-products are minimised. The methodology utilises a safer cyanide source than traditional methodology and is tolerant to a wide range of functional groups. Furthermore, the products can be derivatised towards 1,2-amido-amines and α-amido-esters under standard conditions. However, the methodology is not currently applicable towards isoindolinone-derived *N*-acyliminium ions due to the alcohol and nitrogen amide of the precursors reacting directly with the TMSCN.

7.5. Future Work

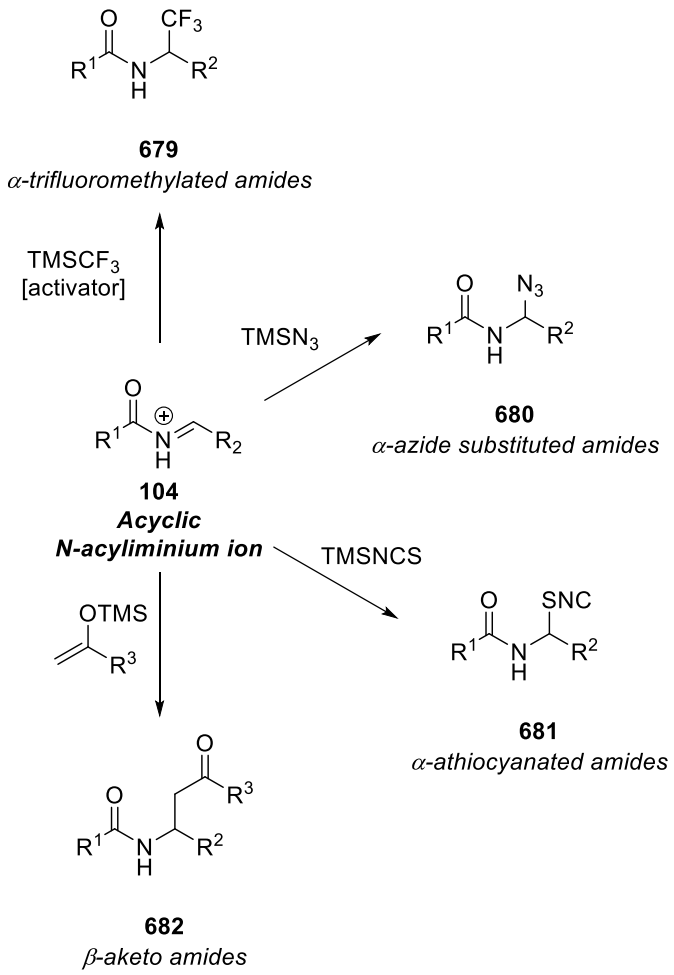
The synthesis of **673** is not well reported within the literature, however they offer potential as *N*-alkoxycarbonyliminium ion precursors **674** due to their ease of

deprotection upon addition of any nucleophile. Catalytic generation of *N*-alkoxycarbonyliminium ions **674** using calcium has not yet been explored, and the subsequent trapping with TMSCN would provide access to highly versatile building blocks **675** that could be applied to a range of transformations (Scheme 126). Hydrolysis in the presence of acid would provide access to amino acid derivatives **676**. Reduction in the presence of $LiAlH_4$, would result in the formation of singly protected 1,2-diamines **677**. Additionally, addition of an organometallic reagent such as a Grignard, would provides access to α-amino-ketones **678**.



Scheme 126. Application towards *N*-alkoxycarbonyliminium ions and subsequent derivatisation.

In addition to cyanide based silicon nucleophiles, other TMS-based nucleophiles could also be explored (Scheme 127). The addition of $TMSCF_3$ in the presence of an activator would provide an efficient and modular way to access trifluoromethylated amides **679** with ease. Trapping of the *N*-acyliminium ion with an azide would form an azide-substituted amide **680** which has the potential as a precursor in copper-catalysed click reactions[193] for modular access to amido-substituted triazoles. Furthermore, the synthesis of thiocyanated amides **681** which have a broad range of applications including reduction to the thiol.[194] Silyl-enol ethers would also provide access to useful *β*-keto amide building blocks **682** which depending on the nitrogen protecting group, could be deprotected and cyclised *via* an intramolecular reductive amination to access azetidines.



Scheme 127. Addition of other TMS-derived nucleophiles.

8. Chapter 8: Conclusions & Future Work

8.1. Conclusions

This project set out to explore the calcium catalysed generation of *N*-acyliminium ions and subsequent trapping with a broad range of nucleophiles. Overall, this has proven successful in which calcium has been shown to be a mild and highly versatile earth abundant Lewis acid catalyst for catalytic generation of nitrogen containing reactive intermediates.

The catalytic generation of isoindolinone derived *N*-acyliminium ions has been demonstrated. These can be trapped intermolecularly with indole derived carbon nucleophiles, and heteroatomic sulfur and nitrogen containing nucleophiles. Both indoles and thiols proved highly effective and affording 3,3-disubstituted lactam products in high yield. Nitrogen containing nucleophiles proved to be more difficult due to the acidic proton of the *N*-acyliminium ion either being deprotonated or facilitating a decomposition pathway. Despite this, *N*-benzyl substituted *N*-acyliminium ions were effective electrophiles for the addition of nitrogen nucleophiles and a range of amines, amides, carbamates and sulfonamides were all tolerated under the optimised conditions.

Owing to this success, the intramolecular trapping of isoindolinone derived *N*-acyliminium ions was then explored. A library of 3-hydroxyisoindolinones with tethered thiols, indoles and amides was assembled in a modular fashion and could be subjected to a calcium catalysed dehydrative cyclisation which afforded a range of fused polycyclic scaffolds baring heteroatoms. The cyclisation of indoles and thiols proceeded using a calcium-HFIP catalysed pathway which rapidly (< 1 h) afforded the products under mild conditions. The cyclisation of amides required the Lewis acid pathways for *N*-acyliminium ion formation due to the competing Lewis basic sites.

Having successfully demonstrated the calcium catalysed intermolecular addition and cyclisation of carbon and heteroatomic nucleophiles into *N*-acyliminium ions, the catalytic generation of acyclic *N*-acyliminium ions from *N*-acyl-*N,O*-acetals was then explored. The addition of isocyanides into acyclic *N*-acyliminium ions was found to

afford 5-aminooxazoles through an addition-cyclisation-aromatisation sequence. This methodology proved to be highly modular with all sites of the resulting oxazole being varied. Furthermore, the methodology was applied to the synthesis of 5-aminothiazoles from *N*-thioacyl-*N,O*-acetals *via* an *N*-thioacyliminium ion. Catalytic turnover studies showed the calcium catalyst to be re-usable for up to 3 iterative additions of starting material reagents further demonstrating the sustainable nature of alkaline Earth metal catalysis.

As calcium had been shown to be a mild and effective Lewis acid at catalysing the formation of acyclic *N*-acyliminium ions, the addition photoredox generated radicals in to them to access 1,2-diamines was then studied. However, this proved to be unsuccessful with the *N,N*-dimethyl aniline precursors acting as C4-nucleophiles and forming the aza-Friedel craft product. Adding a substituent at the C4-position resulted in rapid degradation of *N*-acyl-*N,O*-acetal occurring. Addition of stoichiometric radicals generated from $(Bu_3Sn)_2$ and alkyl iodides also proved to be unsuccessful with the reduction product being isolated.

Intrigued by the aza-Friedel crafts product formed by addition of *N,N*-dimethyl aniline, this was then explored further. A modular assembly of unsymmetrical amide derivatives were accessed using this methodology. Owing to this reactivity, the effect of *N*-substitution on the reaction outcome was then studied, with tertiary alkyl anilines proving to be the most successful. This was tolerant to both *N*-acyl-*N,O*-acetals and 3-hydroxyisoindolinones. More electron-deficient C4-amino derived nucleophiles was also studied however carbamate protecting groups proved to be ineffective due to their decreased nucleophilicity.

As the addition of isocyanides had been studied and proven successful, the addition of nitriles was then investigated. This required more considerable optimisation due to the capricious nature of both the product and cyanide source. Under the optimised conditions, a range of α-amido nitrile products were synthesised with both sites of diversification proving successful. Furthermore, the α-amido nitrile products could be further manipulated to access previously desired 1,2-diamines and α-amido esters.

In conclusion, the addition of a broad range of nucleophiles into cyclic and acyclic isoindolinones has proven fruitful in providing access to medicinally relevant scaffolds for fragment libraries and small building blocks with multiple sites of diversification for further manipulation. The catalyst used throughout this thesis has remained unchanged, with only solvent and temperature being adjusted as part of the optimisation. This not only demonstrates the wide versatility of calcium as an earth abundant Lewis acid, but also offers a real alternative to the existing moisture and functional group sensitive Lewis acids. The choice of leaving group has shown to not be of importance with OH, OMe, OEt and O^{i}Pr all proving to be successfully activated by the calcium catalyst offering flexibility in *N*-acyliminium ion precursor synthesis. Furthermore, there is no requirement for any of these reactions to be carried out under anhydrous conditions, and many proceed to completion in under 1h allowing rapid library assembly. Overall, this robust methodology offers huge potential for future work in terms of both the type of reactive intermediate that calcium can generate, along with type of nucleophile that can be employed.

8.2. Future Work

8.2.1. Enantioselective Calcium Catalysis

The work carried out within this project has been concerned with the seminal study into calcium catalysed generation of *N*-acyliminium ions and the subsequent trapping with a wide range of nucleophiles affording racemic products. The future direction for this project would be to explore whether the same transformations can be performed using chiral calcium complexes. BINOL-derived calcium phosphate complexes have shown impressive activity as Lewis acids for the enantioselective addition to imines, carbonyls, activated alkenes and in cyclisations.[195] Extending this methodology towards catalytic generation of *N*-acyliminium ion generation would be advantageous, particularly for the synthesis of α-amido nitriles which could then provide access to enantioenriched amino acid derivatives.

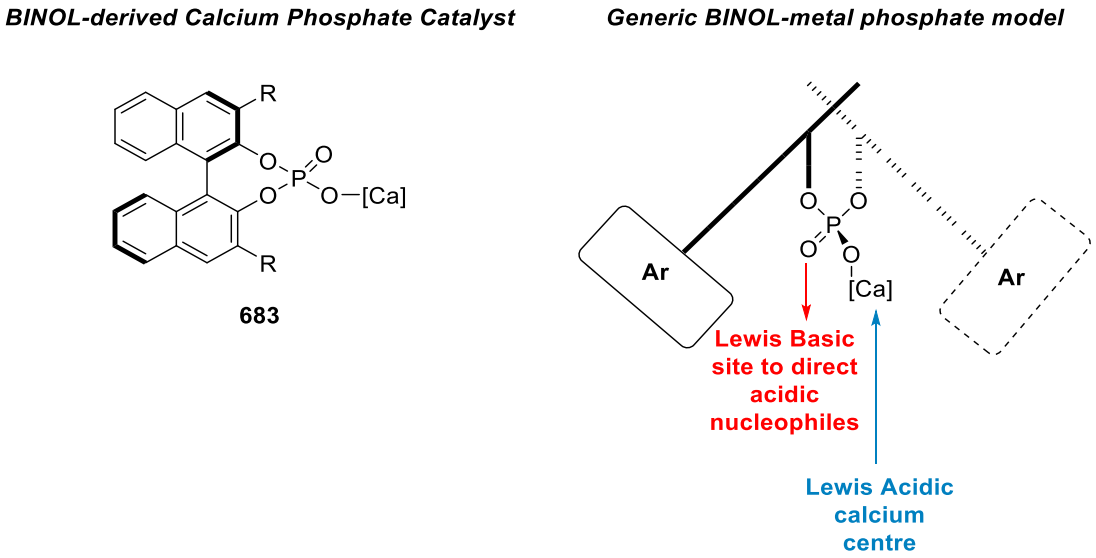


Figure 57. General structure of chiral BINOL-calcium phostaphte with a more representative 3D-generic model.

8.2.2. Solvent Applicability

An underlying aim of this project was to synthesise medicinally relevant scaffolds in a rapid, modular, and sustainable manner. The project has proven that these scaffolds can be accessed rapidly and in a modular manner, however there is still more work to be done with regards to the sustainability. Much of the methodology reported within this project was carried out at 80 °C in 1,2-DCE at which has been characterised as a hazardous solvent.[111] This was largely in part due to solubility of both the catalyst and substrate and therefore still remains a limitation.

9. Chapter 9: Experimental

9.1. General Information

General Information

Solvents & reagents Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, TCI, Fisher Scientific or Merck. All solvents were purchased from commercial sources and used without purification (reagent grade). Metal salts and ligands were stored in a desiccator when not in use. Anhydrous solvent was prepared by storing solvent over activated 4Å MS for 72 hours. Standard vacuum line techniques were used and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na_2SO_4. All reactions were performed using DrySyn heating mantles and pressure regulated vials or round bottom flasks.

Purification and chromatography

Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) and developed with iodine and basic permanganate solution. Flash chromatography was performed on VWR Silica gel 60, 40–63 microns RE as the stationary phase and the solvents employed were of reagent grade.

Characterisation

^{1}H NMR spectroscopic data were obtained at 400 MHz (Bruker Ultrashield 400 Plus) and $^{13}C\{^{1}H\}$ NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K. The chemical shifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm, central line.) The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Assignments were carried out for each table of novel compounds and are applied to any variations therein. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass

spectrometer. Calculated and observed masses containing halogens refers to the ^{35}Cl and ^{79}Br isotopes respectively.

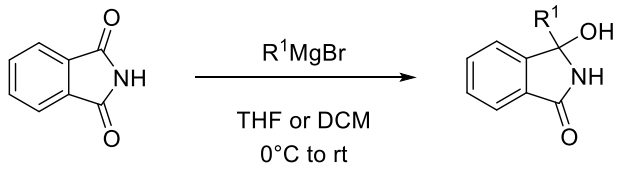
Handling and Storage of Catalyst

While no addition efforts were made to keep the calcium catalysed reactions free from air or moisture, it should be noted that over time that $Ca(NTf_2)_2$ loses it's catalytic efficiency upon prolonged exposure to moisture and/or incorrect storage. The catalyst was stored in a desiccator throughout this project. Should catalytic efficiency decrease, it can be dried at 100 °C under vacuum.

9.2. Chapter 2 Experimental

9.2.1. General Procedures for Chapter 2

General Procedure A – Synthesis of 3-hydroxyisoindolinones by Grignard Addition

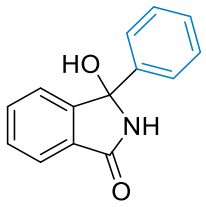


Phthalimide (1.0 equiv.) was added to a flame dried RBF and purged with argon. Dry THF or DCM (0.25 M) was added, and the solution was cooled to 0°C. The Grignard reagent* (3.0 equiv.) was then added dropwise, and the reaction was warmed to room temperature. Upon completion of the reaction (approx. 1h) which was indicated by the TLC, the reaction was quenched with NH_4Cl, and extracted into DCM (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The product was then purified by FCC (EtOAc:Hex) to afford the pure compound.

*Grignard reagents were either purchased or freshly prepared by suspending magnesium turnings (3.10 equiv.) in dry THF (1.0 M) under argon with 1,2-dibromoethane (0.1 equiv.) as an initiator. Dropwise addition of aryl halide (3.0 equiv.) and stirring for 2 h afforded the Grignard reagent which was then diluted to 0.5 M before being added to the electrophile.

9.2.2. Starting Materials – Synthesis of 3-hydroxyisoindolinones

3-hydroxy-3-phenylisoindolin-1-one (198a)



The title compound was prepared according to general procedure **A** from phthalimide (500 mg, 3.40 mmol), phenylmagnesium bromide (3.0 M in Et_2O) (6.80 mL, 20.4 mmol) in DCM (27 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (1.21 g, 79%).

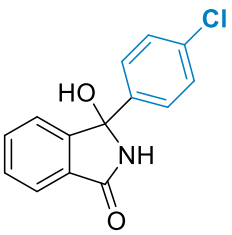
RF (1:1 EtOAc:Hex): 0.32

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.40 (m, 4H), 7.40 – 7.22 (m, 4H), 6.91 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.4, 150.9, 142.2, 132.4, 130.6, 129.0, 128.3, 127.8, 125.5, 122.8, 122.6, 87.3.

Data in accordance with literature[85]

3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (198b)



The title compound was prepared according to general procedure **A** from phthalimide (500 mg, 3.40 mmol) and 4-chlorophenyl magnesium bromide (1.0 M in Et_2O) (10.2 mL, 10.2 mmol) in DCM (14 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (567 mg, 64%).

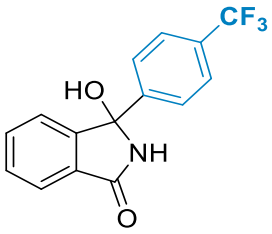
RF (1:1 EtOAc:Hex): 0.31

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.03 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.5, 141.2, 132.6, 132.5, 130.6, 129.2, 128.3, 127.6, 122.8, 122.7, 87.0.

Data in accordance with literature[85]

3-hydroxy-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (198c)



The title compound was prepared according to general procedure **A** from phthalimide (300 mg, 2.04 mmol), (4-(trifluoromethyl)phenyl)magnesium bromide (1 M in THF, 7.0 mL, 7.14 mmol), in DCM (8 mL). The Grignard reagent was freshly prepared from magnesium turnings (154 mg, 3.10 mmol), 4-bromobenzotrifluoride (1.61 g, 7.14 mmol) and 1,2-dibromoethane (18 µL, 0.0063 mmol) in THF (7 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (493 mg, 82%).

RF (1:1 EtOAc:Hex): 0.31

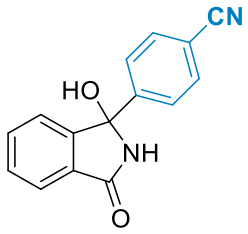
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 1H), 7.75 – 7.64 (m, 5H), 7.55 (td, *J* = 7.4, 1.3 Hz, 1H), 7.50 (td, *J* = 7.3, 1.0 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.14 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.4, 150.2, 146.8, 132.6, 130.6, 129.3, 128.4 (q, *J* = 31.7 Hz), 126.5, 125.3 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.0 Hz), 122.8, 122.7, 86.9.

^{19}F NMR (376 MHz, DMSO-d_6): 60.97.

Data in accordance with literature[85]

4-(1-hydroxy-3-oxoisoindolin-1-yl)benzonitrile (198d)



To a solution of 4-bromobenzonitrile (1.86 g, 10.2 mmol) in dry THF (7 mL) under argon, cooled to 0 °C was added *i*-PrMgCl.LiCl (1.3 M in THF) (8.63 mL, 11.2 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 4h. The resulting solution was then added dropwise to a solution of phthalimide (500 mg, 3.40 mmol) in dry DCM (7 mL) at 0 °C and the reaction mixture was warmed to room temperature and stirred for overnight. The reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with water, brine, dried with Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography (3:1 EtOAc: cyclohexane) to afford the pure product as an off white solid (130 mg, 15%).

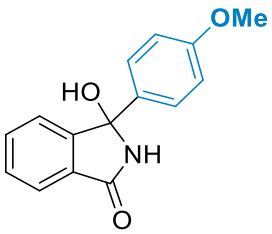
RF (3:1 EtOAc:CycHex): 0.5

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.61 (m, 1H), 7.59 – 7.46 (m, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.20 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.4, 149.9, 147.6, 132.7, 132.4, 130.6, 129.4, 126.7, 122.9, 122.8, 118.7, 110.7, 86.9.

Data in accordance with literature[196]

3-hydroxy-3-(4-methoxyphenyl)isoindolin-1-one (198e)



The title compound was prepared according to general procedure **A** from phthalimide (250 mg, 1.70 mmol) and 4-methoxyphenyl magnesium bromide (0.5 M in THF, 10.2 mL,

5.10 mmol) in DCM (7mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (181 mg, 42%).

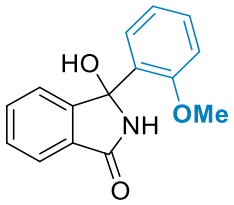
RF (1:1 EtOAc:Hex): 0.19

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.52 (td, *J* = 7.5, 1.1 Hz, 1H), 7.45 (td, *J* = 7.3, 0.8 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.82 (s, 1H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.33, 158.87, 151.14, 134.08, 132.36, 130.53, 128.83, 126.79, 122.74, 122.53, 113.54, 87.20, 55.13.

Data in accordance with literature[85]

3-hydroxy-3-(2-methoxyphenyl)isoindolin-1-one (198f)



The title compound was prepared according to general procedure **A** from phthalimide (300 mg, 2.04 mmol) and 2-methoxyphenyl magnesium bromide (1.0 M in THF, 6.1 mL, 6.12 mmol) in DCM (8 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (312 mg, 60%).

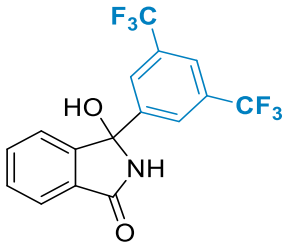
RF (1:1 EtOAc:Hex): 0.20

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.52 – 7.38 (m, 2H), 7.30 (td, *J* = 7.8, 1.7 Hz, 1H), 7.15 (dd, *J* = 6.5, 1.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 3.31 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 156.5, 150.9, 132.4, 131.7, 129.5, 129.3, 128.4, 127.7, 121.9, 121.8, 120.0, 112.4, 85.2, 55.6.

Data in accordance with literature[196]

3-hydroxy-3-(3,5-bis(trifluoromethyl))isoindolin-1-one (198g)



The title compound was prepared according to general procedure **A** from phthalimide (300 mg, 2.04 mmol), (1,3-bis(trifluoromethyl)magnesium bromide (1 M in THF, 7.0 mL, 7.14 mmol), in THF (8 mL). The Grignard reagent was freshly prepared from magnesium turnings (154 mg, 3.10 mmol), 1,3-bis(trifluoromethyl)-5-bromobenzene (2.09 g, 1.30 mL, 7.1 mmol) and 1,2-dibromoethane (18 µL, 0.0204 mmol) in THF (7 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (493 mg, 82%).

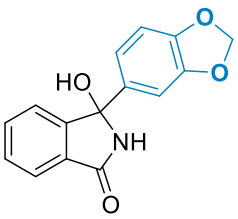
RF (40:60 EtOAc:Hex): 0.20

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.44 (s, 1H), 8.13 (s, 1H), 8.03 (s, 2H), 7.73 – 7.69 (m, 1H), 7.59 (td, *J* = 7.4, 1.4 Hz, 1H), 7.54 (td, *J* = 7.4, 1.2 Hz, 1H), 7.47 (s, 1H), 7.41 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): 168.4, 149.3, 145.8, 134.4, 133.0, 130.6, 130.6 (q, *J* = 32.9 Hz), 129.8, 126.3, 123.2 (q, *J* = 273.0 Hz), 123.1, 122.9, 122.2, 86.6.

Data in accordance with literature[197]

3-(benzo[d][1,3]dioxol-5-yl)isoindolin-1-one (198h)



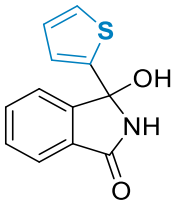
The title compound was prepared according to general procedure **A** from phthalimide (500 mg, 3.40 mmol) and 3,4-(Methylenedioxy)phenylmagnesium bromide solution (0.8 M in THF: toluene (1:1), 12.7 mL, 10.2 mmol) in DCM (14 mL). Following completion of the reaction (2 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (484 mg, 53%).

RF (1:1 EtOAc:Hex): 0.20

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 6.97 – 6.80 (m, 3H), 6.00 (d, *J* = 4.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.9, 147.3, 146.9, 136.2, 132.4, 130.5, 128.9, 122.7, 122.6, 118.8, 107.9, 106.3, 101.2, 87.2.

3-hydroxy-3-(thiophen-2-yl)isoindolin-1-one (198l)



Phthalimide (500 mg, 3.40 mmol) was dissolved in dry THF (13.6 mL) at -78 °C. 2-Thienyllithium solution (10.2 mL, 10.2 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with water, brine, dried with Na_2SO_4, filtered and concentrated. The pure product was isolated by crystallisation from a Hexane: DCM (3:1) solution to afford an orange solid (562 mg, 72%).

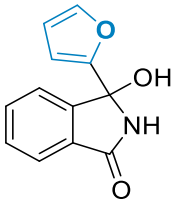
RF (1:1 EtOAc:CycHex): 0.20

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (s, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 6.3 Hz, 2H), 7.16 (s, 1H), 7.06 – 6.86 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.0, 150.2, 146.7, 132.6, 130.1, 129.3, 127.0, 125.9, 124.2, 122.7, 86.0.

Data in accordance with literature[79]

3-hydroxy-3-(furan-2-yl)isoindolin-1-one (198m)



Furan (0.75 mL, 10.2 mmol) was dissolved in dry THF (13.6 mL) . n-buthyllithium (4.76 mL, 11.9 mmol) (2.5 M in Hexane) was added dropwise and the mixture was stirred at room temperature for 4h. The solution was cooled to -78 °C and phthalimide (500 mg, 3.40 mmol) was added in a single portion. The reaction mixture was allowed to warm to room temperature and stirred overnight. Upon completion of the reaction, indicated by TLC, the reaction mixture was quenched with sat. NH_4Cl and extracted with Et_2O. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The pure product was obtained by recrystallisation from Hexane:DCM (3:1) to afford a brown solid (172 mg, 24 %).

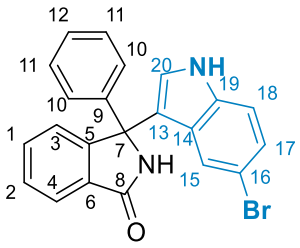
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 7.70 – 7.56 (m, 3H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.05 (s, 1H), 6.54 – 6.38 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.1, 153.7, 148.2, 143.0, 132.5, 130.8, 129.5, 123.0, 122.7, 110.4, 106.9, 83.9.

Data in accordance with literature[79]

9.2.3. Addition of Indoles

3-(5-bromo-1H-indol-3-yl)-3-phenyl-2,3-dihydro-1H-isoindol-1-one (200a)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0022 mmol) and *n*Bu_4NPF_6 (1 mg, 0.0022 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 5-bromoindole (65 mg, 0.33 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated

conversion to the product, the reaction was concentrated and purified by flash column chromatography (3:1 EtOAc:Hex) to afford a cream solid (73 mg, 82%)

RF (3:1 EtOAc:Hex): 0.37

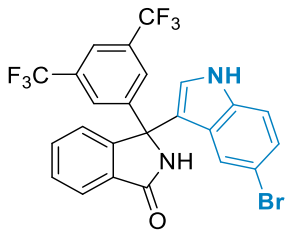
IR ν_{max} (cm^{-1}): 3209, 3058, 1978, 1671, 1491, 1314

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}BrN_2O$ 403.0446; Found 403.0441

^1H NMR (400 MHz, DMSO-d_6): δ 11.30 (s, 1H, **NH_{indole}**), 9.73 (s, 1H, **NH**), 7.74 (d, *J* = 7.4 Hz, 1H, **H3**), 7.64 – 7.57 (m, 2H, **ArH**), 7.53 (m, 1H, **ArH**), 7.45 (d, *J* = 7.2 Hz, 2H, **ArH**), 7.40 – 7.25 (m, 4H, **ArH**), 7.16 (dd, *J* = 8.6, 1.6 Hz, 1H, **ArH**), 6.94 (m, 2H, **ArH**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.6 (**C7**), 150.6 (**C5**), 142.5 (**C9**), 135.8 (**ArC**), 132.1 (**ArC**), 130.9 (**ArC**), 128.5 (**ArC**), 127.6 (**ArC**), 126.9 (**ArC**), 126.3 (**ArC**), 125.9 (**ArC**), 124.2 (**ArC**), 123.9 (**ArC**), 123.3 (**ArC**), 122.1 (**ArC**), 116.5 (**ArC**), 113.8 (**C18**), 111.4 (**C13**), 65.9 (**C7**).

3-[3,5-bis(trifluoromethyl)phenyl]-3-(5-bromo-1*H*-indol-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (200b)



To a 4 mL vial was added 3-hydroxy-3-(3,5-bis(trifluoromethyl))isoindolin-1-one (50 mg, 0.14 mmol), $Ca(NTf_2)_2$ (4 mg, 0.0069 mmol) and $n$$Bu_4NPF_6$ (3 mg, 0.0069 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-bromoindole (41 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC for 30 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAC:Hex) to afford a cream solid (68 mg, 91%)

RF (1:1 EtOAc:Hex): 0.33

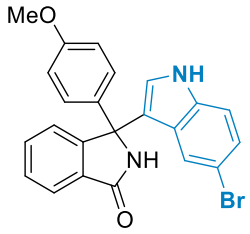
IR ν_{max} (cm^{-1}): 3333, 3185, 3052, 1978, 1669, 1368

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{14}BrF_6N_2O$ 539.0194; Found 539.0188

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.44 (s, 1H), 9.91 (s, 1H), 8.16 (s, *J* = 17.6 Hz, 1H), 8.11 (s, 2H), 7.79 (dd, *J* = 15.3, 7.5 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.19 (dd, *J* = 8.7, 1.3 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.83 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.4, 149.0, 145.9, 135.8, 132.8, 130.8, 130.5 (q, *J* = 32.7 Hz), 129.3, 127.0, 126.9, 126.3, 124.3, 124.2, 123.6, 123.2 (q, *J* = 272.7 Hz), 122.1, 121.4, 115.1, 114.1, 111.7, 65.5.

3-(5-bromo-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one (200c)



To a 4 mL vial was added 3-(4-methoxyphenyl)-3-hydroxyisoindolin-1-one (50 mg, 0.20 mmol mmol), $Ca(NTf_2)_2$ (1.1 mg, 0.002 mmol) and *n*Bu_4NPF_6 (0.8 mg, 0.002 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-bromoindole (58 mg, 0.29 mmol) was added in a single portion and stirred at 80 ºC for 30 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (79 mg, 93%)

RF (1:1 EtOAc:DCM): 0.41

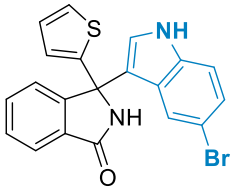
IR ν_{max} (cm^{-1}): 3169, 3040, 2838, 1668, 1608, 1255

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}BrN_2O_2$ 433.0552; Found 433.0549

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 9.67 (s, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.65 – 7.46 (m, 3H), 7.34 (t, *J* = 8.6 Hz, 3H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.01 (s, 1H), 6.99 – 6.79 (m, 3H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.5, 158.6, 150.9, 135.8, 134.4, 132.0, 130.9, 128.4, 127.6, 126.9, 125.9, 124.1, 123.9, 123.2, 122.2, 116.7, 113.8, 113.7, 111.4, 65.50, 55.11.

3-(5-bromo-1*H*-indol-3-yl)-3-(thiophen-2-yl)-2,3-dihydro-1*H*-isoindol-1-one (200d)



To a 4 mL vial was added 3-hydroxy-3-(thiophen-2-yl)isoindolin-1-one (50 mg, 0.22 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0022 mmol) and nBu$_4$NPF$_6$ (0.9 mg, 0.0022 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-bromoindole (64 mg, 0.32 mmol) was added in a single portion and stirred at 80 ºC for 30 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1 EtOAc:DCM) to afford a light brown solid (85 mg, 96%)

RF (1:1 EtOAc:DCM): 0.38

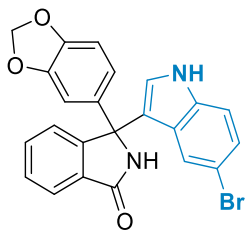
IR ν_{max} (cm^{-1}): 3172, 3041, 2851, 1667, 1466, 1356

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{14}BrN_2OS$ 409.0010; Found 409.0007

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (m, 1H), 9.85 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.68 – 7.51 (m, 3H), 7.45 (d, *J* = 5.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.17 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.08 (s, 2H), 7.05 – 6.92 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.6, 147.3, 135.7, 132.3, 130.5, 128.8, 127.2, 126.7, 126.0, 125.7, 125.5, 124.0, 123.9, 123.2, 121.9, 115.4, 113.9, 111.6, 63.53.

3-(2*H*-1,3-benzodioxol-5-yl)-3-(5-bromo-3a,7a-dihydro-1*H*-indol-2-yl)-2,3-dihydro-1*H*-isoindol-1-one (200e)



To a 4 mL vial was added 3-(benzo[d][1,3]dioxol-5-yl)isoindolin-1-one (50 mg, 0.19 mmol), $Ca(NTf_2)_2$ (1.1 mg, 0.0019 mmol) and nBu$_4$NPF$_6$ (0.7 mg, 0.0019 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-bromoindole (64 mg, 0.32

mmol) was added in a single portion and stirred at 80 ºC for 30 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (2:1, EtOAc:Hex) to afford a cream solid (78 mg, 94%)

RF (2:1 EtOAc:Hex): 0.17

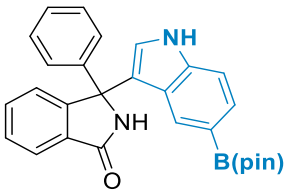
IR ν_{max} (cm^{-1}): 3219, 2896, 1674, 1611, 1485, 1237

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{16}BrN_2O_3$ 447.0344; Found 447.0350

^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.63 – 7.40 (m, 3H), 7.31 – 7.21 (m, 2H), 7.16 (s, 1H), 6.96 – 6.85 (m, 3H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.95 (dd, *J* = 6.6, 1.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 150.9, 148.3, 147.7, 135.9, 135.3, 132.6, 128.8, 127.3, 125.9, 124.6, 124.3, 123.7, 122.7, 119.9, 117.7, 113.7, 113.3, 108.5, 107.2, 101.5, 66.5.

3-phenyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1*H*-indol-2-yl]-2,3-dihydro-1*H*-isoindol-1-one (200f)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0022 mmol) and $n$$Bu_4NPF_6$ (0.9 mg, 0.0022 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (81 mg, 0.33 mmol) was added in a single portion and stirred at 80 ºC for 1h. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (2:1, EtOAc:Hex) to afford a white solid (90 mg, 90%)

RF (3:1 EtOAc:Hex): 0.48

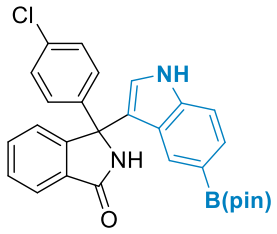
IR ν_{max} (cm^{-1}): 3257, 2976, 1683, 1613, 1352, 1142

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}BN_2O_3$ 451.2193; Found 451.2204

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20 (s, 1H), 9.73 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.65 – 7.44 (m, 4H), 7.44 – 7.22 (m, 7H), 6.88 (d, *J* = 2.2 Hz, 1H), 1.22 (s, 12H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.6, 151.1, 142.9, 139.2, 131.9, 131.0, 128.4, 128.3, 127.7, 127.5, 127.5, 126.5, 124.8, 124.3, 124.2, 123.2, 117.2, 111.2, 83.0, 66.2, 24.8, 24.6.

3-(4-chlorophenyl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1*H*-indol-2-yl]-2,3-dihydro-1*H*-isoindol-1-one (200g)



To a 4 mL vial was added 3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (50 mg, 0.19 mmol), $Ca(NTf_2)_2$ (1mg, 0.0019 mmol) and nBu$_4$NPF$_6$ (0.8 mg, 0.0019 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (70 mg, 0.29 mmol) was added in a single portion and stirred at 80 ºC for 30 mins. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (87 mg, 93%)

RF (1:1 EtOAc:Hex): 0.19

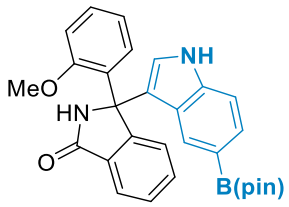
IR ν_{max} (cm^{-1}): 3237, 2977, 1673, 1613, 1469, 1352

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}BClN_2O_3$ 485.1803; Found 485.1815

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.24 (d, *J* = 1.9 Hz, 1H), 9.77 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.46 – 7.29 (m, 7H), 6.89 (d, *J* = 2.1 Hz, 1H), 1.23 (d, *J* = 0.6 Hz, 12H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.6, 150.7, 142.0, 139.2, 132.2, 132.2, 131.0, 128.5, 128.4, 127.6, 127.6, 124.9, 124.7, 124.1, 123.3, 116.7, 111.3, 83.03, 65.8, 24.8, 24.7.

3-(2-methoxyphenyl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1*H*-indol-2-yl]-2,3-dihydro-1*H*-isoindol-1-one (200h)



To a 4 mL vial was added 3-hydroxy-3-(2-methoxyphenyl)isoindolin-1-one (50 mg, 0.20 mmol), $Ca(NTf_2)_2$ (1.2 mg, 0.0020 mmol) and $n$$Bu_4NPF_6$ (0.8 mg, 0.0020 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (71 mg, 0.29 mmol) was added in a single portion and stirred at 80 ºC for 30 mins. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (2:1, EtOAc:Hex) to afford an off white solid (92 mg, 98%)

RF (2:1 EtOAc:Hex): 0.17

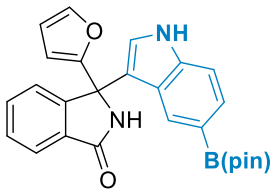
IR ν_{max} (cm^{-1}): 3414, 3264, 3008, 1680, 1612, 1351

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{29}H_{30}BN_2O_4$ 481.2299; Found 481.2314

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (d, *J* = 1.9 Hz, 1H), 9.16 (s, 1H), 7.79 – 7.69 (m, 1H), 7.58 – 7.46 (m, 4H), 7.40 – 7.28 (m, 3H), 7.21 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.93 – 6.85 (m, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 3.51 (s, 3H), 1.23 (d, *J* = 4.5 Hz, 12H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.6, 157.9, 150.7, 139.0, 131.6, 131.4, 129.7, 129.5, 128.1, 127.7, 127.4, 127.2, 124.7, 124.6, 123.5, 123.1, 119.9, 117.1, 112.6, 111.1, 83.0, 79.2, 65.4, 55.4, 24.1, 24.7.

3-(furan-2-yl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1*H*-indol-2-yl]-2,3-dihydro-1*H*-isoindol-1-one (200i)



To a 4 mL vial was added 3-hydroxy-3-(furan-2-yl)isoindolin-1-one (50 mg, 0.23 mmol), $Ca(NTf_2)_2$ (1.4 mg, 0.0023 mmol) and $n$$Bu_4NPF_6$ (0.9 mg, 0.0023 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (85 mg, 0.35 mmol) was added in a single portion and stirred at 80 ºC for 30 mins. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a pale orange solid (84 mg, 82%)

RF (2:1 EtOAc:Hex): 0.35

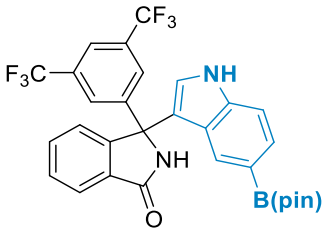
IR ν_{max} (cm^{-1}): 3295, 3059, 2869, 1679, 1614, 1377

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}BN_2O_4$ 441.1989; Found 441.1993

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.25 (d, *J* = 2.1 Hz, 1H), 9.70 (s, 1H), 7.80 – 7.73 (m, 1H), 7.70 – 7.65 (m, 1H), 7.63 – 7.50 (m, 3H), 7.41 – 7.30 (m, 3H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 0.6 Hz, 1H), 1.24 (d, *J* = 5.4 Hz, 12H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.0, 155.3, 149.5, 143.7, 139.4, 132.6, 131.6, 129.2, 127.9, 127.5, 125.0, 124.4, 123.6, 115.5, 111.8, 110.9, 107.5, 83.5, 62.6, 25.3, 25.2.

3-[3,5-bis(trifluoromethyl)phenyl]-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1*H*-indol-2-yl]-2,3-dihydro-1*H*-isoindol-1-one (200j)



To a 4 mL vial was added 3-hydroxy-3-(3,5-bis(trifluoromethyl))isoindolin-1-one (50 mg, 0.14 mmol), $Ca(NTf_2)_2$ (0.8 mg, 0.0014 mmol) and $n$$Bu_4NPF_6$ (0.5 mg, 0.0014 mmol) in

DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (51 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC for 30 mins. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford an off white solid (66 mg, 81%)

RF (1:1 EtOAc:Hex): 0.30

IR ν_{max} (cm^{-1}): 3273, 2980, 1695, 1355, 1275, 1131

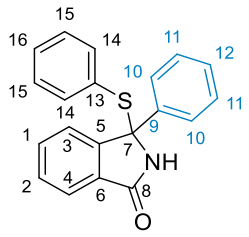
HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{30}H_{26}BF_6N_2O_3$ 587.1941; Found 587.1947

^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.99 – 7.88 (m, 3H), 7.81 (s, 1H), 7.69 – 7.57 (m, 2H), 7.57 – 7.48 (m, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.18 (s, 1H), 1.28 (d, *J* = 7.9 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 149.6, 145.3, 139.4, 133.0, 132.2 (q, *J* = 33.5 Hz), 130.1, 129.3, 129.3, 126.8, 126.8, 125.0, 124.7, 123.8, 123.6, 123.2 (q, *J* = 273.0 Hz), 122.2, 120.8, 119.4, 116.3, 111.6, 83.8, 66.2, 24.9, 24.8.

9.2.4. Addition of Thiols

3-phenyl-3-phenylsulfanyl-2,3-dihydro-isoindol-1-one (203a)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0022 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0022 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (29 mg, 0.27 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (54 mg, 77%)

RF (1:1 EtOAc:Hex): 0.43

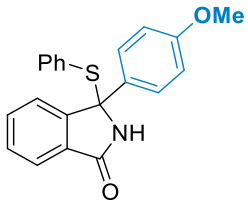
IR ν_{max} (cm^{-1}): 3062, 2848, 1696, 1494, 1345, 742

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}NOS$ 318.0953; Found 318.0947

^1H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.75 (m, 2H, **H3**), 7.73 – 7.67 (m, 1H, **ArH**), 7.56 (td, *J* = 7.5, 1.1 Hz, 1H, **H1**), 7.51 – 7.29 (m, 6H, **ArH**), 7.24 – 7.18 (m, 1H, **ArH**), 7.14 (dt, *J* = 8.2, 1.7 Hz, 1H, **ArH**), 7.08 – 7.02 (m, 2H, **ArH**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2 (**C8**), 148.7 (**C5**), 139.1 (**C9**), 137.1 (**ArC**), 132.6 (**ArC**), 129.9 (**ArC**), 129.8 (**ArC**), 129.4 (**ArC**), 129.2 (**ArC**), 129.0 (**ArC**), 128.7 (**ArC**), 128.6 (**ArC**), 126.1 (**ArC**), 123.9 (**ArC**), 123.4 (**ArC**), 75.79 (**C7**).

3-(4-methoxyphenyl)-3-(phenylthio)isoindolin-1-one (203b)



To a 4 mL vial was added 3-(4-methoxyphenyl)-3-hydroxyisoindolin-1-one (60 mg, 0.24 mmol), $Ca(NTf_2)_2$ (1.5 mg, 0.0024 mmol) and $n$$Bu_4NPF_6$ (1 mg, 0.0024 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (39 mg, 0.353 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a white solid (70 mg, 86%)

RF (1:1 EtOAc:CycHex): 0.53

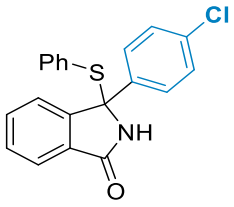
IR ν_{max} (cm^{-1}): 3057, 2930, 2849, 1700, 1606, 1509

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}NO_2S$ 348.1058; Found 348.1053

^1H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.64 (m, 3H), 7.61 – 7.51 (m, 1H), 7.50 – 7.43 (m, 1H), 7.35 – 7.28 (m, 1H), 7.24 – 7.18 (m, 1H), 7.17 – 7.11 (m, 3H), 7.11 – 7.01 (m, 2H), 6.97 – 6.88 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 169.1, 160.0, 148.9, 137.1, 132.5, 131.1, 131.04, 129.9, 129.8, 129.6, 128.6, 127.5, 123.8, 123.4, 114.4, 75.5, 55.5.

3-(4-chlorophenyl)-3-(phenylthio)isoindolin-1-one (203c)



To a 4 mL vial was added 3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (100 mg, 0.39 mmol), $Ca(NTf_2)_2$ (2 mg, 0.0039 mmol) and $n$$Bu_4NPF_6$ (1.5 mg, 0.0039 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (64 mg, 0.578 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAC:Hex) to afford a white solid (116 mg, 86%)

RF (1:1 EtOAc:CycHex): 0.6

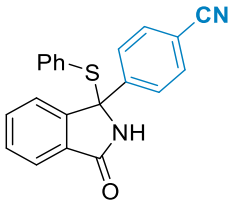
IR ν_{max} (cm^{-1}): 3130, 3062, 2851, 1702, 1470, 1096

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}ClNOS$ 352.0563; Found 352.0559

^1H NMR (400 MHz, DMSO-d_6): 9.84 (s, 1H), 7.98 – 7.72 (m, 3H), 7.72 – 7.59 (m, 1H),7.58-7.56 (m, 2H), 7.45 – 7.20 (m, 3H), 7.20 – 6.90 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6): δ167.7, 147.5, 138.5, 136.71, 133.4, 132.4, 130.3, 129.7, 129.1, 128.9, 128.8, 128.4, 128.0, 124.0, 122.4, 74.9.

4-(1-Hydroxy-3-oxoisoindolin-1-yl)benzonitrile (203d)



To a 4 mL vial was added 4-(1-hydroxy-3-oxoisoindolin-1-yl)benzonitrile (50 mg, 0.20 mmol), $Ca(NTf_2)_2$ (1.2 mg, 0.002 mmol) and $n$$Bu_4NPF_6$ (0.8 mg, 0.002 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (33 mg, 0.3 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (54 mg, 79%)

RF (1:1 EtOAc:CycHex): 0.50

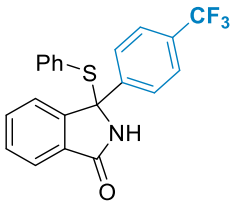
IR ν_{max} (cm^{-1}): 3215, 3075, 2229, 1714, 1679, 1497

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{15}N_2OS$ 343.0905; Found 343.0907

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.68 – 7.57 (m, 2H), 7.54 – 7.46 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.11 – 7.04 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 147.7, 144.5, 137.1, 133.0, 132.9, 130.2, 129.3, 128.9, 128.7, 127.2, 123.8, 123.7, 118.4, 112.9, 75.1.

3-(4-trifluoromethylphenyl)-3-(phenylthio)isoindolin-1-one (203e)



To a 4 mL vial was added 3-hydroxy-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (60 mg, 0.21 mmol), $Ca(NTf_2)_2$ (1.2 mg, 0.0021 mmol) and nBu$_4$NPF$_6$ (0.8 mg, 0.0021 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (34 mg, 0.307 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (76 mg, 96%)

RF (1:1 EtOAc:CycHex): 0.60

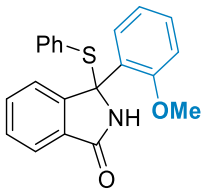
IR ν_{max} (cm^{-1}): 3126, 3071, 1699, 1496, 1392

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{15}F_3NOS$ 386.0826; Found 386.0823

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.3 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.24 - 7.23 (m, 3.6 Hz, 1H), 7.15 – 7.07 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 148.1, 143.3, 137.1, 132.9, 130.1, 129.7, 129.2, 128.9, 128.8, 126.7, 126.2, 126.2, 123.7, 75.2.

3-(2-methoxyphenyl)-3-(phenylthio)isoindolin-1-one (203f)



To a 4 mL vial was added 3-(2-methoxyphenyl)-3-hydroxyisoindolin-1-one (100 mg, 0.39 mmol), $Ca(NTf_2)_2$ (2.4 mg, 0.0039 mmol) and nBu$_4$NPF$_6$ (1.5 mg, 0.0039 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (65 mg, 0.353 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (115 mg, 84%)

RF (1:1 EtOAc:CycHex): 0.40

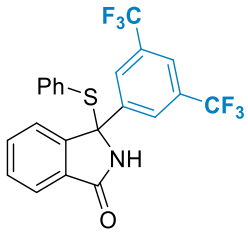
IR ν_{max} (cm^{-1}): 3283, 3051, 2932, 1692, 1489, 1249

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}NO_2S$ 348.1058; Found 348.1050

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.80 (m, 2H), 7.64 (td, J = 7.6, 1.1 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.44 – 7.32 (m, 2H), 7.21 – 7.14 (m, 1H), 7.14 – 7.09 (m, 2H), 7.08 – 7.01 (m, 3H), 6.92 (td, J = 7.7, 1.1 Hz, 1H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 157.8, 146.4, 136.8, 131.5, 131.4, 130.5, 129.4, 128.7, 128.4, 127.4, 126.5, 125.6, 123.5, 120.8, 112.8, 74.5, 56.2.

3-(3,5-bis(trifluoromethyl))-3-(phenylthio)isoindolin-1-one (203g)



To a 4 mL vial was added 3-hydroxy-3-(3,5-bis(trifluoromethyl))isoindolin-1-one (100 mg, 0.28 mmol), $Ca(NTf_2)_2$ (1.7 mg, 0.0028 mmol) and nBu$_4$NPF$_6$ (1 mg, 0.0028 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (46 mg, 0.42 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC

analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (2:3, EtOAc:Hex) to afford a white solid (113 mg, 90%)

RF (2:3 EtOAc:CycHex): 0.56

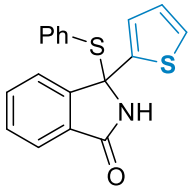
IR ν_{max} (cm^{-1}): 3208, 3094, 1715, 1469, 1312, 1280

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{14}F_6NOS$ 454.0700; Found 454.0699

^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 2H), 7.89 (s, 1H), 7.64 – 7.62 (m, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.47 – 7.36 (m, 1H), 7.28 – 7.24 (m, 2H), 7.20 – 7.05 (m, 4H).

^{13}C NMR (101 MHz,) δ 169.2, 147.4, 142.4, 137.1, 133.2, 132.6 (d, *J* = 33.8 Hz), 130.5, 129.6, 129.6, 129.0, 128.3, 126.6, 124.0, 123.4, 123.1 (d, *J* = 273.1 Hz), 122.9, 74.7.

3-(thiophen-2-yl)-3-(phenylthio)isoindolin-1-one (203h)



To a 4 mL vial was added 3-hydroxy-3-(thiophen-2-yl)isoindolin-1-one (100 mg, 0.43 mM), $Ca(NTf_2)_2$ (2.4 mg, 0.0043 mmol) and $n$$Bu_4NPF_6$ (1.5 mg, 0.0043 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (72 mg, 0.65 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a light brown solid (120 mg, 86%)

RF (1:1 EtOAc:CycHex): 0.60

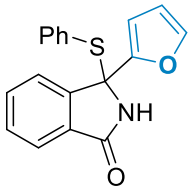
IR ν_{max} (cm^{-1}): 3155, 3060, 2836, 1691, 1470, 1354

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}NOS_2$ 324.0517; Found 324.0516

^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.59 (td, *J* = 7.5, 0.9 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.24 – 7.23 (m, 1H), 7.18 – 7.16 (m, 2H), 7.13 – 7.05 (m, 2H), 7.01 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.92 – 6.91 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 148.2, 143.0, 136.9, 132.7, 130.0, 129.5, 129.5, 129.1, 128.7, 127.6, 126.4, 125.7, 123.8, 123.4, 72.8.

3-(furan-2-yl)-3-(phenylthio)isoindolin-1-one (203i)



To a 4 mL vial was added 3-hydroxy-3-(furan-2-yl)isoindolin-1-one (50 mg, 0.23 mmol), $Ca(NTf_2)_2$ (1.4 mg, 0.0023 mmol) and nBu$_4$NPF$_6$ (1 mg, 0.0023 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (38 mg, 0.35 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a light brown solid (70 mg, 98%)

RF (1:1 EtOAc:CycHex): 0.6

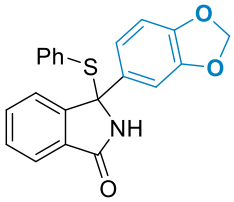
IR ν_{max} (cm^{-1}): 3153, 3060, 1689, 1500, 1307, 1154

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}NO_2S$ 308.0745; Found 308.0748

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (t, J = 10.3 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.51 (d, J = 0.9 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.18 – 7.10 (m, 4H), 6.94 (s, 1H), 6.37 – 6.28 (m, 2H).

^{13}C NMR (101 MHz, DMSOd-$_6$): δ 167.6, 150.7, 145.8, 144.0, 136.7, 132.4, 130.4, 129.7, 129.2, 128.6, 128.5, 124.1, 122.4, 110.9, 108.2, 70.6.

3-(benzo[d][1,3]dioxol-5-yl)-3-(phenylthio)isoindolin-1-one (203j)



To a 4 mL vial was added 3-(benzo[d][1,3]dioxol-5-yl)isoindolin-1-one (80 mg, 0.30 mmol), $Ca(NTf_2)_2$ (1.8 mg, 0.003 mmol) and nBu$_4$NPF$_6$ (1.2 mg, 0.003 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and thiophenol (33 mg, 0.3 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis

indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a peach solid (98 mg, 91%)

RF (1:1 EtOAc:CycHex): 0.56

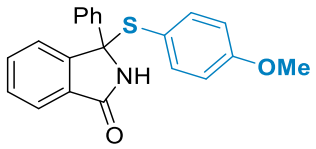
IR ν_{max} (cm^{-1}): 3209, 2902, 1706, 1671, 1485, 1246

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}NO_3S$ 362.0851; Found 362.0852

^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.18 (m, 4H), 7.10 (d, *J* = 4.3 Hz, 5H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): ^{13}C NMR (101 MHz,) δ 167.6, 147.7, 147.4, 136.6, 133.2, 132.1, 130.4, 129.7, 129.5, 128.6, 128.3, 124.2, 122.3, 119.3, 108.2, 106.8, 101.6, 75.30.

3-((4-methoxyphenyl)thio)-3-phenylisoindolin-1-one (205a)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-methoxythiophenol (75 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (121 mg, 78%)

RF (1:1 EtOAc:Hex): 0.26

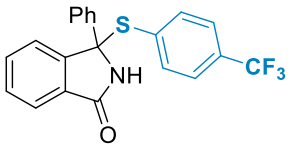
IR ν_{max} (cm^{-1}): 3198, 3078, 2840, 1698, 1589, 1243

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}NO_2S$ 348.1058; Found 348.1059

^1H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.23 (m, 3H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.8, 160.4, 148.0, 139.5, 138.4, 132.1, 130.5, 128.8, 128.6, 128.5, 126.0, 124.0, 122.3, 120.1, 113.9, 75.4, 55.2.

3-((4-(trifluoromethyl)phenyl)thio)-3-phenylisoindolin-1-one (205b)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (2.7 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-(trifluoromethyl)thiophenol (95 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (142 mg, 83%)

RF (1:1 EtOAc:Hex): 0.54

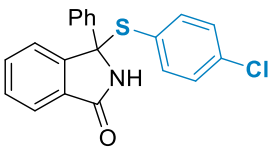
IR ν_{max} (cm^{-1}): 3160, 3062, 2850, 1694, 1319, 1124

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{15}F_3NOS$ 386.0826; Found 386.0828

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.54 – 7.45 (m, 4H), 7.45 – 7.35 (m, 2H), 7.35 – 7.27 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.7, 147.5, 139.1, 137.0, 134.9, 132.5, 130.2, 129.6 (q, J = 31.9 Hz), 129.0, 128.8, 126.0, 125.1, 125.1, 124.1, 123.9 (q, J = 272.2 Hz), 122.4, 75.8.

3-((4-chlorophenyl)thio)-3-phenylisoindolin-1-one (205c)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (2.67 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.72 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-chlorothiophenol (77 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC

analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (136 mg, 88%)

RF (1:1 EtOAc:Hex): 0.50

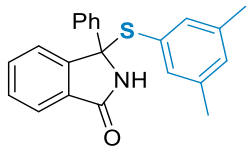
IR ν_{max} (cm^{-1}): 3162, 3060, 2828, 1694, 1469, 1312

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}ClNOS$ 352.0563; Found 352.0562

^1H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.63 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.52 – 7.42 (m, *J* = 7.3 Hz, 2H), 7.42 – 7.29 (m, *J* = 15.2, 7.3Z Hz, 3H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.8, 147.6, 139.2, 138.4, 134.9, 132.4, 130.3, 129.0, 128.9, 128.7, 128.5, 126.0, 124.0, 122.4, 75.6.

3-((3,5-dimethylphenyl)thio)-3-phenylisoindolin-1-one (205d)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 3,5-dimethylthiophenol (74 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (132 mg, 86%)

RF (1:1 EtOAc:Hex): 0.75

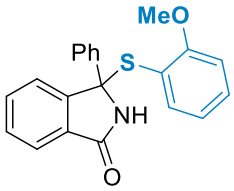
IR ν_{max} (cm^{-1}): 3173, 3062, 2920, 2855, 1699, 1312

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}NOS$ 346.1266; Found 346.1263

^1H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.27 (m, 2H), 6.87 (s, 1H), 6.68 (s, 1H), 2.04 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.8, 148.0, 139.5, 137.2, 134.2, 132.0, 130.8, 130.6, 129.0, 128.9, 128.5, 126.0, 124.2, 122.2, 75.5, 20.6.

3-((2-methoxyphenyl)thio)-3-phenylisoindolin-1-one (205e)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 2-methoxythiophenol (93 mg, 0.666 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAC:Hex) to afford a cream solid (151 mg, 98%)

RF (1:1 EtOAc:Hex): 0.25

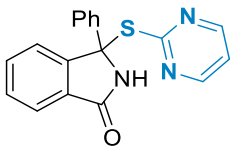
IR ν_{max} (cm^{-1}): 3190, 3065, 2925, 2830, 1695, 1471

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}NO_2S$ 348.1058; Found 348.1060

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.19 (m, 5H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.59 (t, *J* = 7.4 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 148.9, 139.5, 139.3, 132.3, 132.2, 129.0, 128.8, 128.6, 126.0, 124.0, 123.0, 120.7, 117.2, 111.3, 76.3, 55.9.

3-(2-pyrimidinethio)-3-phenylisoindolin-1-one (205f)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 2-mercaptopyrimidine (75 mg, 0.666 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC

analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (3:1, EtOAC:Hex) to afford a white solid (111 mg, 78%)

RF (3:1 EtOAc:Hex): 0.6

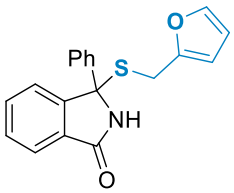
IR ν_{max} (cm^{-1}): 3288, 3057, 2924, 1693, 1609, 1377

HRMS (ESI)m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}N_3NaOS$ 342.0672; Found 342.0671

^1H NMR (400 MHz, $CDCl_3$): δ.81 (s, 1H), 8.42 (d, *J* = 4.9 Hz, 2H), 7.90 (d, *J* = 7.1 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.62 – 7.42 (m, 3H), 7.32 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 6.96 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 169.4, 157.5, 147.7, 140.2, 133.1, 130.2, 129.7, 128.8, 128.3, 126.2, 124.6, 123.2, 117.7, 74.3.

3-(2-furfurylthio)-3-phenylisoindolin-1-one (205g)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 2-furfurylthiol (76 mg, 0.666 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (143 mg, 78%)

RF (1:1 EtOAc:Hex): 0.39

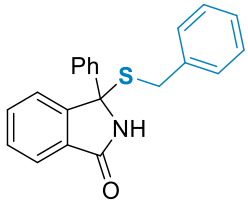
IR ν_{max} (cm^{-1}): 3170, 3061, 2926, 1692, 1467, 1148

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}NO_2S$ 322.0902; Found 322.0901

^1H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.78 – 7.66 (m, *J* = 7.2 Hz, 4H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.56 – 7.48 (m, *J* = 7.3 Hz, 1H), 7.46 (s, 1H), 7.43 – 7.36 (m, *J* = 7.1 Hz, 2H), 7.36 – 7.26 (m, 1H), 6.25 (s, 1H), 5.92 (s, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 3.42 (d, *J* = 14.0 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.1, 149.7, 148.0, 142.5, 139.7, 132.8, 130.5, 129.2, 128.9, 128.5, 125.9, 123.8, 123.0, 110.7, 107.8, 72.9, 26.4.

3-(benzylthio)-3-phenylisoindolin-1-one (205h)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and benzylmercaptan (66 mg, 0.53 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAC:Hex) to afford a cream solid (135 mg, 92%)

RF (1:1 EtOAc:Hex): 0.46

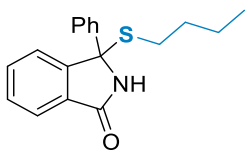
IR ν_{max} (cm^{-1}): 3127, 3056, 2843, 1694, 1609, 1491

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}NOS$ 332.1109; Found 332.1104

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 7.84 – 7.66 (m, 4H), 7.61 (t, J = 7.1 Hz, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.38 – 7.27 (m, 1H), 7.26 – 7.12 (m, 3H), 7.11 – 7.03 (m, 2H), 3.45 (d, J = 12.2 Hz, 1H), 3.30 (d, J = 12.2 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.1, 148.2, 139.9, 136.5, 132.8, 130.6, 129.1, 128.9, 128.8, 128.4, 127.0, 125.9, 123.8, 123.0, 73.1, 34.1.

3-(butanethio)-3-phenylisoindolin-1-one (205i)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and nBu$_4$NPF$_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and butanethiol (48 mg, 0.53 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated

conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a yellow oil which solidified upon standing (120 mg, 91%)

RF (1:1 EtOAc:Hex): 0.70

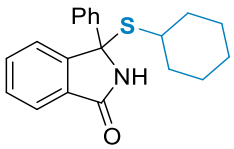
IR ν_{max} (cm^{-1}): 3185, 3066, 2956, 1698, 1310

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NOS$ 298.1266; Found 298.1259

^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.67 – 7.53 (m, 2H), 7.45 (td, *J* = 7.4, 0.8 Hz, 1H), 7.40 – 7.27 (m, 3H), 2.35 – 2.25 (m, 1H), 2.11 – 1.98 (m, 1H), 1.45 – 1.12 (m, 4H), 0.74 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 149.3, 140.0, 132.9, 130.3, 129.0, 128.9, 128.6, 125.8, 123.8, 123.7, 73.2, 30.7, 29.3, 22.1, 13.6.

3-(cyclohexanethio)-3-phenylisoindolin-1-one (205j)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0044 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and cyclohexanethiol (77 mg, 0.66 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a yellow oil which solidified upon standing (134 mg, 93%)

RF (1:1 EtOAc:Hex): 0.52

IR ν_{max} (cm^{-1}): 3156, 3061, 2926, 1690, 1464, 1312

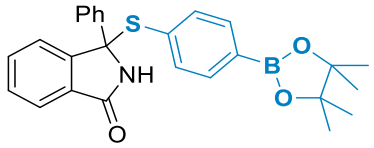
HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NOS$ 324.1422; Found 324.1418

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.75 – 7.68 (m, 3H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.56 (td, *J* = 7.6, 1.0 Hz, 1H), 7.45 (td, *J* = 7.5, 0.9 Hz, 1H), 7.39 – 7.24 (m, 3H),

2.35 – 2.20 (m, 1H), 1.91 – 1.75 (m, 1H), 1.68 – 1.55 (m, 1H), 1.55 – 1.44 (m, 1H), 1.44 – 1.28 (m, 3H), 1.28 – 0.97 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 149.6, 140.3, 132.8, 130.1, 128.9, 128.6, 125.8, 124.0, 123.8, 77.5, 43.3, 35.1, 34.6, 26.0, 25.9, 25.5.

3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzenethiol)-3-phenylisoindolin-1-one (205k)



To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0022 mmol) and $n$$Bu_4NPF_6$ (1.7 mg, 0.0022 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzenethiol (79 mg, 0.33 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a peach solid (73 mg, 74%)

RF (1:1 EtOAc:CycHex): 0.60

IR ν_{max} (cm^{-1}): 3502, 3162, 3067, 2989, 1697, 1358

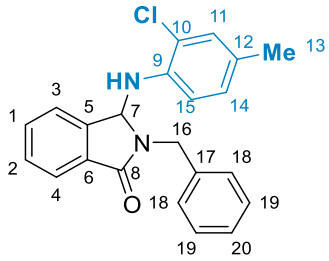
HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{26}H_{27}BNO_3S$ 444.1805; Found 444.1813

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.4 Hz, 2H), 7.68 – 7.61 (m, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.38 (q, J = 8.1 Hz, 4H), 7.30 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 1.25 (s, 12H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.8, 147.8, 139.4, 135.9, 134.1, 133.1, 132.3, 130.3, 128.9, 128.8, 128.7, 126.0, 124.1, 122.4, 84.0, 75.5, 25.0, 24.7, 24.7.

9.2.5. Addition of Amines

2-benzyl-3-(2-chloro-4-methylanilino)-2,3-dihydro-1H-isoindol-1-one (227a)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (13 mg, 0.021 mmol) and $n$$Bu_4NPF_6$ (8 mg, 0.021 mmol) in DCE (1 mL) at room temperature. 2-chloro-4-methylaniline (45 mg, 0.31 mmol) was added in a single portion and the reaction was stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (0 to 2% EtOAc:DCM) to afford the desired product as a cream solid (48 mg, 63%).

RF (1:1 EtOAc:Hex): 0.71

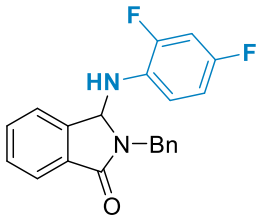
IR ν_{max} (cm^{-1}): 3361, 3031, 2924, 1683, 1615, 1520

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}ClN_2O$ 363.1264; Found 363.1265

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 – 7.78 (m, 1H, **H4**), 7.69 – 7.53 (m, 2H, **ArH**), 7.46 (d, *J* = 7.1 Hz, 1H, **ArH**), 7.33 – 7.22 (m, 2H, **ArH**), 7.22 – 7.17 (m, 2H, **ArH**), 7.09 (d, *J* = 1.5 Hz, 1H, **H11**), 6.68 (dd, *J* = 8.4, 1.5 Hz, 1H, **ArH**), 6.25 (d, *J* = 8.2 Hz, 1H, **NH**), 6.12 (d, *J* = 8.3 Hz, 1H), 6.04 (d, *J* = 8.2 Hz, 1H, **H7**), 4.87 (d, *J* = 15.4 Hz, 1H, **H16$_A$**), 4.21 (d, *J* = 15.5 Hz, 1H, **H16$_B$**), 2.10 (s, 3H, **H13**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6 (**C8**), 143.9 (**C5**), 139.1, 137.5 (**C16**), 132.3 (**ArC**), 132.1 (**ArC**), 129.7 (**ArC**), 129.3 (**ArC**), 128.4 (**ArC**), 128.1 (**ArC**), 128.0 (**C18**), 127.6 (**ArC**), 127.1 (**ArC**), 123.3 (**ArC**), 122.9 (**ArC**), 119.3 (**ArC**), 113.8 (**ArC**), 68.5 (**C7**), 42.4 (**C15**), 19.6 (**C12**).

2-benzyl-3-(2,4-difluoroanilino)-2,3-dihydro-1*H*-isoindol-1-one (227b)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (13 mg, 0.021 mmol) and nBu_4NPF_6 (8 mg, 0.021 mmol) in DCE (1 mL) at room temperature. 2,4-difluoroaniline (41 mg, 0.31 mmol) was added in a single portion and the reaction was stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:10 EtOAc:Hex) to afford the desired product as a colourless oil (48 mg, 63%).

RF (1:1 EtOAc:Hex): 0.58

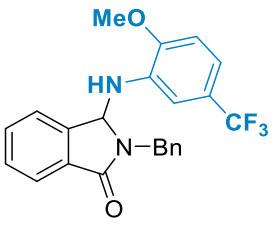
IR ν_{max} (cm^{-1}): 3415, 2917, 1694, 1497, 1113

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}F_2N_2O$ 351.1309; Found 351.1315

^1H NMR (400 MHz, DMSO-d_6): δ 7.94 – 7.92 (m, 1H), 7.57 – 7.53 (m, 2H), 7.47 – 7.43 (m, 1H), 7.32 – 7.24 (m, 3H), 7.21 – 7.19 (m, 2H), 6.79 (ddd, *J* = 11.3, 8.4, 2.8 Hz, 1H), 6.56 (ddd, *J* = 4.3, 3.5, 1.6 Hz, 1H), 6.27 (td, *J* = 9.3, 5.4 Hz, 1H), 5.71 (s, 1H), 5.26 (d, *J* = 15.1 Hz, 1H), 4.29 – 4.11 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.7, 143.2, 137.0, 132.4, 132.1, 129.8, 129.6 (dd, *J* = 11.4, 2.9 Hz), 128.9, 128.2, 127.8, 124.00, 123.1, 115.3 (dd, *J* = 8.9, 3.4 Hz), 111.2 (d, *J* = 3.7 Hz), 111.0 (d, *J* = 3.7 Hz), 104.0 (dd, *J* = 26.4, 23.5 Hz), 68.9, 43.2.

2-benzyl-3-[2-methoxy-5-(trifluoromethyl)anilino]-2,3-dihydro-1*H*-isoindol-1-one (227c)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (13 mg, 0.021 mmol) and *n*Bu_4NPF_6 (8 mg, 0.021 mmol) in DCE (1 mL) at room temperature. 2-methoxy-5-(trifluoromethyl)aniline (60 mg, 0.31 mmol) was added in a single portion and the reaction was stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (0 to 5% EtOAc:DCM) to afford the desired product as a light brown solid (70 mg, 81%).

RF (1:20 EtOAc:DCM): 0.33

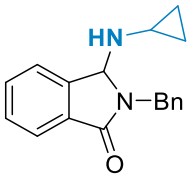
IR ν_{max} (cm^{-1}): 3415, 2917, 1694, 1497, 1113

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}F_3N_2O_2$ 413.1477; Found 413.1497

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, *J* = 6.5 Hz, 1H), 7.70 – 7.52 (m, 2H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.28 – 7.05 (m, 5H), 6.95 – 6.82 (m, 2H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.21 (s, 1H), 6.12 (d, *J* = 8.3 Hz, 1H), 4.79 (d, *J* = 15.4 Hz, 1H), 4.28 (d, *J* = 15.5 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 149.6, 143.7, 137.4, 135.2, 132.3, 132.1, 129.4, 128.2, 127.4, 126.9, 123.4, 122.9, 114.6, 110.0, 107.5, 68.2, 55.8, 42.7.

2-benzyl-3-(cyclopropylamino)-2,3-dihydro-1*H*-isoindol-1-one (227d)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (13 mg, 0.021 mmol) and *n*Bu_4NPF_6 (8 mg, 0.021 mmol) in DCE (1 mL) at room temperature. cyclopropylamine (18 mg, 0.31 mmol) was added in a single

portion and the reaction was stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:5 EtOAc:Hex, 1% NEt_3) to afford the desired product as a colourless oil (39 mg, 67%).

RF (1:5 EtOAc:Hex): 0.48

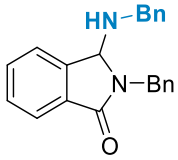
IR ν_{max} (cm^{-1}): 3415, 2917, 1694, 1497, 1113

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O$ 279.1497; Found 279.1492

^1H NMR (400 MHz, DMSO-d_6): δ 7.88 – 7.86 (m, 1H), 7.55 – 7.46 (m, 3H), 7.33 – 7.24 (m, 5H), 5.30 (d, *J* = 15.0 Hz, 1H), 5.16 (s, 1H), 4.27 (d, *J* = 15.0 Hz, 1H), 2.05 – 2.00 (m, 1H), 0.39 – 0.30 (m, 2H), 0.22 – 0.08 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ ^{13}C NMR (101 MHz,) δ 167.8, 144.6, 137.6, 132.5, 131.6, 129.0, 128.9, 128.3, 127.6, 123.6, 123.5, 72.4, 43.1, 24.7, 7.6, 6.0.

2-benzyl-3-(benzylamino)-2,3-dihydro-1*H*-isoindol-1-one (227e)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (12.5 mg, 0.021 mmol) and $n$$Bu_4NPF_6$ (8.1 mg, 0.021 mmol) in DCE (1 mL) at room temperature. benzylamine (34 mg, 0.31 mmol) was added in a single portion and the reaction was stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:5 EtOAc:Hex, 1% NEt_3) to afford the desired product as a colourless oil (64 mg, 93%).

RF (1:1 EtOAc:Hex): 0.61

IR ν_{max} (cm^{-1}): 3320, 3029, 2850, 1678, 1454, 1219

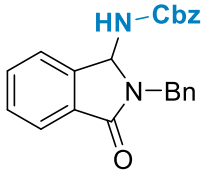
HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2O$ 329.1654; Found 329.1652

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 7.3 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.34 – 7.21 (m, 8H), 7.16 (d, *J* = 6.8 Hz, 2H), 5.34 (s, 1H), 5.19 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 3.36 (d, *J* = 13.0 Hz, 1H), 3.25 (d, *J* = 13.0 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.2, 143.6, 140.0, 137.8, 133.2, 132.3, 129.6, 129.3, 128.8, 128.7, 128.5, 128.1, 127.6, 124.0, 123.6, 72.7, 45.9, 43.6.

9.2.6. Addition of Carbamates

Benzyl (2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbamate (236a)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mM), $Ca(NTf_2)_2$ (1.3 mg, 0.0021 mmol) and $n$$Bu_4NPF_6$ (0.8 mg, 0.0021 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and benzylcarbamate (35 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) followed by trituration with Et_2O to afford the product as a white solid (70 mg, 90%)

RF (1:5 EtOAc:DCM): 0.74

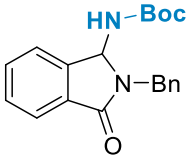
IR ν_{max} (cm^{-1}): 3306, 3034, 2925, 1687, 1528, 1425

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_3$ 373.1552; Found 373.1552

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.55 (dd, *J* = 13.5, 7.3 Hz, 2H), 7.46 – 7.20 (m, 10H), 6.09 (d, *J* = 9.1 Hz, 1H), 5.20 – 4.98 (m, 2H), 4.80 (d, *J* = 15.4 Hz, 1H), 4.32 (d, *J* = 15.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5, 156.3, 143.0, 137.6, 136.7, 132.3, 131.7, 129.4, 128.4, 128.0, 127.8, 127.7, 127.2, 123.5, 122.7, 65.9, 65.8, 43.1.

tert-butyl (2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbamate (236b)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0021 mmol) and $n$$Bu_4NPF_6$ (0.8 mg, 0.0021 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and tert-butylcarbamate (29 mg, 0.25 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1 EtOAC:Hex) followed by trituration with Et_2O to afford the product as a white solid (61 mg, 86%)

RF (1:1 EtOAc:Hex): 0.50

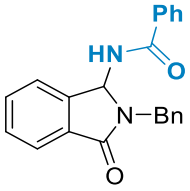
IR ν_{max} (cm^{-1}): 3270, 2985, 2929, 1712, 1684, 1519

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O_2$ 339.1709; Found 339.1696

^1H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, J = 9.1 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.58 – 7.46 (m, 1H), 7.39 – 7.18 (m, 1H), 6.03 (d, J = 9.0 Hz, 1H), 4.83 (d, J = 15.3 Hz, 1H), 4.28 (d, J = 15.5 Hz, 1H), 1.39 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 155.6, 143.3, 137.8, 132.2, 131.7, 129.3, 128.5, 127.6, 127.1, 123.5, 122.6, 79.0, 65.5, 43.1, 28.1.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)benzamide (236c)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol) $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and $n$$Bu_4NPF_6$ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and benzamide (38 mg, 0.3 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis

indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (68 mg, 95%)

RF (1:1 EtOAc:Hex): 0.41

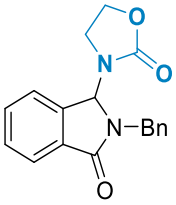
IR ν_{max} (cm^{-1}): 3548, 3278, 3031, 2933, 1705, 1270

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$ 343.1447; Found 343.1441

^1H NMR (400 MHz, DMSO-d_6): δ 9.20 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.71 – 7.51 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.14 (m, 5H), 6.61 (d, *J* = 8.9 Hz, 1H), 4.85 (d, *J* = 15.4 Hz, 1H), 4.37 (d, *J* = 15.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.3, 166.9, 143, 137.7, 133.3, 132.3, 131.9, 131.9, 129.4, 128.5, 128.3, 127.7, 127.6, 127.2, 123.6, 122.8, 63.8, 43.2.

2-benzyl-3-(2-oxo-1,3-oxazolidin-3-yl)-2,3-dihydro-1H-isoindol-1-one (236d)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0021 mmol) and $n$$Bu_4NPF_6$ (1 mg, 0.0021 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2-oxazolidinone (27 mg, 0.31 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the reaction was concentrated and purified by flash column chromatography (1:9, EtOAc:DCM) to afford a white semi-solid (49 mg, 76%)

RF (1:5 EtOAc:DCM): 0.64

IR ν_{max} (cm^{-1}): 2972, 1755, 1701, 1404, 1215

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1239; Found 309.1246

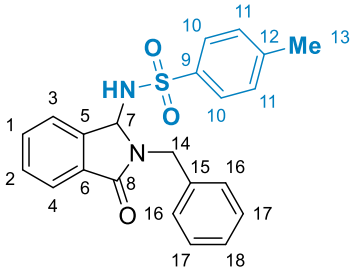
^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 6.9 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.38 – 7.27 (m, 3H), 6.42 (s, 1H), 4.96 (d, *J* = 14.7 Hz, 1H),

4.47 (d, *J* = 14.7 Hz, 1H), 4.06 (td, *J* = 9.0, 6.5 Hz, 1H), 3.53 (td, *J* = 9.0, 7.2 Hz, 1H), 2.75 (dd, *J* = 15.9, 8.8 Hz, 1H), 2.54 (td, *J* = 9.0, 6.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 158.2, 139.7, 137.4, 132.7, 132.4, 130.3, 128.9, 128.8, 128.0, 124.3, 123.0, 68.7, 62.2, 45.1, 38.8.

9.2.7. Addition of Sulfonamides

_N_-(2-benzyl-3-oxo-2,3-dihydro-1_H_-isoindol-1-yl)-4-methylbenzene-1-sulfonamide (240a)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and $n$$Bu_4NPF_6$ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and *p*-toluenesulfonamide (36 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (68 mg, 85%)

RF (1:5 EtOAc:DCM): 0.57

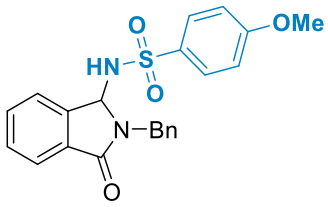
IR ν_{max} (cm^{-1}): 3125, 2935, 2884, 1674, 1495, 1162

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2O_3S$ 393.1273; Found 393.1276

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (d, *J* = 8.8 Hz, 1H, **NH**), 7.75 (d, *J* = 7.9 Hz, 2H, **H10**), 7.69 (d, *J* = 6.0 Hz, 1H, **H4**), 7.58 – 7.46 (m, 2H, **ArH**), 7.43 (d, *J* = 7.9 Hz, 2H, **H11**), 7.35 – 7.20 (m, 3H, **ArH**), 7.16 (d, *J* = 7.2 Hz, 2H, **ArH**), 6.73 (d, *J* = 6.2 Hz, 1H, **H3**), 5.78 (d, *J* = 8.7 Hz, 1H, **H7**), 4.82 (d, *J* = 15.6 Hz, 1H, **H14$_A$**), 4.22 (d, *J* = 15.5 Hz, 1H, **H14$_B$**), 2.44 (s, 3H, **H13**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3 (**C8**), 143.3 (**C12**), 142.7 (**C5**), 139.0 (**C9**), 137.3 (**C15**), 132.3 (**C2**), 131.2, 130.0 (**C11**), 129.7 (**ArC**), 128.4 (**ArC**), 127.50 (**C16**), 127.1 (**ArC**), 126.4 (**ArC**), 123.1 (**C3**), 122.8 (**C4**), 67.6 (**C7**), 42.3 (**C14**), 21.1 (**C13**).

***N*-(2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-4-methoxybenzene-1-sulfonamide (240b)**



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.27 mg, 0.0104 mmol) and $n$$Bu_4NPF_6$ (4.05 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 4-methoxybenezenesulfonamide (39 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (78 mg, 91%)

RF (1:5 EtOAc:DCM): 0.30

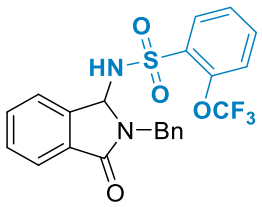
IR ν_{max} (cm^{-1}): 3130, 2929, 2843, 1677, 1594, 1495

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2O_4S$ 409.1222; Found 409.1227

^{1}H NMR (400 MHz, DMSO-d_6): ^{1}H NMR (400 MHz,) δ 8.97 – 8.76 (m, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.70 (s, 1H), 7.57 – 7.47 (m, 2H), 7.35 – 7.09 (m, 7H), 6.77 (s, 1H), 5.86 – 5.65 (m, 1H), 4.82 (d, *J* = 15.6 Hz, 1H), 4.24 (d, *J* = 15.5 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 162.5, 142.8, 137.4, 133.5, 132.3, 131.2, 129.7, 128.6, 128.4, 127.5, 127.1, 123.2, 122.8, 114.6, 67.5, 55.8, 42.3.

***N*-(2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2-(trifluoromethoxy)benzene-1-sulfonamide (240c)**



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.2 mg, 0.0104 mmol) and nBu$_4$NPF$_6$ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2-(trifluoromethoxy)benezenesulfonamide (55 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (75 mg, 78%)

RF (1:5 EtOAc:DCM): 0.56

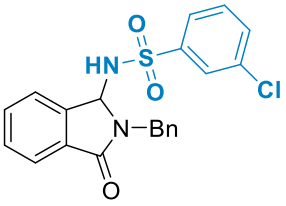
IR ν_{max} (cm^{-1}): 3106, 3063, 1687, 1592, 1444, 1163

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}F_3N_2O_4S$ 463.0939; Found 463.0930

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (d, J = 8.8 Hz, 1H), 8.03 – 7.81 (m, 2H), 7.80 – 7.61 (m, 2H), 7.61 – 7.46 (m, 3H), 7.42 – 7.19 (m, 3H), 7.12 (d, J = 6.8 Hz, 2H), 7.06 – 6.88 (m, 1H), 5.79 (d, J = 8.7 Hz, 1H), 4.90 (d, J = 15.6 Hz, 1H), 4.17 (d, J = 15.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.4, 144.9, 142.5, 137.1, 135.5, 133.6, 132.4, 131.3, 130.1, 129.8, 128.5, 127.8, 127.3, 127.2, 123.0, 122.9, 121.1, 67.5, 42.2.

***N*-(2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-3-chlorobenzene-1-sulfonamide (240d)**



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and nBu$_4$NPF$_6$ (4 mg, 0.0104 mmol) in DCE (1

mL) at 80 ºC. The reaction was stirred for 1 minute and 3-chloro-benezenesulfonamide (44 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC for 2h. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (65 mg, 75%)

RF (1:5 EtOAc:DCM): 0.60

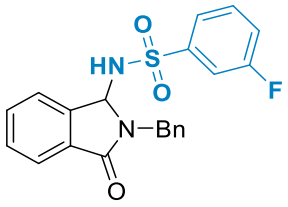
IR v_{max} (cm^{-1}): 3181, 3056, 1687, 1494, 1468, 1157

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}ClN_2O_3S$ 413.0727; Found 413.0727

^1H NMR (400 MHz, DMSO-d_6): δ 9.19 (d, *J* = 8.7 Hz, 1H), 7.89 – 7.78 (m, 3H), 7.76 – 7.64 (m, 2H), 7.53 (p, *J* = 8.1 Hz, 2H), 7.36 – 7.22 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 2H), 6.76 (d, *J* = 6.2 Hz, 1H), 5.90 (d, *J* = 8.7 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.24 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 143.7, 142.4, 137.2, 134.1, 133.0, 132.3, 131.9, 131.2, 129.8, 128.5, 127.5, 127.2, 126.1, 125.0, 123.2, 122.9, 67.7, 42.7.

_N_-(2-benzyl-3-oxo-2,3-dihydro-1_H_-isoindol-1-yl)-3-fluorobenzene-1-sulfonamide (240e)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and $n$$Bu_4NPF_6$ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 3-fluorobenezenesulfonamide (40 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (65 mg, 75%)

RF (1:5 EtOAc:DCM): 0.60

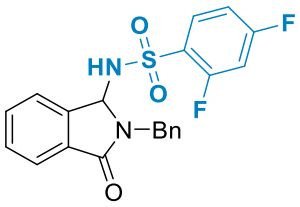
IR v_{max} (cm^{-1}): 3197, 3072, 2936, 1685, 1494, 1345

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}FN_2O_3S$ 397.1022; Found 397.1023

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17 (d, *J* = 8.8 Hz, 1H), 7.80 – 7.57 (m, 5H), 7.52 (p, *J* = 7.7 Hz, 2H), 7.35 – 7.14 (m, 5H), 6.73 (d, *J* = 6.0 Hz, 1H), 5.90 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.25 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 163.1, 160.6, 143.9 (d, *J* = 6.6 Hz), 142.5, 137.3, 132.4, 132.1 (d, *J* = 7.9 Hz), 131.2, 129.8, 128.5, 127.5, 127.1, 123.1, 122.9, 122.6, 120.2 (d, *J* = 21.1 Hz), 113.6 (d, *J* = 24.5 Hz), 67.7, 42.5

_N_-(2-benzyl-3-oxo-2,3-dihydro-1_H_-isoindol-1-yl)-2,4-difluorobenzene-1-sulfonamide (240f)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (43 mg, 0.18 mmol), $Ca(NTf_2)_2$ (6 mg, 0.00906 mmol) and nBu$_4$NPF$_6$ (4 mg, 0.0906 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2,4-difluorobenezenesulfonamide (35 mg, 0.18 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (45 mg, 60%)

RF (1:5 EtOAc:DCM): 0.69

IR v_{max} (cm^{-1}): 3541, 3265, 3091, 1681, 1601, 1418

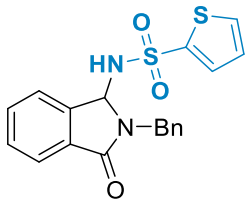
HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}F_2N_2O_3S$ 415.0928; Found 415.0924

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (d, *J* = 8.7 Hz, 1H), 7.80 (dd, *J* = 14.9, 8.5 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.66 – 7.50 (m, 3H), 7.35 – 7.20 (m, 5H), 7.15 (d, *J* = 6.9 Hz, 2H), 7.06 (d, *J* = 6.9 Hz, 1H), 5.79 (d, *J* = 8.6 Hz, 1H), 4.89 (d, *J* = 15.8 Hz, 1H), 4.23 (d, *J* = 15.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5, 166.5, 164.0 (d, *J* = 11.6 Hz), 160.1 (d, *J* = 13.6 Hz), 157.5 (d, *J* = 13.5 Hz), 142.4, 137.1, 132.5, 131.4 (d, *J* = 10.8 Hz), 131.3, 129.8, 128.5,

127.2, 127.2, 126.2 (dd, *J* = 13.9, 3.4 Hz), 123.0 (d, *J* = 24.2 Hz), 112.4 (d, *J* = 22.7 Hz), 67.5, 42.3.

_N_-(2-benzyl-3-oxo-2,3-dihydro-1_H_-isoindol-1-yl)thiophene-2-sulfonamide (240g)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and nBu_4NPF_6 (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2-thiophenesulfonamide (38 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (62 mg, 77%)

RF (1:5 EtOAc:DCM): 0.58

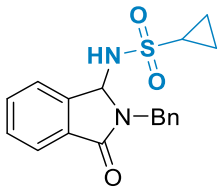
IR ν_{max} (cm^{-1}): 3345, 3105, 2894, 1664, 1467, 1198

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3S_2$ 385.0681; Found 385.0680

^1H NMR (400 MHz, DMSO-d_6): δ 9.25 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 4.8 Hz, 1H), 7.75 – 7.60 (m, 2H), 7.56 – 7.45 (m, 2H), 7.37 – 7.17 (m, 6H), 6.83 – 6.61 (m, 1H), 5.84 (d, *J* = 8.8 Hz, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.29 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 142.7, 142.5, 137.4, 133.4, 132.4, 132.4, 131.2, 129.8, 128.5, 128.1, 127.6, 127.1, 123.1, 122.9, 67.7, 42.5.

_N_-(2-benzyl-3-oxo-2,3-dihydro-1_H_-isoindol-1-yl)cyclopropanesulfonamide (240h)



To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), $Ca(NTf_2)_2$ (6.3 mg, 0.0104 mmol) and nBu_4NPF_6 (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and cyclopropanesulfonamide (28

mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (44 mg, 61%)

RF (1:5 EtOAc:DCM): 0.35

IR ν_{max} (cm^{-1}): 3387, 3277, 3125, 1671, 1470, 1295

HRMS (ESI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O_3S$ 343.1116; Found 343.1118

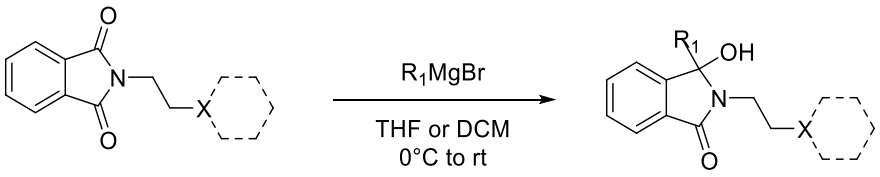
^1H NMR (400 MHz, DMSO-d_6): δ 8.48 (s, 1H), 7.80 – 7.65 (m, 3H), 7.65 – 7.54 (m, 1H), 7.42 – 7.28 (m, 4H), 7.28 – 7.17 (m, 1H), 5.88 (s, 1H), 4.92 (d, *J* = 15.5 Hz, 1H), 4.42 (d, *J* = 15.6 Hz, 1H), 3.08 – 2.80 (m, 1H), 1.13 – 0.97 (m, 2H), 0.96 – 0.83 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 143.2, 137.7, 132.4, 131.3, 129.7, 128.5, 127.7, 127.1, 124.0, 122.7, 67.7, 42.2, 31.6, 5.6, 5.3.

9.3. Chapter 3 Experimental

9.3.1. General Procedures for Chapter 3

General Procedure B – Synthesis of 3-hydroxyisoindolinones by Grignard Addition

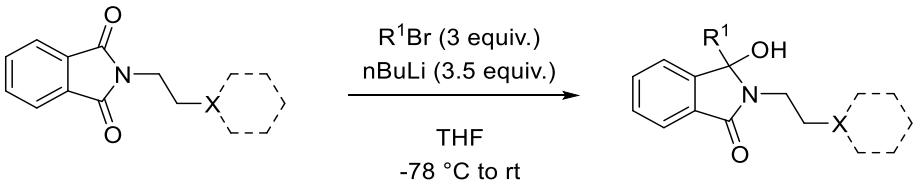


N-(2-mercaptoethyl)-phthalimide (1.0 equiv.) was added to a flame dried RBF and purged with argon. Dry THF or DCM (0.25 M) was added, and the solution was cooled to 0°C. The Grignard reagent* (3.0 equiv.) was then added dropwise, and the reaction was warmed to room temperature. Upon completion of the reaction (30 mins) which was indicated by the TLC, the reaction was quenched with NH_4Cl, and extracted into DCM (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The product was then purified by FCC (EtOAc:Hex) to afford the pure compound.

*Grignard reagents were either purchased or freshly prepared by suspending magnesium turnings (3.10 equiv.) in dry THF (1.0 M) under argon with 1,2-

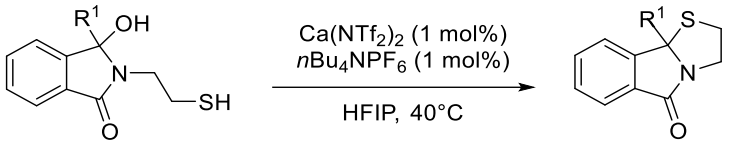
dibromoethane (0.1 equiv.) as an initiator. Dropwise addition of aryl halide (3.0 equiv.) and stirring for 2 h afforded the Grignard reagent which was then diluted to 0.5 M before being added to the electrophile.

General Procedure C – Synthesis of 3-hydroxyisoindolinones by lithium halogen exchange



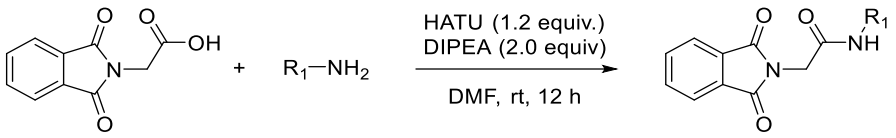
To a flame dried round bottomed flask purged with argon was added the corresponding aryl bromide (3.5 equiv.) and anhydrous THF (0.25 M). The solution was cooled to -78 °C and nBuLi (3 equiv. 2.5 M in hexanes) was added dropwise. The resulting solution was stirred at -78 °C for 1 hour. Phthalimide was then added in one portion and the reaction was stirred warmed to room temperature. Following completion of the reaction, indicated by TLC, the reaction was quenched with sat. aq. NH_4Cl and extracted with DCM (3 x 25 mL). The combined organic layers then dried over Na_2SO_4, filtered and concentrated. The product was then purified by FCC (EtOAc:Hex) to afford the pure compound.

General procedure D – Calcium-HFIP catalysed cyclisation



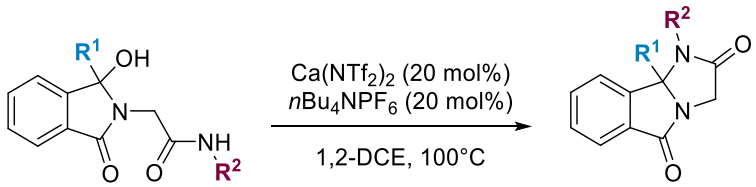
To a 4 mL vial capped with a capped with teflon cap was added $Ca(NTf_2)_2$ (1 mol%) and $n$$Bu_4NPF_6$ (1 mol%) in HFIP (0.2 M). 3-hydroxyisoindolinone (1 equiv.) was added and the reaction was stirred at 40 °C until TLC analysis indicated full conversion to the product. The solution was then concentrated and purified by FCC (EtOAc:Hex) to afford the pure compound.

General Procedure E - Amide Coupling



To an oven-dried vial, with a magnetic stirrer bar was added phthalimidoglycine (1.0 equiv.) and HATU (1.2 equiv.) which was sealed with a septum and then purged with N_2 and dissolved in dry DMF (0.2 M). DIPEA (2.0 equiv.) was then added and the reaction was stirred at room temperature for 5 mins after which the amine (1.1 equiv.) was added and the reaction was stirred at room temperature overnight. Following completion of the reaction, indicated by TLC (DCM:MeOH), the reaction was quenched with $NaHCO_3$ and transferred to a separating funnel which was then extracted into DCM (3 x 20 mL). The combined organic layers were then washed with water (3 x 50 mL) followed by 5% aq. LiCl (1 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The product was then purified by flash column chromatography to afford the pure amide.

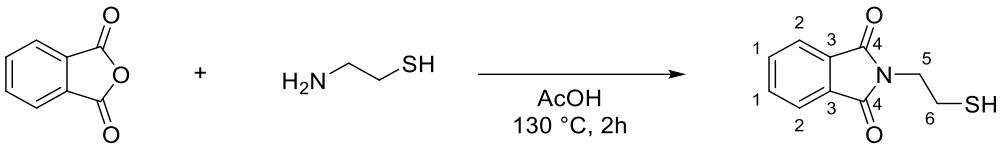
General Procedure F - Calcium catalysed dehydrative cyclisation of tethered amides



To a 4 mL vial capped with a capped with teflon cap was added $Ca(NTf_2)_2$ (20 mol%) and nBu$_4$NPF$_6$ (20 mol%) in 1,2-DCE (0.2 M). 3-hydroxyisoindolinone (1 equiv.) was added and the reaction was stirred at 100 °C until TLC analysis indicated full conversion to the product. The solution was then concentrated and purified by FCC (EtOAc:Hex) to afford the pure compound.

9.3.2. Tethered Thiols

Synthesis of N-(2-mercaptoethyl)-phthalimide (310)



Phthalic anhydride (3.0 g, 20 mmol) and cysteamine (1.7 g, 22 mmol) was dissolved in acetic acid (30 mL) and stirred at 130°C for 2h. Upon completion of the reaction, indicated by TLC the reaction was cooled, and concentrated under reduced pressure by azeotropic removal of acetic acid with cyclohexane. The product was then purified by flash column chromatography (0 to 10% EtOAc:Hex) to afford the pure product as a white solid (1.7 g, 40%).

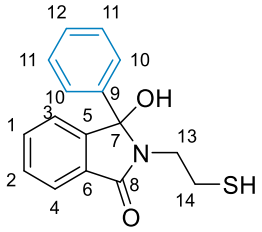
RF (1:1 EtOAc:Hex): 0.71

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 2H, **H2**), 7.75 – 7.72 (m, 2H, **H1**), 3.89 (t, *J* = 7.3 Hz, 2H, **H5**), 2.89 – 2.79 (m, 2H, **H6**), 1.43 (t, *J* = 8.5 Hz, 1H, **SH**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (**C4**), 134.3 (**C2**), 132.1 (**C3**), 123.6 (**C1**), 40.88 (**C5**), 23.1 (**C6**).

Data in accordance with literature[198]

3-hydroxy-3-phenyl-2-(2-sulfanylethyl)isoindolin-1-one (311a)



The title compound was prepared according to general procedure **B** from *N*-(2-mercaptoethyl)-phthalimide (450 mg, 2.20 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 2.20 mL, 6.50 mmol) in THF (9 mL). Following completion of the reaction (2 h), purification by FCC (1:5 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (450 mg, 73%).

RF (1:1 EtOAc:Hex): 0.47

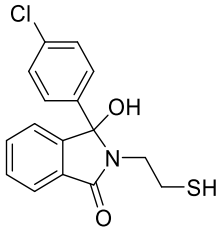
IR ν_{max} (cm^{-1}): 3306, 2957, 1678, 1608, 1425, 1071, 764

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{16}H_{14}NOS$ 268.0796; Found 268.0806

^1H NMR (400 MHz, DMSO-d_6): δ 7.73 (d, *J* = 6.7 Hz, 1H, **H4**), 7.56 (td, *J* = 7.4, 1.4 Hz, 1H, **H1**), 7.51 (td, *J* = 7.4, 1.2 Hz, 1H, **H2**), 7.39 – 7.30 (m, 5H, **H10, H11, H12**), 7.26 (d, *J* = 6.9 Hz, 1H, **H3**), 7.18 (s, 1H, **OH**), 3.60 – 3.49 (m, 1H, **$H13_A$**), 3.11 – 2.99 (m, 1H, **$H13_B$**), 2.69 – 2.52 (m, 3H, **H14, SH**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6 (**C8**), 149.5 (**C9**), 139.9 (**ArC**), 132.7 (**ArC**), 130.2 (**ArC**), 129.3 (**ArC**), 128.6 (**ArC**), 128.2 (**ArC**), 125.8 (**ArC**), 122.8 (**ArC**), 122.6 (**ArC**), 90.5 (**C7**), 42.5 (**C13**), 22.4 (**C14**).

3-(4-chlorophenyl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (311b)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), 4-chlorophenylmagnesium bromide (1.0 M in Et_2O, 2.90 mL, 2.90 mmol) in THF (5 mL). Following completion of the reaction (2 h), purification by FCC (1:5 EtOAc:Hex, 1% NEt_3) afforded the pure product as an off-white solid (218 mg, 71%).

RF (1:1 EtOAc:Hex): 0.49

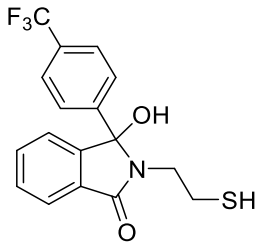
IR ν_{max} (cm^{-1}): 3316, 2860, 2821, 1673, 1608, 1478, 1146, 763

HRMS (APCI)m/z: $[M – H_2O]^+$ Calcd for $C_{16}H_{13}ClNOS$ 302.0406; Found 302.0413

^1H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.78 (m, 1H), 7.56 – 7.45 (m, 2H), 7.37 – 7.29 (m, 4H), 7.29 – 7.26 (m, 1H), 3.85 – 3.70 (m, 1H), 3.40 (br s, 1H), 3.15 – 3.03 (m, 1H), 2.90 – 2.76 (m, 1H), 2.70 – 2.55 (m, 1H), 1.40 (t, *J* = 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 148.6, 137.1, 134.9, 133.3, 130.1, 129.1, 129.0, 127.75, 123.7, 122. 8, 90.8, 42.9, 23.3.

3-hydroxy-2-(2-sulfanylethyl)-3-[4-(trifluoromethyl)phenyl]isoindolin-1-one (311c)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), (4-(trifluoromethyl)phenyl)magnesium bromide (0.5 M in THF, 6.0 mL, 2.90 mmol) in THF (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (73 mg, 3.00 mmol), 4-bromobenzotrifluoride (650 mg, 0.41 mL, 2.90 mmol) and 1,2-dibromoethane (8 µL, 0.0098 mmol) in THF (3 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (277 mg, 81%).

RF (1:1 EtOAc:Hex): 0.55

IR ν_{max} (cm^{-1}): 3200, 1671, 1614, 1325, 1070, 768

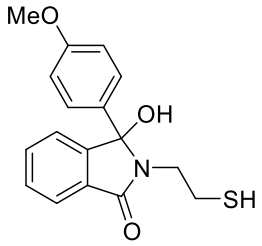
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{17}H_{13}F_3NOS$ 336.0670; Found 336.0661

^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.80 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.47 (m, 4H), 7.30 – 7.26 (m, 1H), 3.86 – 3.74 (m, 1H), 3.48 (br s, 1H), 3.12 – 3.00 (m, 1H), 2.93 – 2.79 (m, 1H), 2.72 – 2.60 (m, 1H), 1.42 (t, *J* = 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 148.4, 142.7, 133.4, 130.9 (q, *J* = 32.7 Hz), 130.2, 130.1, 126.8, 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.3 Hz), 123.8, 122.8, 90.7, 43.0, 23.3.

^{19}F NMR (376 MHz, $CDCl_3$): -62.6

3-hydroxy-3-(4-methoxyphenyl)-2-(2-sulfanylethyl)isoindolin-1-one (311d)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (150 mg, 0.72 mmol), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 4.2 mL, 2.20 mmol) in THF (3 mL). The Grignard reagent was freshly prepared from magnesium turnings (55 mg, 2.20 mmol), 4-bromoanisole (406 mg, 0.28 mL, 2.20 mmol) and 1,2-dibromoethane (6 µL, 0.0072 mmol) in THF (2 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (182 mg, 80%).

RF (1:1 EtOAc:Hex): 0.46

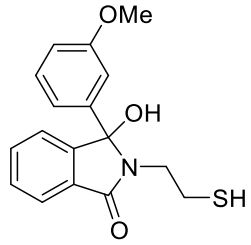
IR ν_{max} (cm^{-1}): 3191, 1670, 1610, 1467, 1092, 770

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_2S$ 298.0902; Found 298.0894

^1H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.76 (m, 1H), 7.56 – 7.43 (m, 2H), 7.34 – 7.26 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 3.78 – 3.68 (m, 1H), 3.34 (s, 1H), 3.18 – 3.08 (m, 1H), 2.86 – 2.73 (m, 1H), 2.63 – 2.47 (m, 1H), 1.38 (t, *J* = 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 148.7, 137.2, 134.9, 133.2, 130.0, 130.0, 129.1, 127.8, 123.6, 122.8, 90.8, 42.9, 23.2. (one resonance missing)

3-hydroxy-3-(3-methoxyphenyl)-2-(2-sulfanylethyl)isoindolin-1-one (311e)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), 3-methoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 2.90 mmol) in THF (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (73 mg, 3.00 mmol), 3-bromoanisole (541 mg, 0.37 mL, 2.90 mmol) and 1,2-dibromoethane (8 µL, 0.0098 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (216 mg, 71%).

RF (1:1 EtOAc:Hex): 0.46

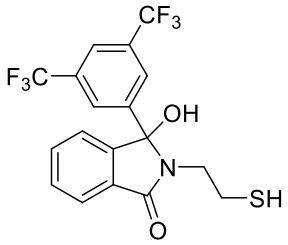
IR ν_{max} (cm^{-1}): 3315, 2960, 2835, 1675, 1586, 1398, 1146, 762

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{17}H_{16}NO_2S$ 298.0902; Found 298.0892

^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.40 (m, 2H), 7.37 – 7.18 (m, 2H), 7.08 – 6.99 (m, 1H), 6.96 – 6.81 (m, 2H), 4.09 (s, 1H), 3.80 (s, 3H), 3.76 – 3.64 (m, 1H), 3.22 – 3.06 (m, 1H), 2.84 – 2.67 (m, 1H), 2.61 – 2.45 (m, 1H), 1.39 (t, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 160.0, 149.0, 140.2, 133.1, 130.1, 129.9, 129.7, 123.5, 122.8, 118.5, 114.0, 112.2, 91.1, 55.5, 43.0, 23.2.

3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (311f)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), 3,5-bis(trifluoromethyl)-

phenylmagnesium bromide (0.5 M in THF, 6.0 mL, 2.90 mmol) in THF (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (73 mg, 3.00 mmol), 1,3-bis(trifluoromethyl)-5-bromobenzene (848 mg, 0.49 mL, 2.90 mmol) and 1,2-dibromoethane (8 µL, 0.0098 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:3 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (361 mg, 89%).

RF (1:1 EtOAc:Hex): 0.66

IR ν_{max} (cm^{-1}): 3161, 2898, 1681, 1282, 1120, 762

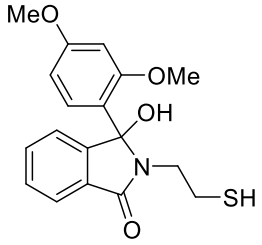
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{18}H_{12}F_6NOS$ 404.0544; Found 404.0536

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.82 (m, 4H), 7.61 – 7.53 (m, 2H), 7.30 – 7.27 (m, 1H), 3.86 (ddd, *J* = 14.1, 7.6, 5.2 Hz, 1H), 3.50 (s, 1H), 3.12 – 3.00 (m, 1H), 2.99 – 2.86 (m, 1H), 2.80 – 2.66 (m, 1H), 1.44 (dd, *J* = 9.0, 8.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 147.7, 142.0, 133.7, 130.7, 130.0, 126.7, 124.1, 132.5 (q, *J* = 33.5 Hz), 123.1 (d, *J* = 272.6 Hz), 123.1 (d, *J* = 3.8 Hz), 122.8, 90.2, 42.9, 23.1.

^{19}F NMR (376 MHz, $CDCl_3$): -62.7

3-(2,4-dimethoxyphenyl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (311g)



The title compound was prepared according to general procedure **B** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), 2,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 2.90 mmol) in THF (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (73 mg, 3.00 mmol), 1-bromo-2,4-dimethoxybenzene (628 mg, 0.37 mL, 2.90 mmol) and 1,2-dibromoethane (8 µL, 0.0098 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:Hex, 1% NEt_3) afforded the pure product as a yellow solid (152 mg, 46%).

RF (1:1 EtOAc:Hex): 0.31

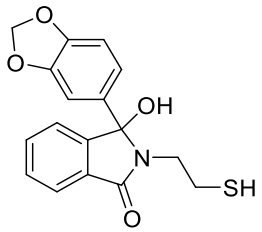
IR ν_{max} (cm^{-1}): 3283, 2995, 2933, 1661, 1582, 1403, 1185, 1033, 837

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{18}H_{19}NO_3S$ 328.1007; Found 328.0894

^1H NMR (400 MHz, DMSO-d_6): 7.88 (d, *J* = 8.7 Hz, 1H), 7.72 – 7.62 (m, 1H), 7.53 – 7.40 (m, 2H), 7.12 (dd, *J* = 6.1, 1.5 Hz, 1H), 6.84 (s, 1H), 6.63 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 3.76 (s, 3H), 3.50 – 3.36 (m, 1H), 3.24 (s, 3H), 3.04 – 2.89 (m, 1H), 2.57-2.52 (m, 1H), 2.48 - 2.43 (m, 1H), 2.42 – 2.29 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 161.7, 157.7, 149.1, 132.4, 131.2, 129.5, 129.2, 123.0, 121.9, 118.3, 104.7, 99.5, 55.7, 55.5, 43.2, 23.2.

3-(1,3-benzodioxol-5-yl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (311m)



The title compound was prepared according to general procedure **C** from N-(2-mercaptoethyl)-phthalimide (200 mg, 0.97 mmol), 1-bromo-3,4-(methylenedioxy)benzene (776 mg, 0.47 mL, 3.86 mmol) and n-butyllithium (2.5 M in Hexane, 1.20 mL, 2.90 mmol) in THF (3 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a dark yellow solid (100 mg, 31%).

RF (1:1 EtOAc:Hex): 0.37

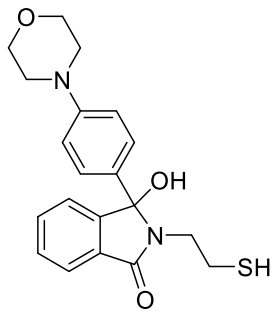
IR ν_{max} (cm^{-1}): 3073, 2939, 2889, 1698, 1608, 1485, 1239, 1034, 807

HRMS (APCI)m/z: $[M – H_2O]^+$ Calcd for $C_{17}H_{14}NO_3S$ 312.0694; Found 312.0691

^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.45 (td, *J* = 7.5, 1.2 Hz, 1H), 7.36 (td, *J* = 7.4, 1.0 Hz, 1H), 7.26 – 7.23 (m, 1H), 6.88 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.76 – 6.70 (m, 2H), 5.92 (dd, *J* = 7.4, 1.4 Hz, 2H), 5.03 (s, 1H), 3.51 (ddd, *J* = 14.2, 9.7, 5.4 Hz, 1H), 3.04 (ddd, *J* = 14.1, 9.7, 5.9 Hz, 1H), 2.67 – 2.53 (m, 1H), 2.45 – 2.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 149.6, 148.2, 147.9, 134.2, 133.1, 129.1, 128.8, 124.5, 122.9, 119.8, 108.2, 106.9, 101.6, 82.1, 43.1, 38.3.

3-hydroxy-3-(4-morpholinophenyl)-2-(2-sulfanylethyl)isoindolin-1-one (311n)



The title compound was prepared according to general procedure **C** from N-(2-mercaptoethyl)-phthalimide (100 mg, 0.48 mmol), 4-(4-bromophenyl)morpholine (409 mg, 1.70 mmol) and n-butyllithium (2.5 M in Hexane, 0.58 mL, 1.45 mmol) in THF (2 mL). Following completion of the reaction (30 mins), purification by FCC (1:3 EtOAc:Hex) afforded the pure product as a white solid (35 mg, 20%).

RF (1:1 EtOAc:Hex): 0.31

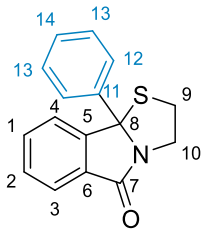
IR ν_{max} (cm^{-1}): 3211, 2952, 2917, 2846, 1672, 1608, 1405, 1122, 930

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{20}H_{21}N_2O_2S$ 353.1324; Found 353.1311

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.80 (m, 1H), 7.54 – 7.43 (m, 2H), 7.32 – 7.26 (m, 3H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.86 – 3.82 (m, 4H), 3.81 – 3.73 (m, 1H), 3.23 – 3.10 (m, 5H), 3.08 (s, 1H), 2.90 – 2.78 (m, 1H), 2.70 – 2.57 (m, 1H), 1.40 (t, *J* = 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 149.2, 134.8, 133.0, 131.8, 129.7, 128.9, 127.2, 123.6, 122.8, 115.3, 91.2, 67.0, 48.9, 42.9, 23.4.

9b-phenyl-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312a)



The title compound was prepared according to general procedure **D** from 3-hydroxy-3-phenyl-2-(2-sulfanylethyl)isoindolin-1-one (50 mg, 0.175 mmol), $Ca(NTf_2)_2$ (1.1 mg, 0.00175 mmol) and $n$$Bu_4NPF_6$ (0.7 mg, 0.00175 mmol) in HFIP (0.9 mL). Following completion of the reaction (30 mins), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a yellow oil (44 mg, 94%).

RF (1:1 EtOAc:Hex): 0.65

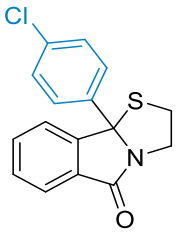
IR ν_{max} (cm^{-1}):): 3054, 3006, 2939, 1702, 1608, 1467, 1323, 1092, 744

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{16}H_{14}NOS$ 268.0796; Found 268.0801

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.78 (m, 1H, **H3**), 7.66 – 7.61 (m, 2H, **H12**), 7.48 (td, *J* = 7.4, 1.4 Hz, 1H, **H2**), 7.43 (td, *J* = 7.4, 1.3 Hz, 1H, **H1**), 7.39 – 7.28 (m, 4H, **H4, H13, H14**), 4.58 – 4.46 (m, 1H, **H10$_A$**), 3.57 – 3.48 (m, 1H, **H10$_B$**), 3.42 – 3.26 (m, 2H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1 (**C7**), 149.6 (**C5**), 140.5 (**C11**), 133.1 (**ArC**), 129.1 (**ArC**), 129.0 (**C6**), 128.8 (**C13**), 128.5 (**ArC**), 126.1 (**C12**), 124.5 (**ArC**), 123.00 (**ArC**), 82.1 (**C8**), 43.1 (**C10**), 38.2 (**C9**).

9b-(4-chlorophenyl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312b)



The title compound was prepared according to general procedure **D** from 3-(4-chlorophenyl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (100 mg, 0.313 mmol), $Ca(NTf_2)_2$ (1.9 mg, 0.00313 mmol) and $n$$Bu_4NPF_6$ (1.2 mg, 0.00313 mmol) in HFIP (1.6

mL). Following completion of the reaction (30 mins), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a colourless oil (94 mg, 92%).

RF (1:1 EtOAc:Hex): 0.71

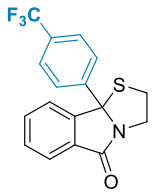
IR ν_{max} (cm^{-1}): 3055, 2941, 1703, 1465, 1321, 1090, 818

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}ClNOS$ 302.0406; Found 302.0416

^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 6.7 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.46 (td, *J* = 7.4, 1.2 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.28 – 7.23 (m, 2H), 4.56 – 4.44 (m, 1H), 3.60 – 3.49 (m, 1H), 3.36 – 3.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 149.3, 139. 2, 134.6 133.3, 129.3, 129.0, 129.0, 127.7, 124.7, 122.9, 81.7, 43.2, 38.4.

9b-[4-(trifluoromethyl)phenyl]-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312c)



The title compound was prepared according to general procedure **D** from 3-hydroxy-2-(2-sulfanylethyl)-3-[4-(trifluoromethyl)phenyl]isoindolin-1-one (100 mg, 0.283 mmol), $Ca(NTf_2)_2$ (1.7 mg, 0.00283 mmol) and $n$$Bu_4NPF_6$ (1.1 mg, 0.00283 mmol) in HFIP (1.4 mL). Following completion of the reaction (1 h), purification by FCC (1:4 EtOAc:Hex) afforded the pure compound as a colourless oil (95 mg, 95%).

RF (1:4 EtOAc:Hex): 0.42

IR ν_{max} (cm^{-1}): 3051, 2941, 1707, 1608, 1467, 1320, 1111, 740

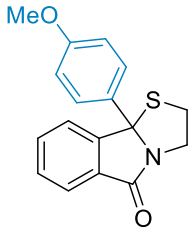
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}F_3NOS$ 336.0670; Found 336.0664

^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 6.7, 1.5 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.43 (m, 2H), 7.28 (dd, *J* = 6.7, 1.1 Hz, 1H), 4.59 – 4.48 (m, 1H), 3.60 – 3.51 (m, 1H), 3.37 – 3.26 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 148.9, 144.9, 133.4, 130.8 (q, *J* = 32.6 Hz), 129.5, 129.0, 126.7, 125.9 (q, *J* = 3.5 Hz), 124.9, 124.0 (q, *J* = 272.6 Hz), 123.0, 81.6, 43.4, 38.3.

^{19}F NMR (376 MHz, CDCl3): δ -62.54

9b-(4-methoxyphenyl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312d)



The title compound was prepared according to general procedure **D** from 3-hydroxy-3-(4-methoxyphenyl)-2-(2-sulfanylethyl)isoindolin-1-one (80 mg, 0.254 mmol), $Ca(NTf_2)_2$ (1.5 mg, 0.00254 mmol) and nBu$_4$NPF$_6$ (1.0 mg, 0.00254 mmol) in HFIP (1.3 mL). Following completion of the reaction (30 mins), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a colourless oil (72 mg, 95%).

RF (1:5 EtOAc:Hex): 0.62

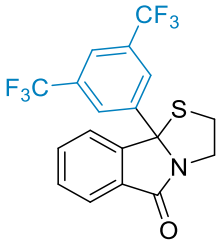
IR ν_{max} (cm^{-1}): 3051, 2935, 2837, 1700, 1608, 1508, 1247, 1169, 1031

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_2S$ 298.0902; Found 298.0894

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.52 – 7.40 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 4.55 – 4.43 (m, 1H), 3.80 (s, 3H), 3.60 – 3.47 (m, 1H), 3.39 – 3.28 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 159.8, 149.9, 133.1, 132.3, 129.0, 128.9, 127.6, 124.5, 123.0, 114.1, 81.9, 55.5, 43.1, 38.3.

9b-[3,5-bis(trifluoromethyl)phenyl]-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312e)



The title compound was prepared according to general procedure **D** from 3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (100 mg,

0.237 mmol), $Ca(NTf_2)_2$ (1.4 mg, 0.00237 mmol) and nBu_4NPF_6 (1.0 mg, 0.00237 mmol) in HFIP (1.2 mL). Following completion of the reaction (20 mins), purification by FCC (3:10 EtOAc:Hex) afforded the pure compound as a white solid (90 mg, 94%).

RF (1:1 EtOAc:Hex): 0.77

IR ν_{max} (cm^{-1}): 3040, 2950, 1716, 1608, 1279, 1122, 742

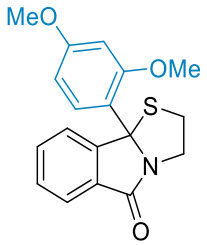
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{12}F_6NOS$ 404.0544; Found 404.0557

^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 2H), 7.90 – 7.79 (m, 2H), 7.60 – 7.48 (m, 2H), 7.25 – 7.22 (m, 1H), 4.64 – 4.51 (m, 1H), 3.65 – 3.51 (m, 1H), 3.40 – 3.25 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 148.3, 144.1, 133.7, 132.4 (q, *J* = 33.6 Hz), 129.9, 128.8, 126.5, 125.2, 123.2 (q, *J* = 273.0 Hz), 122.8, 122.7 (d, *J* = 3.7 Hz), 81.3, 43.6, 38.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6

9b-(2,4-dimethoxyphenyl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312f)



The title compound was prepared according to general procedure **D** from 3-(2,4-dimethoxyphenyl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (100 mg, 0.290 mmol), $Ca(NTf_2)_2$ (1.7 mg, 0.00290 mmol) and nBu_4NPF_6 (1.1 mg, 0.00290 mmol) in HFIP (1.5 mL). Following completion of the reaction (20 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as white solid (90 mg, 95%).

RF (1:1 EtOAc:Hex): 0.60

IR ν_{max} (cm^{-1}): 3070, 2933, 2835, 1698, 1343, 1267, 1023

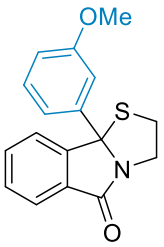
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_3S$ 328.1007; Found 328.1003

^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 (td, *J* = 7.5, 0.9 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.59 (d, *J* = 2.4 Hz,

1H), 6.39 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.75 (ddd, *J* = 11.6, 6.4, 1.6 Hz, 1H), 4.00 (s, 3H), 3.79 (s, 3H), 3.38 – 3.30 (m, 1H), 3.28 – 3.20 (m, 1H), 3.07 (ddd, *J* = 10.0, 5.9, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 161.1, 158.1, 152.0, 133.4, 128.9, 128.6, 124.9, 124.1, 123.6, 123.0, 104.2, 100.8, 79.0, 55.9, 55.6, 44.4, 36.4.

9b-(3-methoxyphenyl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312g)



The title compound was prepared according to general procedure **D** from 3-hydroxy-3-(3-methoxyphenyl)-2-(2-sulfanylethyl)isoindolin-1-one (80 mg, 0.254 mmol), $Ca(NTf_2)_2$ (1.5 mg, 0.00254 mmol) and *n*Bu_4NPF_6 (1.0 mg, 0.00254 mmol) in HFIP (1.3 mL). Following completion of the reaction (15 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as white solid (71 mg, 94%).

RF (1:1 EtOAc:Hex): 0.63

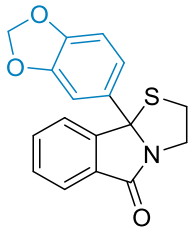
IR ν_{max} (cm^{-1}): 3068, 2954, 1698, 1579, 1347, 1247, 1049, 874

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_2S$ 298.0902; Found 298.0883

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (ddd, *J* = 7.2, 1.4, 0.8 Hz, 1H), 7.49 (td, *J* = 7.4, 1.4 Hz, 1H), 7.44 (td, *J* = 7.4, 1.3 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.31 – 7.26 (m, 1H), 7.23 (ddd, *J* = 7.8, 1.7, 1.2 Hz, 1H), 7.19 – 7.15 (m, 1H), 6.84 (ddd, *J* = 8.0, 2.6, 1.1 Hz, 1H), 4.54 – 4.45 (m, 1H), 3.80 (s, 3H), 3.58 – 3.47 (m, 1H), 3.42 – 3.28 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 160.0, 149.5, 142.3, 133.1, 130.0, 129.2, 129.0, 124.6, 123.0, 118.6, 113.7, 112.0, 82.1, 55.5, 43.3, 38.3.

9b-(1,3-benzodioxol-5-yl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312h)



The title compound was prepared according to general procedure **D** from 3-(1,3-benzodioxol-5-yl)-3-hydroxy-2-(2-sulfanylethyl)isoindolin-1-one (50 mg, 0.152 mmol), $Ca(NTf_2)_2$ (1.0 mg, 0.00152 mmol) and $n$$Bu_4NPF_6$ (0.6 mg, 0.00152 mmol) in HFIP (0.8 mL). Following completion of the reaction (15 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as white solid (39 mg, 83%).

RF (1:1 EtOAc:Hex): 0.52

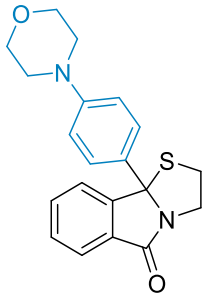
IR ν_{max} (cm^{-1}): 3060, 2939, 1702, 1608, 1485, 1243, 1029, 746

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}NO_3S$ 312.0694; Found 312.0703

^1H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.77 (m, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 (td, *J* = 7.4, 1.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.17 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 5.96 (dd, *J* = 6.7, 1.4 Hz, 2H), 4.56 – 4.40 (m, 1H), 3.61 – 3.47 (m, 1H), 3.42 – 3.29 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 149.7, 148.2, 147.9, 134.3, 133.1, 129.1, 128.9, 124.6, 122.9, 119.9, 108.2, 107.0, 101.6, 82.1, 43.1, 38.4.

9b-(4-morpholinophenyl)-2,3-dihydrothiazolo[2,3-a]isoindol-5-one (312i)



The title compound was prepared according to general procedure **D** from 3-hydroxy-3-(4-morpholinophenyl)-2-(2-sulfanylethyl)isoindolin-1-one (30 mg, 0.081 mmol),

$Ca(NTf_2)_2$ (0.5 mg, 0.00081 mmol) and $n$$Bu_4NPF_6$ (0.3 mg, 0.00081 mmol) in HFIP (0.4 mL). The reaction was stirred overnight and purification by FCC (1:5 EtOAc:DCM) afforded the pure compound as a colourless oil (8 mg, 28%).

RF (1:1 EtOAc:Hex): 0.43

IR ν_{max} (cm^{-1}): 3062, 2934, 2843, 1698, 1247, 1032

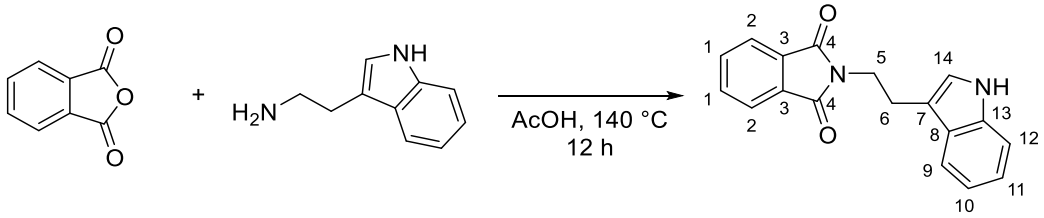
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2O_2S$ 353.1324; Found 353.1325

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 6.9 Hz, 1H), 7.61 – 7.37 (m, 4H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.58 – 4.42 (m, 1H), 3.91 – 3.79 (m, 4H), 3.63 – 3.48 (m, 1H), 3.43 – 3.28 (m, 2H), 3.19 (dd, *J* = 5.6, 4.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 151.3, 150.0, 133.1, 132.2, 129.0, 128.7, 127.3, 124.5, 123.0, 115.3, 82.0, 67.0, 49.0, 43.1, 38.3.

9.3.3. Tethered Indoles

Synthesis of 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (315)



Phthalic anhydride (1.0 g, 6.75 mmol) and tryptamine (1.3 g, 8.10 mmol) was dissolved in acetic acid (14 mL) and stirred at 140 °C overnight. Upon completion of the reaction, indicated by TLC, the mixture was cooled, diluted with water (50 mL) and quenched slowly with sat. aq. $NaHCO_3$. The solution was transferred to a separating funnel and extracted into DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by FCC (1:3 EtOAc:Hex) afforded the title compound as a yellow solid (1.6 g, 81%).

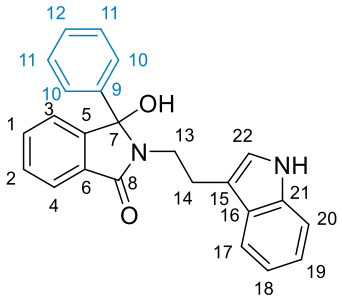
RF (1:1 EtOAc:Hex): 0.71

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H, **NH**), 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, **H2**), 7.77 – 7.68 (m, 3H, **H1**, **H9**), 7.35 (d, *J* = 8.0 Hz, 1H, **ArH**), 7.22 – 7.16 (m, 1H, **ArH**), 7.16 – 7.09 (m, 2H, **ArH**), 4.07 – 3.96 (m, 2H, **H5**), 3.21 – 3.12 (m, 2H, **H6**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5 (**C4**), 136.4 (**ArC**), 134.0 (**ArC**), 132.4 (**ArC**), 127.6 (**ArC**), 123.3 (**ArC**), 122.3 (**ArC**), 122.1 (**ArC**), 119.7 (**ArC**), 119.0 (**ArC**), 112.6 (**C7**), 111.2 (**C12**), 38.7 (**C5**), 24.6 (**C6**).

*Data in accordance with literature[199]

3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-phenyl-isoindolin-1-one (316a)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (300 mg, 1.03 mmol), Phenylmagnesium bromide (3.0 M in Et_2O, 1.03 mL, 3.10 mmol) in DCM (4 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (250 mg, 66%).

RF (1:1 EtOAc:Hex): 0.31

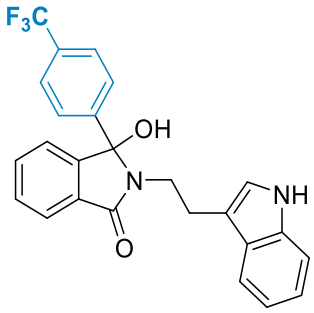
IR ν_{max} (cm^{-1}): 3368, 3230, 1657, 1614, 1414, 1198, 1055, 850

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{19}N_2O$ 351.1497; Found 351.1509

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H, **NH**), 7.79 – 7.74 (m, 1H, **H4**), 7.55 (pd, *J* = 7.4, 1.4 Hz, 2H, **ArH**), 7.44 – 7.34 (m, 5H, **ArH**), 7.34 – 7.26 (m, 3H, **ArH**), 7.20 (s, 1H, **OH**), 7.10 (d, *J* = 2.3 Hz, 1H, **ArH**), 7.07 – 7.01 (m, 1H, **H19**), 6.95 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, **H18**), 3.61 (ddd, *J* = 13.5, 12.0, 5.1 Hz, 1H, **H13$_A$**), 3.19 (ddd, *J* = 13.6, 12.0, 5.0 Hz, 1H, **H13$_B$**), 3.04 – 2.92 (m, 1H, **H14$_A$**), 2.80 – 2.66 (m, 1H, **H14$_A$**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (**C8**), 149.2 (**C5**), 138.7 (**ArC**), 136.3 (**ArC**), 132.8 (**ArC**), 130.7 (**ArC**), 129.6 (**ArC**), 128.7 (**ArC**), 128.6 (**ArC**), 127.4 (**ArC**), 126.4 (**ArC**), 123.3 (**ArC**), 122.8 (**ArC**), 122.1 (**ArC**), 122.1 (**ArC**), 119.4 (**ArC**), 119.1 (**ArC**), 113.5 (**ArC**), 111.2 (**ArC**), 91.5 (**C7**), 40.5 (**C13**), 24.5 (**C14**).

3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-[4-(trifluoromethyl)phenyl]isoindolin-1-one (316b)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), (4-(trifluoromethyl)phenyl)magnesium bromide (0.5 M in THF, 6.2 mL, 2.60 mmol) in DCM (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (65 mg, 2.68 mmol), 4-bromobenzotrifluoride (581 mg, 0.39 mL, 2.60 mmol) and 1,2-dibromoethane (7 µL, 0.0086 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a pale-yellow solid (250 mg, 67%).

RF (1:1 EtOAc:Hex): 0.27

IR ν_{max} (cm^{-1}): 3342, 3056, 2939, 1659, 1612, 1321, 1066, 822

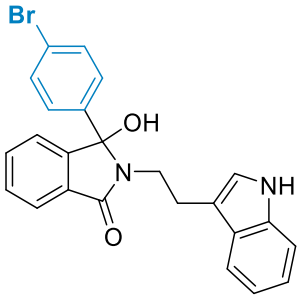
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{25}H_{18}F_3N_2O$ 419.1371; Found 419.1382

^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 7.81 – 7.77 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.44 (s, 1H), 7.35 – 7.26 (m, 3H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.96 – 6.89 (m, 1H), 3.60 (ddd, *J* = 13.6, 11.8, 5.2 Hz, 1H), 3.19 (ddd, *J* = 13.7, 11.8, 5.1 Hz, 1H), 3.06 – 2.91 (m, 1H), 2.81 – 2.65 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 149.0, 145.0, 136.2, 132.7, 130.6, 129.6, 128.7 (q, *J* = 32.1 Hz), 127.0, 126.9, 125.5 (q, *J* = 3.4 Hz), 122.8, 122.6, 120.9, 118.2, 117.9, 111.4, 111.3, 90.2, 24.5. (C-$\underline{C}F_3$ not observed)

^{19}F NMR (376 MHz, CDCl3): δ -61.1

3-(4-bromophenyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (316c)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 4-bromophenylmagnesium bromide (0.5 M in THF, 6.2 mL, 2.60 mmol) in DCM (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (65 mg, 2.68 mmol), 1,4-dibromobenzene (610 mg, 2.60 mmol) and 1,2-dibromoethane (7 µL, 0.0086 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:3 EtOAc:Hex) afforded the pure product as a pale-yellow solid (248 mg, 64%).

RF (1:1 EtOAc:Hex): 0.33

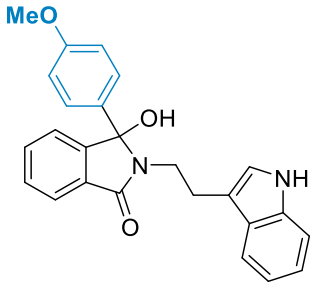
IR ν_{max} (cm^{-1}): 3330, 3068, 1657, 1610, 1403, 1068, 805

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{18}BrN_2O$ 429.0603; Found 429.0611

^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 7.80 – 7.73 (m, 1H), 7.64 – 7.48 (m, 4H), 7.45 – 7.21 (m, 6H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.99 – 6.92 (m, 1H), 3.58 (ddd, *J* = 13.6, 11.9, 5.2 Hz, 1H), 3.18 (ddd, *J* = 13.7, 11.8, 5.0 Hz, 1H), 3.03 – 2.88 (m, 1H), 2.81 – 2.69 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 149.2, 139.8, 136.2, 132.6, 131.4, 130.6, 129.4, 128.5, 128.3, 126.9, 122.8, 122.6, 122.5, 121.5, 121.0, 118.3, 118.0, 111.4, 90.2, 24.6. (one resonance missing)

3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-(4-methoxyphenyl)isoindolin-1-one (316d)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 6.2 mL, 2.60 mmol) in DCM (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (65 mg, 2.68 mmol), 4-bromoanisole (483 mg, 0.32 mL, 2.60 mmol) and 1,2-dibromoethane (7 µL, 0.0086 mmol) in THF (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (150 mg, 44%).

RF (1:1 EtOAc:Hex): 0.20

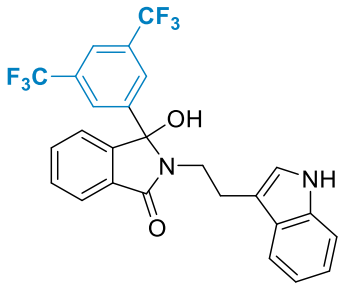
IR ν_{max} (cm^{-1}): 3364, 3010, 2919, 1677, 1605, 1407, 1019, 828

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{25}H_{22}N_2O_2$ 381.1603; Found 381.1590

^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 7.79 – 7.72 (m, 1H), 7.54 (dqd, *J* = 14.4, 7.4, 1.2 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.24 (m, 4H), 7.15 – 7.09 (m, 2H), 7.09 – 7.02 (m, 1H), 6.98 – 6.88 (m, 3H), 3.72 (s, 3H), 3.68 – 3.53 (m, 1H), 3.30 – 3.12 (m, 1H), 3.07 – 2.92 (m, 1H), 2.75 (td, *J* = 13.4, 5.0 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 159.1, 149.9, 136.3, 132.5, 132.0, 130.7, 129.1, 127.3, 127.0, 122.8, 122.6, 122.4, 121.0, 118.3, 118.2, 113.8, 111.6, 111.4, 90.6, 55.1, 24.6. (one resonance missing)

3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (316e)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 3,5-bis(trifluoromethyl)-phenylmagnesium bromide (0.5 M in THF, 6.2 mL, 2.60 mmol) in DCM (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (65 mg, 2.68 mmol), 1,3-bis(trifluoromethyl)-5-bromobenzene (757 mg, 0.45 mL, 2.60 mmol) and 1,2-dibromoethane (7 µL, 0.0086 mmol) in THF (3 mL). Following completion of the reaction (1 h), purification by FCC (1:3 EtOAc:Hex) afforded the pure product as an off-white solid (122 mg, 28%).

RF (1:1 EtOAc:Hex): 0.19

IR ν_{max} (cm^{-1}): 3465, 3263, 1668, 1619, 1364, 1277, 1131, 900

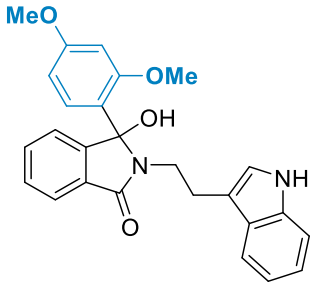
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{26}H_{17}F_6N_2O$ 487.1245; Found 487.1258

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.89 – 7.79 (m, 4H), 7.57 – 7.50 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.21 – 7.16 (m, 1H), 7.12 – 7.05 (m, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 3.96 – 3.80 (m, 1H), 3.27 (ddd, *J* = 13.8, 9.2, 6.4 Hz, 1H), 3.22 – 3.12 (m, 1H), 3.11 (s, 1H), 2.93 (ddd, *J* = 14.4, 9.1, 5.7 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.8, 148.1, 144.1, 136.2, 133.0, 130.7 (q, *J* = 33.1 Hz), 130.6, 130.0, 126.8, 126.7, 126.7, 123.1 (q, *J* = 273.1 Hz), 122.9, 122.9, 122.7, 122.5 (q, *J* = 3.6 Hz), 121.0, 118.2, 117.7, 111.5, 111.0, 89.6, 24.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8

3-(2,4-dimethoxyphenyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (316f)



The title compound was prepared according to general procedure **B** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 2,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 6.2 mL, 2.60 mmol) in DCM (4 mL). The Grignard reagent was freshly prepared from magnesium turnings (65 mg, 2.68 mmol), 1-bromo-2,4-dimethoxybenzene (561 mg, 0.37 mL, 2.60 mmol) and 1,2-dibromoethane (7 µL, 0.0086 mmol) in THF (3 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as an off-white solid (350 mg, 95%).

RF (1:1 EtOAc:Hex): 0.21

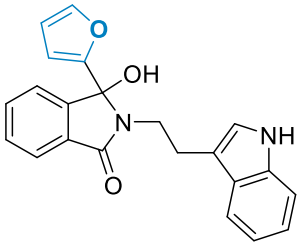
IR ν_{max} (cm^{-1}): 3293, 2935, 2835, 1655, 1435, 1029, 759

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{26}H_{23}N_2O_3$ 411.1709; Found 411.1698

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.74 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.42 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.95 – 6.88 (m, 1H), 6.81 (s, 1H), 6.69 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 3.76 (s, 3H), 3.55 – 3.37 (m, 1H), 3.24 (s, 3H), 3.21 – 3.05 (m, 1H), 3.02 – 2.86 (m, 1H), 2.61 – 2.52 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.0, 161.0, 157.3, 149.6, 136.2, 132.3, 131.5, 129.4, 128.4, 126.9, 122.5, 121.7, 121.6, 120.9, 119.4, 118.1, 118.1, 111.7, 111.4, 104.5, 99.2, 88.3, 79.2, 55.4, 55.2, 24.0.

3-(2-furyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (316g)



Furan (0.23 mL, 3.10 mmol) was dissolved in dry THF (7 mL). n-buthyllithium (2.5 M in Hexane, 1.03 mL, 2.60 mmol) was added dropwise at -78 °C and the mixture was stirred at room temperature for 2h. The solution was then cooled to -78 ºC and 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol) was added in a single porition. The reaction mixture was allowed to warm to room temperature and stirred for 2h. Upon completion of the reaction, indicated by TLC, the reaction mixture was quenched with sat. NH_4Cl and extracted with DCM (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a yellow solid (167 mg, 54 %).

RF (1:1 EtOAc:Hex): 0.17

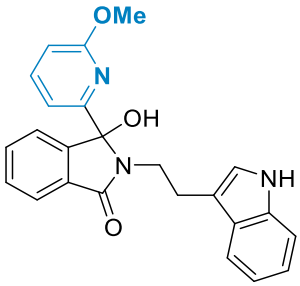
IR ν_{max} (cm^{-1}): 3412, 3293, 1661, 1410, 1152, 818, 742

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{22}H_{17}N_2O_2$ 341.1290; Found 341.1301

^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.85 – 7.79 (m, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.43 – 7.38 (m, 1H), 7.36 – 7.32 (m, 1H), 7.32 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.13 – 7.07 (m, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.60 (dd, *J* = 3.3, 0.9 Hz, 1H), 6.39 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.87 (ddd, *J* = 14.0, 10.1, 5.3 Hz, 1H), 3.49 (ddd, *J* = 14.0, 10.0, 6.3 Hz, 1H), 3.14 (ddd, *J* = 14.2, 9.8, 6.2 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.77 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 150.8, 146.2, 143.2, 136.3, 132.7, 131.0, 130.2, 127.5, 123.5, 122.7, 122.2, 122.2, 119.5, 119.2, 113.6, 111.2, 110.8, 109.4, 88.1, 40.4, 24.4.

3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-(6-methoxy-2-pyridyl)isoindolin-1-one (316h)



The title compound was prepared according to general procedure **C** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 2-bromo-6-methoxypyridine (650 mg, 0.47 mL, 3.44 mmol) and n-butyllithium (2.5 M in Hexane, 1.21 mL, 3.01 mmol) in THF (6 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a pale-yellow solid (186 mg, 54%).

RF (1:1 EtOAc:Hex): 0.23

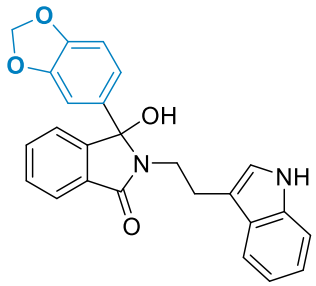
IR ν_{max} (cm^{-1}): 3300, 2932, 2861, 1675, 1575, 1269, 800

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{20}N_3O_2$ 382.1556; Found 382.1548

^1H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.77 (m, 2H), 7.55 – 7.40 (m, 4H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.20 – 7.13 (m, 1H), 7.11 – 7.05 (m, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.76 – 6.69 (m, 1H), 6.52 (dd, *J* = 7.4, 0.6 Hz, 1H), 6.47 (s, 1H), 4.07 (s, 3H), 3.74 (ddd, *J* = 13.9, 11.0, 5.6 Hz, 1H), 3.39 (ddd, *J* = 14.0, 11.0, 5.4 Hz, 1H), 3.18 – 3.02 (m, 1H), 2.89 (ddd, *J* = 14.2, 10.9, 5.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 163.1, 154.8, 147.9, 140.6, 136.3, 132.6, 131.8, 129.8, 127.5, 123.4, 122.5, 122.1, 122.0, 119.3, 118.9, 113.6, 113.5, 111.2, 111.1, 89.8, 54.0, 40.4, 24.8.

3-(1,3-benzodioxol-5-yl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (316i)



The title compound was prepared according to general procedure **C** from 2-[2-(1H-indol-3-yl)ethyl]isoindoline-1,3-dione (250 mg, 0.86 mmol), 1-bromo-3,4-(methylenedioxy)benzene (692 mg, 0.42 mL, 3.44 mmol) and n-butyllithium (2.5 M in Hexane, 1.21 mL, 3.01 mmol) in THF (7 mL). Following completion of the reaction (1 h), purification by FCC (1:3 EtOAc:DCM) afforded the pure product as a light-brown solid (271 mg, 76%).

RF (1:1 EtOAc:Hex): 0.23

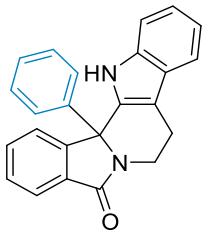
IR ν_{max} (cm^{-1}): 3314, 3056, 2898, 1661, 1405, 1239, 1036, 766

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{25}H_{19}N_2O_3$ 395.1396; Found 395.1408

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 7.79 – 7.70 (m, 1H), 7.57 (td, *J* = 7.4, 1.4 Hz, 1H), 7.52 (td, *J* = 7.4, 1.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.15 (s, 1H), 7.12 (s, 1H), 7.09 – 7.01 (m, 1H), 7.00 – 6.92 (m, 1H), 6.92 – 6.83 (m, 3H), 5.99 (dd, *J* = 4.7, 0.9 Hz, 2H), 3.60 (ddd, *J* = 13.5, 11.9, 5.2 Hz, 1H), 3.26 – 3.13 (m, 1H), 3.08 – 2.88 (m, 1H), 2.88 – 2.68 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5, 149.7, 147.4, 147.1, 136.3, 134.1, 132.4, 130.6, 129.2, 127.0, 122.7, 122.6, 122.4, 121.0, 119.5, 118.2, 118.1, 111.6, 111.4, 108.1, 106.4, 101.2, 90.5, 39.9, 24.6.

2-phenyl-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317a)



The title compound was prepared according to general procedure **D** from 3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-phenyl-isoindolin-1-one (80 mg, 0.22 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0022 mmol) and $n$$Bu_4NPF_6$ (0.8 mg, 0.0022 mmol) in HFIP (1.1 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a yellow solid (68 mg, 89%).

RF (1:1 EtOAc:Hex): 0.47

IR ν_{max} (cm^{-1}): 3261, 3058, 2935, 1659, 1394, 1448, 932

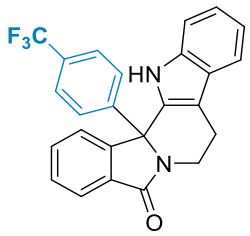
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O$ 351.1497; Found 351.1510

^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.98 – 7.89 (m, 1H), 7.64 – 7.56 (m, 1H), 7.55 – 7.49 (m, 3H), 7.38 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.32 – 7.20 (m, 4H), 7.17 – 7.11 (m, 1H), 7.03 – 6.97 (m, 2H), 4.68 – 4.56 (m, 1H), 3.24 – 3.03 (m, 2H), 2.99 – 2.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 148.7, 140.3, 136.5, 132.5, 132.2, 132.0, 129.2, 128.8, 128.7, 127.9, 126.8, 124.7, 123.1, 122.7, 120.3, 119.1, 111.3, 111.2, 68.0, 35.1, 21.7.

*Absolute structure confirmed by X-ray crystallography

2-[4-(trifluoromethyl)phenyl]-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317b)



The title compound was prepared according to general procedure **D** from 3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-[4-(trifluoromethyl)phenyl]isoindolin-1-one (120 mg, 0.28 mmol), $Ca(NTf_2)_2$ (1.7 mg, 0.0028 mmol) and $n$$Bu_4NPF_6$ (1.1 mg, 0.0028 mmol) in HFIP (1.4 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (100 mg, 87%).

RF (1:1 EtOAc:Hex): 0.60

IR ν_{max} (cm^{-1}): 3258, 3014, 2939, 1664, 1320, 1113, 742

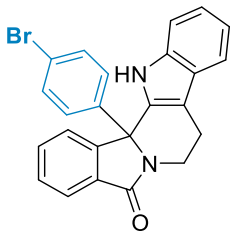
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{25}H_{18}F_3N_2O$ 419.1371; Found 419.1380

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.58 – 7.46 (m, 4H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.20 – 7.12 (m, 3H), 4.71 – 4.59 (m, 1H), 3.18 – 3.02 (m, 2H), 2.97 – 2.81 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.1, 148.0, 145.2, 136.6, 132.8, 131.2, 130.8, 129.3, 128.9 (q, *J* = 32.0 Hz), 128.1, 125.8 – 125.6 (m), 124.0, 124.0 (q, *J* = 272.3 Hz), 123.5, 122.2, 119.2, 118.6, 111.5, 109.3, 79.2, 67.0, 35.0, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8

2-(4-bromophenyl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317c)



The title compound was prepared according to general procedure **D** from 3-(4-bromophenyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (100 mg, 0.22 mmol), $Ca(NTf_2)_2$ (1.3 mg, 0.0022 mmol) and $n$$Bu_4NPF_6$ (0.9 mg, 0.0022 mmol) in HFIP (1.1 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as an off-white solid (90 mg, 94%).

RF (1:1 EtOAc:Hex): 0.57

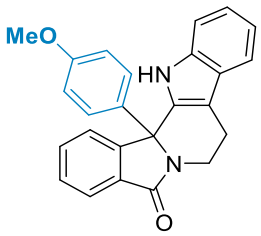
IR ν_{max} (cm^{-1}): 3263, 3058, 2932, 1661, 1487, 1340, 941

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{18}BrN_2O$ 429.0603; Found 429.0590

^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.98 – 7.87 (m, 1H), 7.63 – 7.57 (m, 1H), 7.56 – 7.49 (m, 3H), 7.43 – 7.33 (m, 3H), 7.25 – 7.20 (m, 1H), 7.19 – 7.11 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.72 – 4.53 (m, 1H), 3.17 – 2.99 (m, 2H), 2.97 – 2.74 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 148.2, 139.5, 136.6, 132.7, 132.0, 131.9, 131.5, 129.7, 129.4, 126.7, 124.8, 123.2, 123.1, 122.6, 120.5, 119.2, 111.4, 111.3, 67.5, 35.1, 21.6.

2-(4-methoxyphenyl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317d)



The title compound was prepared according to general procedure **D** from 3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-(4-methoxyphenyl)isoindolin-1-one (40 mg, 0.1 mmol), $Ca(NTf_2)_2$ (0.6 mg, 0.001 mmol) and $n$$Bu_4NPF_6$ (0.4 mg, 0.001 mmol) in HFIP (0.5 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a pale yellow solid (35 mg, 92%).

RF (1:1 EtOAc:Hex): 0.45

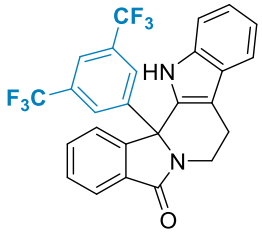
IR ν_{max} (cm^{-1}): 3230, 2935, 2840, 1643, 1662, 1508, 1394, 1252, 740

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{25}H_{21}N_2O_2$ 381.1603; Found 381.1592

^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.96 – 7.91 (m, 1H), 7.64 – 7.56 (m, 1H), 7.56 – 7.49 (m, 3H), 7.38 – 7.34 (m, 1H), 7.25 – 7.19 (m, 1H), 7.18 – 7.11 (m, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 4.68 – 4.53 (m, 1H), 3.76 (s, 3H), 3.22 – 2.99 (m, 2H), 2.92 – 2.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 159.9, 148.8, 136.5, 132.4, 132.4, 132.2, 132.1, 129.3, 129.1, 126.8, 124.6, 123.0, 122.7, 120.3, 119.1, 114.0, 111.3, 111.1, 67.6, 55.5, 35.0, 21.7.

2-[3,5-bis(trifluoromethyl)phenyl]-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317e)



The title compound was prepared according to general procedure **D** from 3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (57 mg, 0.11 mmol), $Ca(NTf_2)_2$ (0.7 mg, 0.0011 mmol) and nBu$_4$NPF$_6$ (0.4 mg, 0.0011 mmol) in HFIP (0.6 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (50 mg, 91%).

RF (1:1 EtOAc:Hex): 0.57

IR ν_{max} (cm^{-1}): 3263, 3056, 2950, 1675, 1370, 1277, 1172, 902

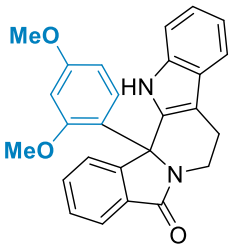
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{26}H_{17}F_6N_2O$ 487.1245; Found 487.1256

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (s, 1H), 8.19 (s, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.75 (td, *J* = 7.6, 1.2 Hz, 1H), 7.63 (td, *J* = 7.5, 0.8 Hz, 1H), 7.57 (s, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.09 – 7.02 (m, 1H), 4.55 – 4.43 (m, 1H), 3.10 – 2.97 (m, 1H), 2.97 – 2.78 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.4, 147.4, 144.0, 136.6, 133.2, 130.8 (q, *J* = 33.0 Hz), 130.5, 130.2, 129.7, 127.3, 127.3, 125.6, 123.8, 122.9 (q, *J* = 273.1 Hz), 122.9 (q, *J* = 3.6 Hz), 122.6, 119.4, 118.9, 111.6, 109.8, 66.7, 35.2, 21.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.7

2-(2,4-dimethoxyphenyl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317f)



The title compound was prepared according to general procedure **D** from 3-(2,4-dimethoxyphenyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (100 mg, 0.23 mmol), $Ca(NTf_2)_2$ (1.4 mg, 0.0023 mmol) and $n$$Bu_4NPF_6$ (0.9 mg, 0.0023 mmol) in HFIP (1.2 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (67 mg, 70%).

RF (1:1 EtOAc:Hex): 0.35

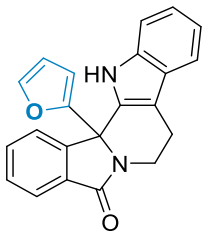
IR ν_{max} (cm^{-1}): 3194, 3055, 2842, 1657, 1576, 1265, 939

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{26}H_{23}N_2O_3$ 411.1709; Found 2411.1715

^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.89 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.47 – 7.40 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.15 – 7.09 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.38 – 6.29 (m, 2H), 4.70 – 4.59 (m, 1H), 3.76 (s, 3H), 3.30 (s, 3H), 3.24 – 3.02 (m, 2H), 2.91 – 2.74 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 161.7, 159.1, 149.6, 136.4, 133.0, 132.5, 132.0, 131.7, 128.1, 126.8, 124.1, 122.8, 121.1, 120.0, 119.9, 119.0, 111.3, 110.8, 103.8, 100.1, 66.9, 55.5, 55.4, 35.3, 21.7.

2-(2-furyl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317g)



The title compound was prepared according to general procedure **D** from 3-(2-furyl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (100 mg, 0.28 mmol), $Ca(NTf_2)_2$ (1.7 mg, 0.0028 mmol) and $n$$Bu_4NPF_6$ (1.1 mg, 0.0028 mmol) in HFIP (0.7 mL). Following completion of the reaction (1.5 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as an off-white solid (78 mg, 82%).

RF (1:1 EtOAc:Hex): 0.43

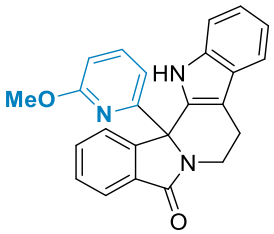
IR ν_{max} (cm^{-1}): 3256, 2920, 2846, 1655, 1398, 1146, 1014

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}N_2O_2$ 341.1290; Found 341.1301

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 (td, *J* = 7.5, 0.9 Hz, 2H), 7.38 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.36 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.20 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.80 – 4.71 (m, 1H), 3.41 (ddd, *J* = 13.4, 11.6, 4.9 Hz, 1H), 3.05 (ddd, *J* = 15.7, 11.6, 6.2 Hz, 1H), 2.93 – 2.81 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 152.2, 145.9, 143.7, 136.6, 132.4, 131.5, 131.0, 129.4, 126.6, 124.7, 123.1, 122.6, 120.2, 119.2, 111.4, 110.6, 110.5, 109.2, 63.7, 36.4, 21.8.

2-(6-methoxy-2-pyridyl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317h)



The title compound was prepared according to general procedure **D** from 3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-3-(6-methoxy-2-pyridyl)isoindolin-1-one (55 mg, 0.14 mmol), $Ca(NTf_2)_2$ (0.8 mg, 0.0014 mmol) and $n$$Bu_4NPF_6$ (0.5 mg, 0.0014 mmol) in 1,2-DCE (0.7 mL) at 80 °C. Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as an off-white solid (49 mg, 93%).

RF (1:1 EtOAc:Hex): 0.49

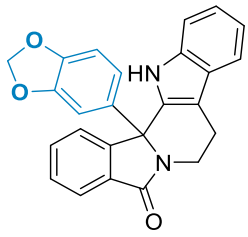
IR ν_{max} (cm^{-1}): 3324, 2946, 2892, 1655, 1573, 1415, 1267, 1033

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_2$ 382.1556; Found 382.1548

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.36 (m, 5H), 7.23 – 7.15 (m, 1H), 7.14 – 7.05 (m, 1H), 6.99 (dd, *J* = 7.4, 0.6 Hz, 1H), 6.67 (dd, *J* = 8.3, 0.6 Hz, 1H), 4.97 (dd, *J* = 13.3, 5.3 Hz, 1H), 4.18 (s, 3H), 3.42 (ddd, *J* = 13.1, 11.7, 4.6 Hz, 1H), 3.08 (ddd, *J* = 15.6, 11.6, 5.9 Hz, 1H), 2.85 (dd, *J* = 15.5, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 164.3, 156.9, 147.7, 140.3, 136.8, 133.3, 132.3, 130.6, 128.9, 126.6, 124.4, 123.3, 122.7, 120.0, 119.0, 111.3, 110.7, 110.3, 109.8, 67.9, 53.7, 37.7, 22.0.

2-(1,3-benzodioxol-5-yl)-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317i)



The title compound was prepared according to general procedure **D** from 3-(1,3-benzodioxol-5-yl)-3-hydroxy-2-[2-(1H-indol-3-yl)ethyl]isoindolin-1-one (100 mg, 0.24 mmol), $Ca(NTf_2)_2$ (1.5 mg, 0.0024 mmol) and $n$$Bu_4NPF_6$ (0.9 mg, 0.0024 mmol) in HFIP (1.2 mL). The reaction was stirred overnight. Purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a pale yellow solid (20 mg, 21%).

RF (1:1 EtOAc:Hex): 0.43

IR ν_{max} (cm^{-1}): 3252, 3056, 2920, 1659, 1485, 1398, 1236, 1111, 930

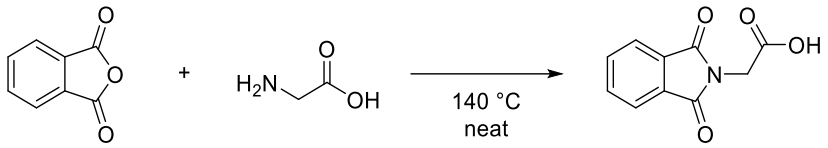
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{25}H_{19}N_2O_3$ 395.1396; Found 395.1405

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.44 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.71 (td, *J* = 7.5, 1.2 Hz, 1H), 7.58 (td, *J* = 7.4, 0.9 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.09 (m, 1H), 7.05 – 6.98 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.46 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.34 (d, *J* = 1.8 Hz, 1H), 5.99 (d, *J* = 0.7 Hz, 2H), 4.49 – 4.35 (m, 1H), 3.04 (ddd, *J* = 13.1, 10.4, 6.0 Hz, 2H), 2.92 – 2.75 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 148.6, 147.6, 147.3, 136.4, 134.3, 132.5, 132.1, 130.8, 129.0, 125.7, 124.0, 123.3, 122.1, 121.1, 119.0, 118.5, 111.4, 108.7, 108.0, 107.1, 101.4, 67.3, 34.7, 21.2.

9.3.4. Tethered Amides

(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid (Phthalimidoglycine) (323)



Glycine (1.05 g, 14.0 mmol, 1.0 equiv.) was added in one portion to phthalic anhydride (2.27 g, 15.4 mmol), 1.1 equiv.) at room temperature and heated at 140 °C for 30 minutes. The reaction mixture was cooled to room temperature and the resulting solid was purified by recrystallization (dissolved in hot IMS, followed by addition of H_2O) to give phthalimidoglycine (2.55 g, 12.4 mmol, 89%) as a colourless solid.

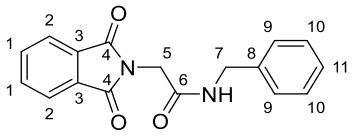
RF (9:1 DCM:MeOH): 0.05

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 – 7.87 (m, 4H), 4.32 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 167.2, 134.8, 131.4, 123.4.

*Data in accordance with literature[200]

N-benzyl-2-(1,3-dioxoisoindolin-2-yl) acetamide (324a)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (1.0 g, 4.90 mmol), HATU (2.2 g, 5.90 mmol), DIPEA (1.70 mL, 9.80 mmol), and benzylamine (0.60 mL, 5.40 mmol) in DMF (25 mL). Following completion of the reaction and work-up, purification by FCC (DCM:MeOH, 95:5) afforded the pure compound as an off-white solid (1.43 g, 68%).

RF (95:5 DCM:MeOH): 0.51

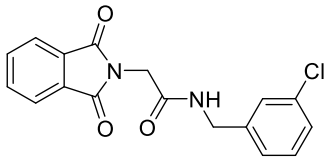
IR ν_{max} (cm^{-1}): 3480, 3286, 3065, 2920, 1776, 1720, 1418, 1115

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_3$ 295.1083; Found 295.1092

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.81 (m, 2H, **H2**), 7.75 – 7.69 (m, 2H, **H1**), 7.35 – 7.27 (m, 2H, **H10**), 7.26 – 7.21 (m, 3H, **H9, H11**), 6.24 (s, 1H, **NH**), 4.43 (d, *J* = 5.7 Hz, 2H, **H7**), 4.35 (s, 2H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (**C4**), 166.1 (**C6**), 137.7 (**C8**), 134.4 (**C1**), 132.1 (**C3**), 128.9 (**C10**), 127.9 (**C9**), 127.8 (**C11**), 123.8 (**C2**), 43.9 (**C7**), 40.9 (**C5**).

N-[(3-chlorophenyl)methyl]-2-(1,3-dioxoisoindolin-2-yl)acetamide (324b)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (200 mg, 0.98 mmol), HATU (440 mg, 1.20 mmol), DIPEA (0.34 mL, 1.95 mmol), and 3-chlorobenzylamine (0.16 mL, 1.10 mmol) in DMF (5 mL). Following completion of the reaction and work-up, purification by FCC (DCM:MeOH, 98:2) afforded the pure compound as a white solid (190 mg, 59%).

RF (95:5 DCM:MeOH): 0.57

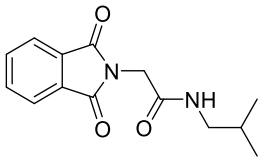
IR ν_{max} (cm^{-1}): 3283, 3062, 1774, 1724, 1653, 1551, 1418, 952

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}ClN_2O_3$ 329.0693; Found 329.0682

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.87 (m, 2H), 7.81 – 7.72 (m, 2H), 7.28 – 7.24 (m, 3H), 7.19 – 7.14 (m, 1H), 6.07 (s, 1H), 4.45 (d, *J* = 5.9 Hz, 2H), 4.39 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 166.2, 139.7, 134.7, 134.5, 132.1, 130.2, 128.0, 128.0, 126.0, 123.9, 43.4, 41.1.

2-(1,3-dioxoisoindolin-2-yl)-N-isobutyl-acetamide (324c)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (200 mg, 0.98 mmol), HATU (440 mg, 1.20 mmol), DIPEA (0.34 mL, 1.95 mmol), and isobutylamine (91 µL, 0.91 mmol) in DMF (5 mL). Following completion of the reaction and work-up, purification by FCC (DCM:MeOH, 95:5) afforded the pure compound a white solid (170 mg, 67%).

RF (95:5 DCM:MeOH): 0.50

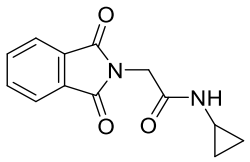
IR ν_{max} (cm^{-1}): 3297, 2958, 1771, 1718, 1416, 1254, 951

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2O_3$ 261.1239; Found 261.1230

^1H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.86 (m, 2H), 7.77 – 7.72 (m, 2H), 5.83 (s, 1H), 4.33 (s, 2H), 3.11 (dd, *J* = 6.6, 6.2 Hz, 2H), 1.78 (hept, *J* = 6.7 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 166.1, 134.4, 132.2, 123.8, 47.3, 41.1, 28.6, 20.2.

N-cyclopropyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (324d)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (200 mg, 0.98 mmol), HATU (440 mg, 1.20 mmol), DIPEA (0.34 mL, 1.95 mmol), and cyclopropylamine (75 µL, 1.10 mmol) in DMF (5 mL). Following completion of the reaction and work-up, purification by FCC (DCM:MeOH, 95:5) afforded the pure compound as an off-white solid (170 mg, 71%).

RF (95:5 DCM:MeOH): 0.30

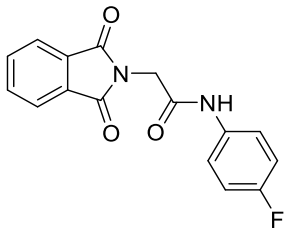
IR ν_{max} (cm^{-1}): 3282, 2920, 1772, 1715, 1318, 1115, 949

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_2O_3$ 245.0926; Found 245.0927

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, *J* = 3.7 Hz, 1H), 7.93 – 7.83 (m, 4H), 4.13 (s, 2H), 2.66 – 2.58 (m, 1H), 0.61 (td, *J* = 7.0, 4.8 Hz, 2H), 0.44 – 0.37 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.5, 167.0, 134.6, 131.8, 123.2, 38.2, 22.3, 5.5.

2-(1,3-dioxoisoindolin-2-yl)-N-(4-fluorophenyl)acetamide (324e)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (200 mg, 0.98 mmol), HATU (440 mg, 1.20 mmol), DIPEA (0.34 mL, 1.95 mmol), and 4-fluoroaniline (0.10 mL, 1.10 mmol) in DMF (5 mL). Following completion of the reaction and work-up, purification by FCC (DCM:EtOAc, 3:1) afforded the pure compound as a white solid (147 mg, 51%).

RF (95:5 DCM:MeOH): 0.53

IR ν_{max} (cm^{-1}): 3263, 3075, 1776, 1716, 1511, 1221, 952

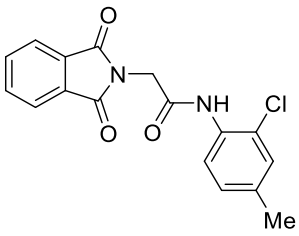
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}FN_2O_3$ 299.0832; Found 299.0827

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.86 (m, 2H), 7.81 – 7.71 (m, 2H), 7.60 (s, 1H), 7.50 – 7.39 (m, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 4.50 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.5, 164.8, 158.2 (d, *J* = 240.1 Hz), 134.9 (d, *J* = 2.5 Hz), 134.7, 131.6, 123.3, 121.0 (d, *J* = 7.9 Hz), 115.4 (d, *J* = 22.3 Hz), 40.7.

^{19}F NMR (376 MHz, CDCl3): δ -117.3

N-(2-chloro-4-methyl-phenyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (324f)



The title compound was prepared according the General Procedure **E** from phthalimidoglycine (200 mg, 0.98 mmol), HATU (440 mg, 1.20 mmol), DIPEA (0.34 mL, 1.95 mmol), and 2-chloro-4-methylaniline (0.13 mL, 1.10 mmol) in DMF (5 mL). Following completion of the reaction and work-up, purification by FCC (DCM:EtOAc, 3:1) afforded the pure compound as a white solid (148 mg, 46%).

RF (95:5 DCM:MeOH): 0.77

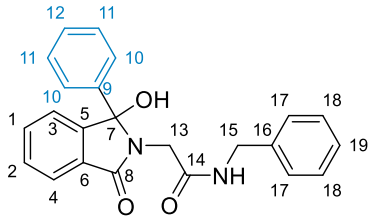
IR ν_{max} (cm^{-1}): 3248, 3047, 1769, 1722, 1668, 1538, 1412, 949

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}ClN_2O_3$ 329.0693; Found 329.0685

^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.94 – 7.90 (m, 2H), 7.86 (s, 1H), 7.79 – 7.75 (m, 2H), 7.18 (d, *J* = 1.0 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.4 Hz, 1H), 4.56 (s, 2H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 164.1, 135.4, 134.5, 132.1, 131.5, 129.5, 128.52, 123.9, 122.7, 121.7, 41.8, 20.8.

N-benzyl-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (327a)



The title compound was prepared according to general procedure **B** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (500 mg, 1.70 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 1.70 mL, 5.10 mmol) in THF (9 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a yellow solid (414 mg, 65%).

RF (1:1 EtOAc:Hex): 0.30

IR ν_{max} (cm^{-1}): 3289, 3062, 2922, 1638, 1541, 1370, 1055, 934

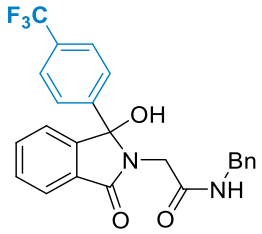
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{23}H_{19}N_2O_2$ 355.1477; Found 355.1487

^1H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.61 (m, 1H, **H3**), 7.51 (td, *J* = 7.5, 1.2 Hz, 1H, **H1**), 7.46 – 7.40 (m, 1H, **H2**), 7.40 – 7.30 (m, 6H, **ArH**), 7.28 – 7.18 (m, 5H, **ArH**), 6.69 (s, 1H, **OH**), 4.55 (d, *J* = 16.5 Hz, 1H, **H13$_A$**), 4.43 (dd, *J* = 14.7, 5.9 Hz, 1H **H15$_A$**), 4.33 (dd, *J* = 14.7, 5.3 Hz, 1H, **H15$_B$**), 3.57 (d, *J* = 16.4 Hz, 1H, **H13$_B$**), 0.94 – 0.85 (m, 1H, **NH**).

4.38 (ddd, *J* = 41.3, 14.7, 5.6 Hz, 2H),

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 169.0, 150.1 (**C5**), 139.0 (**ArC**), 137.3 (**ArC**), 133.4 (**ArC**), 129.3 (**ArC**), 129.1 (**ArC**), 128.8 (**ArC**), 128.8 (**ArC**), 128.8 (**ArC**), 128.0 (**ArC**), 127.7 (**ArC**), 126.4 (**ArC**), 123.5 (**ArC**), 123.0 (**ArC**), 91.2 (**C7**), 44.2 (**C13**), 43.5 (**C15**).

N-benzyl-2-[1-hydroxy-3-oxo-1-[4-(trifluoromethyl)phenyl]isoindolin-2-yl]acetamide (327b)



The title compound was prepared according to general procedure **B** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (200 mg, 0.68 mmol), (4-(trifluoromethyl)phenyl)magnesium bromide (0.5 M in THF, 4.0 mL, 2.04 mmol), in DCM (3 mL). The Grignard reagent was freshly prepared from magnesium turnings (51 mg, 2.11 mmol), 4-bromobenzotrifluoride (460 mg, 2.04 mmol) and 1,2-dibromoethane (6 µL, 0.0068 mmol) in THF (2 mL). Following completion of the reaction (2 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (193 mg, 64%).

RF (1:1 EtOAc:Hex): 0.36

IR ν_{max} (cm^{-1}): 3297, 3055, 2889, 2822, 1690, 1644, 1323, 1109, 1068

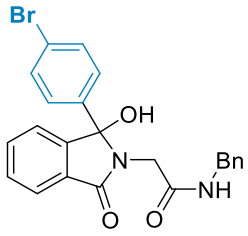
HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{18}F_3N_2O_2$ 423.1320; Found 423.1310

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.75 (m, 1H), 7.63 – 7.55 (m, 4H), 7.55 – 7.45 (m, 2H), 7.36 – 7.26 (m, 5H), 6.41 (s, 1H), 6.37 (s, 1H), 4.52 (d, *J* = 16.3 Hz, 1H), 4.49 – 4.39 (m, 2H), 3.53 (d, *J* = 16.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 168.9, 149.6, 143.4, 137.0, 133.6, 131.0 (q, *J* = 32.4 Hz), 129.6, 129.0, 128.9, 128.0, 127.9, 127.0, 125.9 (q, *J* = 3.5 Hz), 124.0 (q, *J* = 272.3 Hz), 123.7, 123.0, 90.6, 44.4, 43.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.7

N-benzyl-2-[1-(4-bromophenyl)-1-hydroxy-3-oxo-isoindolin-2-yl]acetamide (327c)



The title compound was prepared according to general procedure **B** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (400 mg, 1.36 mmol), 4-bromophenylmagnesium bromide (0.5 M in THF, 8.0 mL, 4.08 mmol), in DCM (6 mL). The Grignard reagent was freshly prepared from magnesium turnings (102 mg, 4.21 mmol), 1,4-dibromobenzene (960 mg, 4.08 mmol) and 1,2-dibromoethane (12 µL, 0.0136 mmol) in THF (4 mL). Following completion of the reaction (30 mins), purification by FCC (1:3 EtOAc:DCM, 1% NEt_3) afforded the pure product as a white solid (270 mg, 44%).

RF (1:1 EtOAc:Hex): 0.33

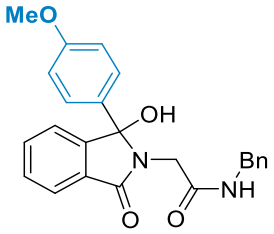
IR ν_{max} (cm^{-1}): 3297, 3066, 2982, 1690, 1644, 1379, 1060, 937

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{23}H_{18}BrN_2O_2$ 433.0552; Found 433.0564

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.32 – 7.21 (m, 8H), 7.15 (t, *J* = 5.6 Hz, 1H), 6.78 (s, 1H), 4.55 (d, *J* = 16.4 Hz, 1H), 4.45 (dd, *J* = 14.7, 5.9 Hz, 1H), 4.34 (dd, *J* = 14.7, 5.2 Hz, 1H), 3.55 (d, *J* = 16.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 168.9, 149.7, 138.3, 137.1, 133.5, 132.0, 129.5, 128.9, 128.9, 128.3, 128.0, 127.8, 126.4, 123.6, 123.0, 90.8, 44.3, 43.4.

N-benzyl-2-[1-hydroxy-1-(4-methoxyphenyl)-3-oxo-isoindolin-2-yl]acetamide (327d)



The title compound was prepared according to general procedure **B** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (200 mg, 0.68 mmol), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 4.0 mL, 2.04 mmol), in DCM (3 mL). The Grignard reagent was freshly prepared from magnesium turnings (51 mg, 2.11 mmol), 4-bromoanisole (381 mg, 0.26 mL, 2.04 mmol) and 1,2-dibromoethane (6 µL, 0.0068 mmol) in THF (2 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:DCM, 1% NEt_3) afforded the pure product as a white solid (165 mg, 60%).

RF (1:1 EtOAc:Hex): 0.27

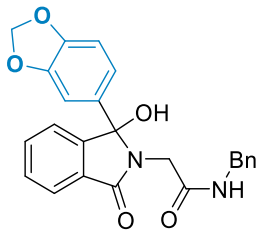
IR ν_{max} (cm^{-1}): 3286, 3062, 2932, 2837, 1638, 1608, 1249, 1170

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{21}N_2O_3$ 385.1552; Found 385.1555

^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.4 Hz, 1H), 7.49 (td, *J* = 7.5, 1.2 Hz, 1H), 7.41 (td, *J* = 7.5, 1.0 Hz, 1H), 7.31 – 7.26 (m, 4H), 7.25 – 7.18 (m, 4H), 7.10 (t, *J* = 5.5 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.51 (s, 1H), 4.49 (d, *J* = 16.4 Hz, 1H), 4.42 (dd, *J* = 14.7, 5.9 Hz, 1H), 4.32 (dd, *J* = 14.7, 5.3 Hz, 1H), 3.79 (s, 3H), 3.56 (d, *J* = 16.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 168.9, 159.9, 150.3, 137.3, 133.3, 130.8, 129.2, 129.1, 128.8, 128.0, 127.8, 127.7, 123.5, 123.0, 114.2, 91.1, 55.4, 44.2, 43.4.

2-[1-(1,3-benzodioxol-5-yl)-1-hydroxy-3-oxo-isoindolin-2-yl]-N-benzyl-acetamide (327e)



The title compound was prepared according to general procedure **C** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (500 mg, 1.70 mmol), 1-bromo-3,4-(methylenedioxy)benzene (478 mg, 0.29 mL, 2.40 mmol) and n-butyllithium (2.5 M in Hexane, 0.82 mL, 2.04 mmol) in THF (6 mL). Following completion of the reaction (1 h), purification by FCC (1:3 EtOAc:DCM, 1% NEt_3) afforded the pure product as a yellow solid (108 mg, 38%).

RF (1:1 EtOAc:Hex): 0.21

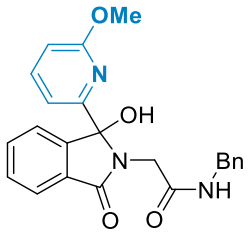
IR ν_{max} (cm^{-1}): 3286, 3081, 2900, 1687, 1638, 1374, 1239, 1034

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{24}H_{19}N_2O_4$ 399.1345; Found 399.1352

^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.26 – 7.21 (m, 3H), 6.97 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.81 – 6.73 (m, 3H), 6.38 (s, 1H), 5.95 (dd, *J* = 6.6, 1.4 Hz, 2H), 4.50 (d, *J* = 16.4 Hz, 1H), 4.47 – 4.32 (m, 2H), 3.60 (d, *J* = 16.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 168.7, 150.1, 148.2, 148.0, 137.2, 133.4, 132.9, 129.3, 129.1, 128.9, 128.0, 127.9, 123.6, 122.9, 120.2, 108.4, 107.0, 101.5, 91.0, 44.3, 43.4.

N-benzyl-2-[1-hydroxy-1-(6-methoxy-2-pyridyl)-3-oxo-isoindolin-2-yl]acetamide (327f)



The title compound was prepared according to general procedure **C** from N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (300 mg, 1.02 mmol), 2-bromo-6-methoxypyridine (770 mg, 0.50 mL, 4.09 mmol) and n-butyllithium (2.5 M in Hexane, 1.43 mL, 3.57 mmol) in THF (8 mL). Following completion of the reaction (1 h), purification by FCC (1:3 EtOAc:DCM, 1% NEt_3) afforded the pure product as a yellow solid (63 mg, 15%).

RF (1:1 EtOAc:Hex): 0.15

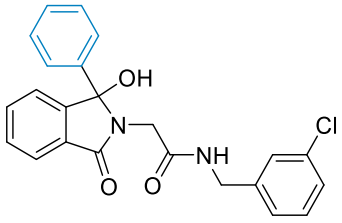
IR ν_{max} (cm^{-1}): 3286, 2928, 1707, 1638, 1467, 1267, 1027, 803

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{23}H_{20}N_3O_3$ 386.1505; Found 386.1492

^1H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.86 (m, 1H), 7.62 – 7.49 (m, 3H), 7.36 – 7.29 (m, 3H), 7.28 – 7.18 (m, 3H), 6.93 (s, 1H), 6.78 (dd, *J* = 8.3, 0.6 Hz, 1H), 6.68 (s, 1H), 6.61 (dd, *J* = 7.4, 0.6 Hz, 1H), 4.42 (dd, *J* = 5.9, 1.6 Hz, 2H), 4.38 (d, *J* = 16.8 Hz, 1H), 4.01 (s, 3H), 3.61 (d, *J* = 16.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 168.6, 163.5, 153.5, 147.8, 140.8, 138.1, 133.3, 130.4, 130.1, 128.8, 127.7, 127.5, 123. 9, 122.8, 113.3, 111.7, 90.0, 54.0, 43.7, 43.6.

N-[(3-chlorophenyl)methyl]-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (327g)



The title compound was prepared according to general procedure **B** from N-[(3-chlorophenyl)methyl]-2-(1,3-dioxoisoindolin-2-yl)acetamide (150 mg, 0.46 mmol),

phenylmagnesium bromide (3.0 M in Et_2O, 0.46 mL, 1.37 mmol) in DCM (2 mL). Following completion of the reaction (1 h), purification by FCC (1:5 EtOAc:DCM, 1% NEt_3) afforded the pure product as a white solid (104 mg, 56%).

RF (1:1 EtOAc:Hex): 0.27

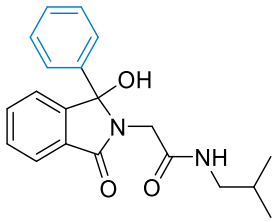
IR ν_{max} (cm^{-1}): 3289, 2920, 1702, 1638, 1541, 1420, 1055, 768

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{23}H_{18}ClN_2O_2$ 389.1057; Found 389.1045

^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.3 Hz, 1H), 7.46 (td, *J* = 7.4, 1.1 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.29 (m, 4H), 7.25 – 7.20 (m, 3H), 7.16 – 7.09 (m, 1H), 6.68 (s, 1H), 4.50 (d, *J* = 16.4 Hz, 1H), 4.44 (dd, *J* = 15.0, 6.1 Hz, 1H), 4.34 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.60 (d, *J* = 16.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 172.4, 145.4, 138.1, 136.2, 134.3, 132.9, 132.2, 130.9, 130.0, 129.7, 129.5, 127.6, 127.2, 126.9, 125.2, 125.0, 125.0, 86.6, 46.3, 44.8.

2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)-N-isobutyl-acetamide (327h)



The title compound was prepared according to general procedure **B** from 2-(1,3-dioxoisoindolin-2-yl)-N-isobutyl-acetamide (150 mg, 0.58 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 0.6 mL, 1.73 mmol) in DCM (3 mL). Following completion of the reaction (1 h), purification by FCC (1:5 EtOAc:DCM, 1% NEt_3) afforded the pure product as a pale yellow solid (115 mg, 59%).

RF (1:1 EtOAc:Hex): 0.30

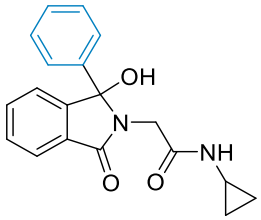
IR ν_{max} (cm^{-1}): 3293, 2958, 2924, 1709, 1638, 1368, 934

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1603; Found 321.1591

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.75 (m, 1H), 7.52 (td, *J* = 7.4, 1.3 Hz, 1H), 7.46 (td, *J* = 7.4, 1.1 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.37 – 7.29 (m, 4H), 6.58 (s, 1H), 6.50 (s, 1H), 4.51 (d, *J* = 16.2 Hz, 1H), 3.55 (d, *J* = 16.2 Hz, 1H), 3.16 – 2.98 (m, 2H), 1.76 (hept, *J* = 6.7 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 168.9, 150.3, 139.2, 133.4, 129.3, 129.3, 128.8, 128.8, 126.5, 123.5, 123.1, 91.0, 47.6, 43.6, 28.5, 20.2.

N-cyclopropyl-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (327i)



The title compound was prepared according to general procedure **B** from N-cyclopropyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (150 mg, 0.61 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 0.6 mL, 1.84 mmol) in DCM (3 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:DCM, 1% NEt_3) afforded the pure product as a yellow oil (80 mg, 40%).

RF (1:1 EtOAc:Hex): 0.12

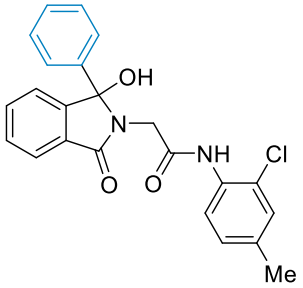
IR ν_{max} (cm^{-1}): 3267, 3058, 2924, 1705, 1648, 1370, 1054, 934

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1290; Found 305.1303

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.1 Hz, 1H), 7.54 (td, *J* = 7.4, 1.3 Hz, 1H), 7.49 (td, *J* = 7.4, 1.2 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.31 (m, 4H), 6.51 (s, 1H), 6.36 (s, 1H), 4.44 (d, *J* = 16.3 Hz, 1H), 3.53 (d, *J* = 16.2 Hz, 1H), 2.77 – 2.68 (m, 1H), 0.83 – 0.70 (m, 2H), 0.62 – 0.48 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 171.5, 168.8, 150.2, 139.1, 133.4, 129.4, 129.3, 128.8, 128. 8, 126.4, 123.5, 123.1, 91.1, 43.4, 38.8, 23.1, 6.5, 6.5.

N-(2-chloro-4-methyl-phenyl)-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (327j)



The title compound was prepared according to general procedure **B** from N-(2-chloro-4-methyl-phenyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (120 mg, 0.37 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 0.37 mL, 1.10 mmol) in DCM (2 mL). Following completion of the reaction (30 mins), purification by FCC (1:9 EtOAc:DCM, 1% NEt_3) afforded the pure product as a white solid (104 mg, 56%).

RF (1:1 EtOAc:Hex): 0.39

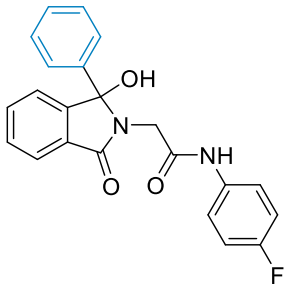
IR ν_{max} (cm^{-1}): 3293, 3032, 2917, 1694, 1670, 1523, 1295, 936

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{23}H_{18}ClN_2O_2$ 389.1057; Found 389.1066

^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.97 (s, 1H), 7.88 (d, *J* = 6.7 Hz, 1H), 7.55 (td, *J* = 7.4, 1.4 Hz, 1H), 7.50 (td, *J* = 7.4, 1.3 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.41 – 7.30 (m, 4H), 7.17 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 4.82 (s, 1H), 4.62 (d, *J* = 16.5 Hz, 1H), 3.77 (d, *J* = 16.4 Hz, 1H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 168.1, 149.8, 145.3, 138.5, 133.5, 129.7, 129.6, 129.4, 129.2, 128.9, 128.5, 126.4, 123.9, 123.2, 123.1, 122.1, 91.1, 44.2, 31.1, 20.8.

N-(4-fluorophenyl)-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (327k)



The title compound was prepared according to general procedure **B** from 2-(1,3-dioxoisoindolin-2-yl)-N-(4-fluorophenyl)acetamide (100 mg, 0.34 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 0.34 mL, 1.01 mmol) in DCM (2 mL). Following completion of the reaction (30 mins), purification by FCC (1:5 EtOAc:DCM, 1% NEt_3) afforded the pure product as a colourless oil (80 mg, 63%).

RF (1:5 EtOAc:DCM): 0.40

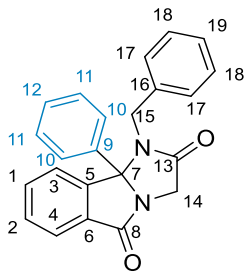
IR ν_{max} (cm^{-1}): 3360, 3159, 3090, 2926, 1681, 1507, 1215, 1057

HRMS (APCI)m/z: $[M - H_2O]^+$ Calcd for $C_{22}H_{16}FN_2O_2$ 359.1196; Found 359.1209

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.54 (td, *J* = 7.5, 1.1 Hz, 1H), 7.47 (td, *J* = 7.5, 0.9 Hz, 1H), 7.41 – 7.27 (m, 8H), 6.83 (t, *J* = 8.7 Hz, 2H), 6.40 (s, 1H), 4.68 (d, *J* = 16.6 Hz, 1H), 3.74 (d, *J* = 16.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.6, 168.3, 159.6 (d, *J* = 244.0 Hz), 150.3, 138.5, 133.7, 133.5, 133.4, 129.6, 129.1, 129.0, 128.9, 126.4, 123.4, 123.3, 121.9 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 22.5 Hz), 91.5, 44.3.

1-benzyl-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328a)



The title compound was prepared according to general procedure **F** from 2-[1-(1,3-benzodioxol-5-yl)-1-hydroxy-3-oxo-isoindolin-2-yl]-N-benzyl-acetamide (70 mg, 0.168 mmol), $Ca(NTf_2)_2$ (20 mg, 0.034 mmol) and $n$$Bu_4NPF_6$ (10 mg, 0.034 mmol) in 1,2-DCE

(0.7 mL). Following completion of the reaction (15 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (62 mg, 42%).

RF (1:9 EtOAc:DCM): 0.59

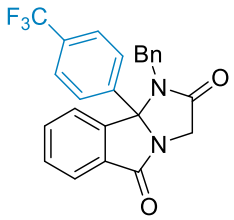
IR ν_{max} (cm^{-1}): 2911, 2853, 1709, 1388, 1079, 872

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_2$ 355.1447; Found 355.1460

^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 1H, **H4**), 7.51 (td, *J* = 7.5, 0.9 Hz, 1H, **H1**), 7.45 – 7.37 (m, 3H, **ArH**), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H, **H2**), 7.16 (d, *J* = 7.7 Hz, 1H, **H3**), 7.10 – 7.00 (m, 5H, **ArH**), 6.82 – 6.77 (m, 2H, **ArH**), 5.31 (d, *J* = 16.0 Hz, 1H, **H15$_A$**), 4.64 (d, *J* = 16.4 Hz, 1H, **H14$_A$**), 4.28 (d, *J* = 16.0 Hz, 1H, **H15$_B$**), 3.77 (d, *J* = 16.4 Hz, 1H, **H14$_B$**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (**C13**), 172.3 (**C8**), 145.5 (**C5**), 136.5 (**ArC**), 136.0 (**ArC**), 132.8 (**ArC**), 132.3 (**ArC**), 130.6 (**ArC**), 129.8 (**ArC**), 129.4 (**ArC**), 128.4 (**ArC**), 127.3 (**ArC**), 126.9 (**ArC**), 126.9 (**ArC**), 125.2 (**ArC**), 125.0 (**ArC**), 86.7 (**C7**), 46.4 (**C14**), 45.4 (**C15**).

1-benzyl-9b-[4-(trifluoromethyl)phenyl]-3H-imidazo[2,1-a]isoindole-2,5-dione (328b)



The title compound was prepared according to general procedure **F** from N-benzyl-2-[1-hydroxy-3-oxo-1-[4-(trifluoromethyl)phenyl]isoindolin-2-yl]acetamide (80 mg, 0.182 mmol), $Ca(NTf_2)_2$ (22 mg, 0.036 mmol) and $n$$Bu_4NPF_6$ (14 mg, 0.036 mmol) in 1,2-DCE (0.9 mL). Following completion of the reaction (2 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (56 mg, 73%).

RF (1:1 EtOAc:Hex): 0.70

IR ν_{max} (cm^{-1}): 3027, 2948, 2922, 1710, 1399, 1320, 760

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{18}F_3N_2O_2$ 423.1230; Found 423.1236

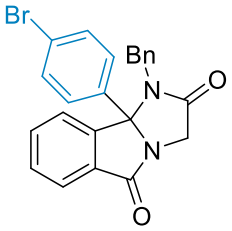
^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.54 (td, *J* = 7.6, 0.9 Hz, 1H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.7 Hz,

1H), 7.10 – 6.99 (m, 3H), 6.82 – 6.75 (m, 2H), 5.30 (d, *J* = 15.9 Hz, 1H), 4.66 (d, *J* = 16.5 Hz, 1H), 4.31 (d, *J* = 15.9 Hz, 1H), 3.74 (d, *J* = 16.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.0, 144.9, 140.9, 135.6, 133.2, 132.1, 132.1 (d, *J* = 32.7 Hz), 131.0, 128.5, 127.5, 127.5, 127.0, 126.4 (q, *J* = 3.7 Hz), 125.3, 125.0, 86.1, 46.3, 45.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9

1-benzyl-9b-(4-bromophenyl)-3H-imidazo[2,1-a]isoindole-2,5-dione (328c)



The title compound was prepared according to general procedure **F** from N-benzyl-2-[1-(4-bromophenyl)-1-hydroxy-3-oxo-isoindolin-2-yl]acetamide (70 mg, 0.155 mmol), $Ca(NTf_2)_2$ (19 mg, 0.031 mmol) and *n*Bu_4NPF_6 (12 mg, 0.031 mmol) in 1,2-DCE (0.8 mL). Following completion of the reaction (2 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (58 mg, 86%).

RF (1:1 EtOAc:Hex): 0.73

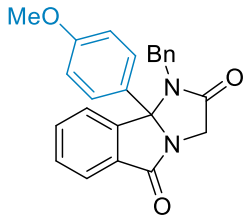
IR ν_{max} (cm^{-1}): 3032, 2924, 2249, 1707, 1392, 870

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}BrN_2O_2$ 433.0552; Found 433.0561

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 3H), 7.41 – 7.33 (m, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.07 – 6.99 (m, 3H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.84 – 6.74 (m, 2H), 5.26 (d, *J* = 15.9 Hz, 1H), 4.63 (d, *J* = 16.5 Hz, 1H), 4.27 (d, *J* = 15.9 Hz, 1H), 3.73 (d, *J* = 16.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.0, 145.0, 135.7, 133.0, 132.5, 132.0, 130.8, 128.6, 128.4, 127.4, 126.9, 125.1, 125.0, 124.2, 86.2, 77.4, 46.2, 45.2.

1-benzyl-9b-(4-methoxyphenyl)-3H-imidazo[2,1-a]isoindole-2,5-dione (328d)



The title compound was prepared according to general procedure **F** from N-benzyl-2-[1-hydroxy-1-(4-methoxyphenyl)-3-oxo-isoindolin-2-yl]acetamide (80 mg, 0.20 mmol), $Ca(NTf_2)_2$ (24 mg, 0.040 mmol) and nBu$_4$NPF$_6$ (15 mg, 0.040 mmol) in 1,2-DCE (1.0 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (61 mg, 80%).

RF (1:1 EtOAc:Hex): 0.52

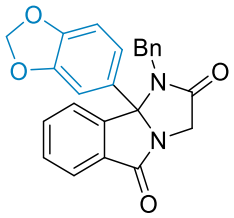
IR ν_{max} (cm^{-1}): 3021, 2922, 2838, 1707, 1418, 1397, 1258, 1028

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2O_3$ 385.1552; Found 285.1545

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.5 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz, 1H), 7.34 (td, *J* = 7.6, 1.1 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.05 – 7.02 (m, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.83 – 6.75 (m, 2H), 5.27 (d, *J* = 16.0 Hz, 1H), 4.63 (d, *J* = 16.4 Hz, 1H), 4.26 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H), 3.77 (d, *J* = 16.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 172.3, 160.7, 145.6, 136.1, 132.8, 132.3, 130.6, 128.4, 128.4, 128.1, 127.3, 126.9, 125.1, 125.0, 114.7, 86.6, 55.6, 46.3, 45.3.

9b-(1,3-benzodioxol-5-yl)-1-benzyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328e)



The title compound was prepared according to general procedure **F** from N-benzyl-2-[1-hydroxy-3-oxo-1-[4-(trifluoromethyl)phenyl]isoindolin-2-yl]acetamide (80 mg, 0.182 mmol), $Ca(NTf_2)_2$ (22 mg, 0.036 mmol) and nBu$_4$NPF$_6$ (14 mg, 0.036 mmol) in 1,2-DCE (0.9 mL). Following completion of the reaction (30 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (56 mg, 84%).

RF (1:1 EtOAc:Hex): 0.48

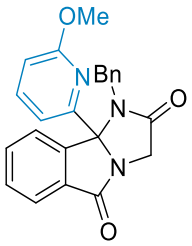
IR ν_{max} (cm^{-1}): 2994, 2906, 1716, 1702, 1489, 1313, 1251, 926

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O_4$ 399.1345; Found 399.1338

^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.50 (td, *J* = 7.6, 0.9 Hz, 1H), 7.35 (td, *J* = 7.6, 1.1 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.78 – 6.75 (m, 1H), 6.62 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 5.99 (s, 2H), 5.26 (d, *J* = 16.0 Hz, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 4.27 (d, *J* = 16.0 Hz, 1H), 3.77 (d, *J* = 16.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 172.2, 149.0, 148.8, 145.4, 136.0, 132.8, 132.2, 130.7, 130.2, 128.4, 127.3, 126.9, 125.1, 125.0, 120.7, 108.6, 107.5, 101.9, 86.6, 46.3, 45.3.

1-benzyl-9b-(6-methoxy-2-pyridyl)-3H-imidazo[2,1-a]isoindole-2,5-dione (328f)



The title compound was prepared according to general procedure **F** from N-benzyl-2-[1-hydroxy-3-oxo-1-[4-(trifluoromethyl)phenyl]isoindolin-2-yl]acetamide (35 mg, 0.087 mmol), $Ca(NTf_2)_2$ (10 mg, 0.0017 mmol) and $n$$Bu_4NPF_6$ (7 mg, 0.0017 mmol) in 1,2-DCE (0.4 mL). Following completion of the reaction (2h), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a pale yellow oil (25mg, 75%).

RF (1:1 EtOAc:Hex): 0.58

IR ν_{max} (cm^{-1}): 3030, 2932, 2857, 1707, 1575, 1467, 1388, 706

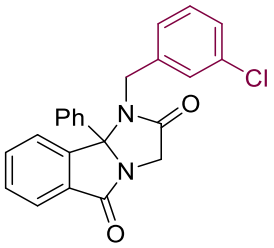
HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}N_3O_3$ 386.1505; Found 386.1510

^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.44 – 7.39 (m, 1H), 7.10 – 7.00 (m, 3H), 6.88 (dd, *J* = 6.4, 3.1 Hz, 2H), 6.79 – 6.69 (m, 2H), 5.09 (d, *J* =

16.1 Hz, 1H), 4.64 (d, *J* = 15.9 Hz, 1H), 4.51 (d, *J* = 16.1 Hz, 1H), 4.02 (d, *J* = 15.9 Hz, 1H), 3.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 172.7, 164.2, 153.1, 143.8, 139.8, 136.6, 132.5, 132.4, 130.6, 128.3, 127.2, 127.2, 125. 4, 125.2, 113.9, 112.2, 85.7, 53.9, 47.6, 45.6.

1-[(3-chlorophenyl)methyl]-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328g)



The title compound was prepared according to general procedure **F** from N-[(3-chlorophenyl)methyl]-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (44 mg, 0.108 mmol), $Ca(NTf_2)_2$ (13 mg, 0.022 mmol) and $n$$Bu_4NPF_6$ (8 mg, 0.022 mmol) in 1,2-DCE (0.6 mL). Following completion of the reaction (40 mins), purification by FCC (1:1 EtOAc:Hex) afforded the pure compound as a white solid (34 mg, 81%).

RF (1:1 EtOAc:Hex): 0.58

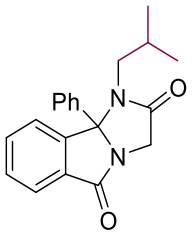
IR ν_{max} (cm^{-1}): 3058, 2924, 1707, 1597, 1467, 1388, 939

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}ClN_2O_2$ 389.1057; Found 389.1062

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.92 (m, 1H), 7.55 (td, *J* = 7.5, 0.9 Hz, 1H), 7.48 – 7.36 (m, 4H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.10 – 7.05 (m, 2H), 7.05 – 7.00 (m, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.5 Hz, 1H), 4.24 (d, *J* = 16.1 Hz, 1H), 3.77 (d, *J* = 16.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 145.4, 138.1, 136.2, 134.3, 132.9, 132.2, 130.9, 130.0, 130.8, 129.5, 127.8, 127.6, 127.2, 126.9, 125.2, 125.0, 125.0, 86.6, 46.3, 44.8.

1-isobutyl-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328h)



The title compound was prepared according to general procedure **F** from 2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)-N-isobutyl-acetamide (60 mg, 0.18 mmol), $Ca(NTf_2)_2$ (21 mg, 0.036 mmol) and $n$$Bu_4NPF_6$ (14 mg, 0.036 mmol) in 1,2-DCE (0.9 mL). Following completion of the reaction (1.5 h), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a white solid (46 mg, 81%).

RF (1:1 EtOAc:Hex): 0.58

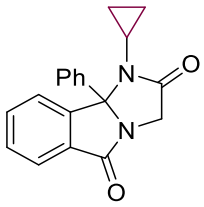
IR ν_{max} (cm^{-1}): 2932, 2904, 2868, 1711, 1450, 1346, 915

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1603; Found 321.1597

^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (ddd, *J* = 5.6, 3.1, 0.7 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.45 – 7.33 (m, 4H), 7.01 (dd, *J* = 8.1, 1.6 Hz, 2H), 4.54 (d, *J* = 16.3 Hz, 1H), 3.75 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.62 (d, *J* = 16.3 Hz, 1H), 2.94 (dd, *J* = 13.8, 6.8 Hz, 1H), 0.72 (d, *J* = 6.7 Hz, 3H), 0.52 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 172.6, 146.4, 136.9, 133.1, 132.8, 131.0, 129.7, 129.3, 126.9, 125.3, 124.8, 86.8, 50.0, 46.2, 28.1, 20.3, 20.1.

1-cyclopropyl-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328i)



The title compound was prepared according to general procedure **F** from N-cyclopropyl-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (40 mg, 0.12 mmol), $Ca(NTf_2)_2$ (15 mg, 0.025 mmol) and $n$$Bu_4NPF_6$ (10 mg, 0.025 mmol) in 1,2-DCE (0.6 mL). Following completion of the reaction (1 h), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a white solid (31 mg, 82%).

RF (1:1 EtOAc:Hex): 0.45

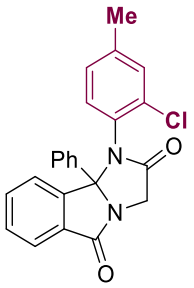
IR ν_{max} (cm^{-1}): 3006, 2926, 1707, 1450, 1325, 1133, 746

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1290; Found 305.1302

^1H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.94 (m, 1H), 7.75 – 7.62 (m, 3H), 7.46 – 7.34 (m, 3H), 7.18 – 7.09 (m, 2H), 4.45 (d, *J* = 16.4 Hz, 1H), 3.69 (d, *J* = 16.4 Hz, 1H), 2.53 – 2.44 (m, 1H), 1.09 – 0.97 (m, 1H), 0.95 – 0.82 (m, 1H), 0.81 – 0.65 (m, 1H), 0.46 – 0.35 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.4, 145.4, 137.4, 132.9, 132.7, 130.8, 129.7, 129.3, 126.6, 126.3, 125.1, 87.0, 46.5, 23.6, 7.4, 5.0.

1-(2-chloro-4-methyl-phenyl)-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328j)



The title compound was prepared according to general procedure **F** from N-(2-chloro-4-methyl-phenyl)-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (34 mg, 0.084 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol) and $n$$Bu_4NPF_6$ (7 mg, 0.017 mmol) in 1,2-DCE (0.4 mL). Following completion of the reaction (12 h), purification by FCC (1:19 EtOAc:Hex) afforded the pure compound as a white solid (24 mg, 74%).

RF (1:1 EtOAc:Hex): 0.57

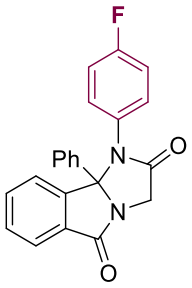
IR ν_{max} (cm^{-1}): 3055, 2967, 2926, 1715, 1497, 1374, 1224, 1055

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}ClN_2O_2$ 389.1057; Found 389.1052

^1H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.99 (m, 1H), 7.64 (td, *J* = 7.6, 1.0 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.45 – 7.41 (m, 3H), 7.18 – 7.12 (m, 2H), 7.08 – 7.03 (m, 1H), 6.75 – 6.70 (m, 1H), 4.74 (d, *J* = 16.6 Hz, 1H), 4.07 (d, *J* = 16.6 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 170.8, 144.0, 140.9, 137.8, 134.3, 132.8, 131.0, 130.6, 129.7, 129.7, 129.2, 129.0, 129.0, 128.3, 126.9, 125.1, 124.5, 87.4, 46.9, 21.0.

1-(4-fluorophenyl)-9b-phenyl-3H-imidazo[2,1-a]isoindole-2,5-dione (328k)



The title compound was prepared according to general procedure **F** from N-(4-fluorophenyl)-2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)acetamide (40 mg, 0.11 mmol), $Ca(NTf_2)_2$ (13 mg, 0.021 mmol) and $n$$Bu_4NPF_6$ (8 mg, 0.021 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (1 h), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a white solid (20 mg, 53%).

RF (1:1 EtOAc:Hex): 0.70

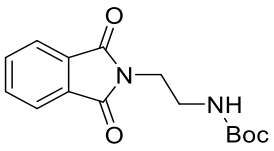
IR ν_{max} (cm^{-1}): 3058, 2919, 2853, 1711, 1510, 1221, 744

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}FN_2O_2$ 359.1196; Found 359.1205

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.99 (m, 1H), 7.66 (td, *J* = 7.5, 0.9 Hz, 1H), 7.55 (td, *J* = 7.6, 1.2 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.37 – 7.29 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.09 – 6.99 (m, 4H), 4.74 (d, *J* = 16.5 Hz, 1H), 4.02 (d, *J* = 16.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 170.9, 161.9 (d, *J* = 248.8 Hz), 145.0, 137.7, 133.0, 132.6, 131.0, 130.9 (d, *J* = 3.3 Hz), 129.9, 129.4, 129.4 (d, *J* = 8.5 Hz), 126.6, 125.7, 125.4, 116.3 (d, *J* = 22.7 Hz), 87.3, 46.8.

tert-Butyl (2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate (332)



Phthalic anhydride (1.5 g, 10.1 mmol) and N-boc-ethylenediamine (1.95 g, 1.92 mL, 12.2 mmol) was dissolved in acetic acid (33 mL) and stirred at 90 °C for 2h. Upon completion of the reaction, indicated by TLC, the mixture was cooled, diluted with water (50 mL) and quenched slowly with sat. aq. $NaHCO_3$. The solution was transferred to a separating funnel and extracted into DCM (3 x 50 mL). The combined organic layers were dried over

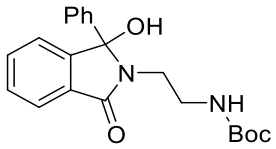
Na_2SO_4 and concentrated. Purification by FCC (1:1 EtOAc:Hex) afforded the title compound as a yellow solid (1.6 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.82 (s, 1H), 3.86 – 3.80 (m, 2H), 3.61 – 3.32 (m, 2H), 1.34 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 139.3, 133.6, 131.8, 131.1, 128.7, 128.4, 127.7, 121.2, 81.2, 55.3.

*Data in accordance with literature[137]

tert-butyl N-[2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)ethyl]carbamate (333a)



The title compound was prepared according to general procedure **B** from tert-Butyl (2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate (150 mg, 0.52 mmol), phenylmagnesium bromide (3.0 M in Et_2O, 0.52 mL, 1.55 mmol) in THF (2 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (151 mg, 79%).

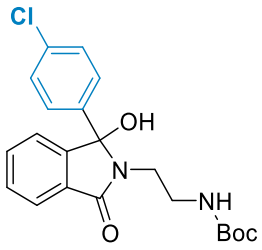
RF (1:1 EtOAc:Hex): 0.24

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.35 (m, 4H), 7.35 – 7.26 (m, 4H), 6.49 (s, 1H), 5.08 (s, 1H), 4.09 – 3.81 (m, 2H), 2.95 (d, *J* = 10.9 Hz, 1H), 2.84 (d, *J* = 11.7 Hz, 1H), 1.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 150.1, 139.4, 132.8, 130.0, 129.0, 128.7, 128.4, 126.1, 123.2, 122.7, 91.9, 80.5, 40.7, 39.3, 28.1.

*Data in accordance with literature[201]

tert-butyl N-[2-[1-(4-chlorophenyl)-1-hydroxy-3-oxo-isoindolin-2-yl]ethyl]carbamate (333b)



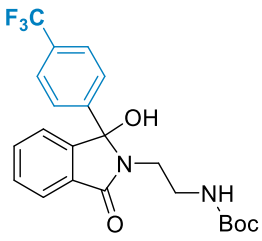
The title compound was prepared according to general procedure **B** from tert-Butyl (2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate (150 mg, 0.52 mmol), 4-chloro-phenylmagnesium bromide (1.0 M in Et_2O, 1.55 mL, 1.55 mmol) in THF (2 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (195 mg, 94%).

RF (1:1 EtOAc:Hex): 0.50

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.4 Hz, 1H), 7.47 (td, *J* = 7.4, 1.1 Hz, 1H), 7.41 (td, *J* = 7.5, 1.0 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.26 (m, 3H), 6.61 (s, 1H), 5.01 (s, 1H), 4.09 – 3.88 (m, 2H), 2.96 (d, *J* = 12.9 Hz, 1H), 2.81 (d, *J* = 11.8 Hz, 1H), 1.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 158.5, 149.7, 138.2, 134.4, 132.9, 129.9, 129.2, 128.9, 127.7, 123.3, 122.6, 91.5, 80.6, 40.7, 39.2, 28.1.

tert-butyl N-[2-[1-hydroxy-3-oxo-1-[4-(trifluoromethyl)phenyl]isoindolin-2-yl]ethyl]carbamate (333c)



The title compound was prepared according to general procedure **B** from tert-Butyl (2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate (150 mg, 0.52 mmol), 4-trifluoromethyl-phenylmagnesium bromide (0.5 M in THF, 3.20 mL, 1.56 mmol), in THF (3 mL). The Grignard reagent was freshly prepared from magnesium turnings (39 mg, 1.60 mmol), 1-bromo-4-(trifluoromethyl)benzene (349 mg, 0.22 mL, 1.56 mmol) and 1,2-dibromoethane (5 µL, 0.0022 mmol) in THF (3 mL). Following completion of the reaction

(1 h), purification by FCC (1:4 to 1:1 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (149 mg, 66%).

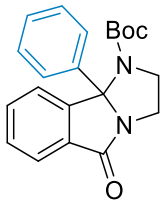
RF (1:1 EtOAc:Hex): 0.58

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.3 Hz, 1H), 7.67 – 7.51 (m, 4H), 7.48 (t, J = 7.1 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.35 – 7.28 (m, 1H), 6.79 (s, 1H), 5.09 (s, 1H), 4.19 – 3.83 (m, 2H), 3.11 – 2.92 (m, 1H), 2.79 (d, J = 11.9 Hz, 1H), 1.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 158.5, 149.4, 143.7, 133.0, 130.6 (q, *J* = 32.8 Hz), 129.3, 126.7, 125.7 (d, *J* = 3.6 Hz), 123.4, 124.1 (q, *J* = 272.4 Hz),122.7, 91.5, 80.7, 40.6, 39.3, 28.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5

tert-butyl 5-oxo-9b-phenyl-2,3-dihydroimidazo[2,1-a]isoindole-1-carboxylate (334a)



The title compound was prepared according to general procedure **D** from tert-butyl N-[2-(1-hydroxy-3-oxo-1-phenyl-isoindolin-2-yl)ethyl]carbamate (50 mg, 0.136 mmol), $Ca(NTf_2)_2$ (1.0 mg, 0.00136 mmol) and $n$$Bu_4NPF_6$ (0.5 mg, 0.00136 mmol) in HFIP (0.7 mL). Following completion of the reaction (12 h), purification by FCC (1:5 EtOAc:Hex) afforded the pure compound as a white solid (44 mg, 93%).

RF (1:1 EtOAc:Hex): 0.75

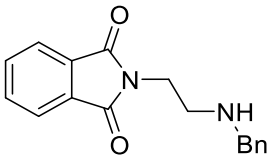
IR ν_{max} (cm^{-1}): 3060, 2940, 1703, 1680, 1321, 1089, 817

HRMS (APCI)m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_3$ 351.1709; Found 351.1701

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 6.7, 2.2 Hz, 2H), 7.62 – 7.50 (m, 2H), 7.37 – 7.28 (m, 3H), 7.24 – 7.16 (m, 2H), 4.26 (ddd, *J* = 12.1, 7.8, 1.8 Hz, 1H), 3.89 (t, *J* = 8.6 Hz, 1H), 3.78 (td, *J* = 10.0, 7.8 Hz, 1H), 3.25 (ddd, *J* = 12.1, 9.8, 7.9 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 153.2, 147.0, 139.3, 132.8, 132.2, 130.0, 128.7, 128.6, 128.3, 126.3, 123.8, 85.7, 81.2, 50.1, 39.2, 28.6.

2-[2-(benzylamino)ethyl]isoindoline-1,3-dione (336)



N-benzylethylenediamine (893 mg, 5.94 mmol, 1.1 equiv.) was added in one portion to a solution of phthalic anhydride (800 mg, 5.40 mmol, 1.0 equiv.) in MeOH (11 mL) and the reaction was heated to 60 °C overnight. Upon completion of the reaction, indicted by TLC, the reaction was allowed to cool and then concentrated under reduced pressure. The pure product was purified by FCC (1:1 EtOAc:Hex) to afford the title compound as a yellow solid (480 mg, 32%).

RF (1:1 EtOAc:Hex): 0.27

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 5.4, 3.1 Hz, 1H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.27 – 7.19 (m, 1H), 3.86 (t, *J* = 6.3 Hz, 1H), 3.84 (s, 1H), 2.96 (t, *J* = 6.3 Hz, 1H), 1.40 (s, 1H).

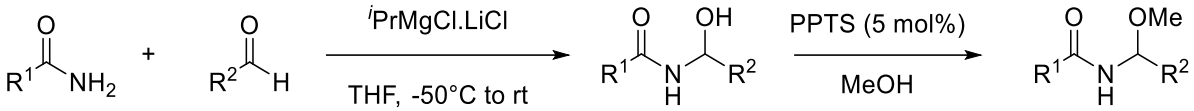
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 140.3, 134.0, 132.3, 128.5, 128.2, 127.1, 123.4, 53.4, 47.3, 37.9.

Data in accordance with literature[202]

9.4. Chapter 4 Experimental

9.4.1. General Procedures for Chapter 4

General Procedure G – Reported by Manolikakes[137]

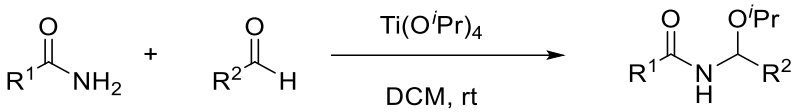


To a flame dried round bottom flask purged with argon was added amide (1.0 equiv) and dry THF (2mmol/amide). The resulting solution was cooled to -50°C and *i*PrMgCl.LiCl (1.05 equiv.) was added dropwise. The resulting solution was then warmed to room temperature and stirred for 30 min. The mixture was then cooled to 0 °C and aldehyde (1.1 equiv) was added in a single portion. The reaction mixture was warmed to room temperature and stirred until TLC analysis indicated full consumption of amide. The mixture was quenched using sat. aq. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted three times with DCM. The combined organic layers were dried with Na_2SO_4, filtered and concentrated to afford the crude hemiaminal. Pure hemiaminals were obtained by crystallisation from DCM:Hexane (9:1)

The hemiaminal was then dissolved in methanol (3mL/mmol) and PPTS (5 mol%) was added. The reaction mixture was stirred at room temperature until complete consumption of the hemiaminal. The mixture was quenched using sat. aq. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted three times with DCM. The combined organic layers were dried with Na_2SO_4, filtered, concentrated and purified by flash column chromatography (EtOAc:Hex, 1% NEt_3) to afford the pure product.

Yields are reported over two steps.

General Procedure H – Adapted literature procedure[143]

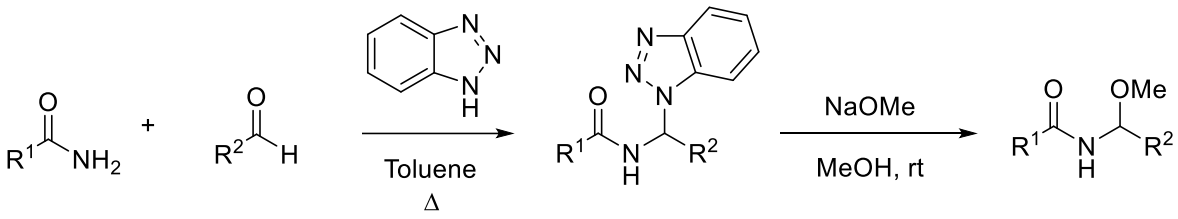


Amide (1.0 equiv) and aldehyde (1.2 equiv) were dissolved in anhydrous DCM (0.25M) under an argon atmosphere. $Ti(O^iPr)_4$ (1.5 equiv) was added dropwise and the reaction

was stirred at room temperature overnight. The reaction was then diluted with isopropanol and quenched by dropwise addition of an aqueous 0.5M K_2CO_3 solution. The resulting precipitate was then removed by slow filtration through celite and washed 3 times with isopropanol. The solution was then concentrated, and the resulting solid was purified by flash column chromatography (EtOAc:Hex) to afford the pure product.

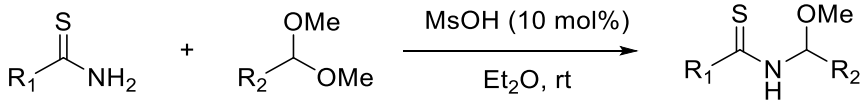
*when using benzaldehyde, excess could be removed by washing the solid with hexane prior to column chromatography which resulted in more efficient purification.

General Procedure I – Reported by Katritzky[139]



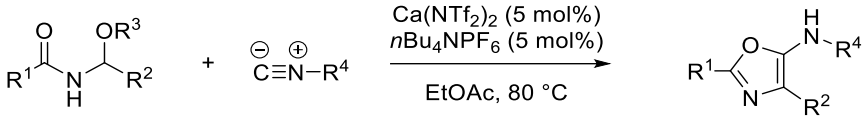
Amide (1 equiv), aldehyde (1 equiv) and benzotriazole (1 equiv) were refluxed in toluene overnight with molecular sieves. The solution was cooled, concentrated and ether was added. The resulting sold was then recrystalised from methanol. The solid was then dissolved in methanol, sodium methoxide (2 equiv) was added and stirred overnight at room temperature. Water was added and the precipitated solid was collected by filtration

General Procedure J – Synthesis of *N*-thioacyl-*N,O*-acetals – Adapted Procedure[148]



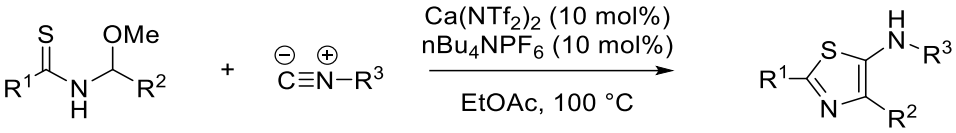
Thioamide (1 equiv) and dimethyl acetal (2 equiv) was dissolved in dry Et_2O (0.2 M) and MsOH (0.1 equiv) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with sat. aq. Na_2CO_3, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. The product was then purified by flash column chromatography (Hex: Et_2O gradient elution) to afford the pure product.

.General Procedure K – Calcium catalysed synthesis of 5-aminooxazoles



To a 4 mL vial was added *N*-Acyl-*N,O*-acetal (1.0 equiv) and isocyanide (1.2 equiv) in EtOAc (1 mL). nBu$_4$NPF$_6$ (5 mol%) and Ca(NTf$_2$)$_2$ (5 mol%) was added and the mixture was stirred at 80°C until TLC analysis indicated complete conversion to the product. The mixture was concentrated and purified by flash column chromatography (EtOAc:Hex, 1% NEt$_3$) to afford the pure product.

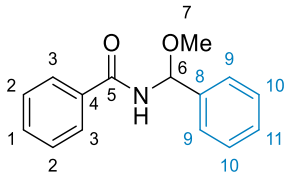
General Procedure L – Calcium catalysed synthesis of 5-aminothiazoles



To a 4 mL vial was added *N*-thioacyl-*N,O*-acetal (1.0 equiv) and isocyanide (1.2 equiv) in EtOAc (1 mL). nBu$_4$NPF$_6$ (10 mol%) and Ca(NTf$_2$)$_2$ (10 mol%) was added and the mixture was stirred at 100°C until TLC anlaysis indicated complete conversion to the product. The mixture was concentrated and purified by flash column chromatography (EtOAc:Hex, 1% NEt$_3$) to afford the pure product.

9.4.2. Synthesis of *N*-acyl-*N,O*-acetals

_N_-(Methoxy(phenyl)methyl)benzamide (392a)



The title compound was prepared according to general procedure **G** from benzamide (1.00 g, 8.25 mmol), *i*PrMgCl.LiCl (6.7 mL, 8.67 mmol, 1.3M in THF) and benzaldehyde (0.93 mL, 9.10 mmol) in THF (20 mL) to afford the hemiaminal. Transacetalisation in MeOH (20 mL) and PPTS (88 mg, 0.35 mmol) followed by column chromatography (1:3 EtOAc:Hex, 1% NEt$_3$) afforded the pure product as a white solid (1.58 g, 79%)

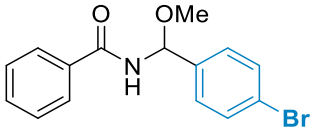
RF (1:3 EtOAc:Hex): 0.33

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (d, *J* = 9.0 Hz, 1H, **NH**), 8.04 – 7.89 (m, 2H, **H3**), 7.59 – 7.53 (m, 1H, **H1**), 7.51 – 7.45 (m, 4H. **H2 & H9**), 7.42 – 7.36 (m, 2H, **H10**), 7.36 – 7.30 (m, 1H, **H11**), 6.28 (d, *J* = 9.0 Hz, 1H, **H6**), 3.40 (s, 3H, **H7**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.9 (**C5**), 139.8 (**C8**), 133.8 (**C4**), 131.7 (**C1**), 128.3 (**ArC**), 128.2 (**ArC**), 128.0 (**ArC**), 127.7 (**ArC**), 126.4 (**ArC**), 81.8 (**C6**), 55.3 (**C7**).

*Data in accordance with literature[137]

***N*-[(4-bromophenyl)(methoxy)methyl]benzamide (392b)**



The title compound was prepared according to general procedure **G** from benzamide (400 mg, 3.30 mmol), *i*PrMgCl.LiCl (3.70 mL, 3.50 mmol, 0.94M in THF) and 4-bromo benzaldehyde (670 mg, 3.60 mmol) in THF (7 mL) to afford the hemiaminal. Transacetalisation in MeOH (5 mL) and PPTS (25 mg, 0.1 mmol) followed by column chromatography (1:4 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (440 mg, 47%)

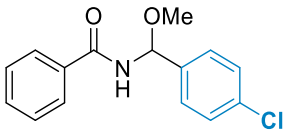
RF (1:3 EtOAc:Hex): 0.43

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (d, *J* = 8.9 Hz, 1H), 7.99 – 7.92 (m, 2H), 7.63 – 7.52 (m, 3H), 7.52 – 7.40 (m, 4H), 6.25 (d, *J* = 8.9 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.9, 139.3, 133.6, 131.8, 131.1, 128.7, 128.4, 127.7, 121.2, 81.2, 55.3.

*Data in accordance with literature[137]

***N*-[(4-chlorophenyl)(methoxy)methyl]benzamide (392c)**



The title compound was prepared according to general procedure **G** from benzamide (300 mg, 2.50 mmol), *i*PrMgCl.LiCl (2 mL, 2.60 mmol, 1.3M in THF) and 4-chloro benzaldehyde (380 mg, 2.70 mmol) in THF (6 mL) to afford the hemiaminal. Transacetalisation in MeOH (4 mL) and PPTS (24 mg, 0.1 mmol) followed by column chromatography (1:9 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (445 mg, 71%)

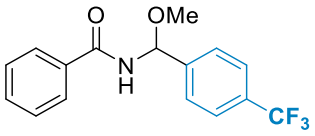
RF (1:3 EtOAc:Hex): 0.30

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (d, *J* = 8.9 Hz, 1H), 8.08 – 7.86 (m, 2H), 7.66 – 7.36 (m, 7H), 6.29 (d, *J* = 8.9 Hz, 1H), 3.40 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.0, 138.9, 133.7, 132.6, 131.7, 128.3, 128.2, 127.8, 81.2, 55.3.

*Data in accordance with literature[137]

***N*-{methoxy[4-(trifluoromethyl)phenyl]methyl}benzamide (392d)**



The title compound was prepared according to general procedure **G** from benzamide (300 mg, 2.50 mmol), *i*PrMgCl.LiCl (2 mL, 2.60 mmol, 1.3M in THF) and 4-(Trifluoromethyl)benzaldehyde (475 mg, 2.72 mmol) in THF (6 mL) to afford the hemiaminal. Transacetalisation in MeOH (4 mL) and PPTS (21 mg, 0.085 mmol) followed by column chromatography (1:4 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (365 mg, 53%)

RF (1:3 EtOAc:Hex): 0.42

IR ν_{max} (cm^{-1}): 3275, 3017, 2970, 1642, 1519, 1325,

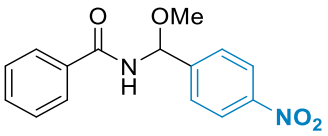
HRMS (ESI) m/z: $[M - CH_4O]^+$ Calcd for $C_{15}H_{10}F_3NO$ 278.0793; Found 278.0796

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (d, *J* = 8.9 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.38 (d, *J* = 8.9 Hz, 1H), 3.44 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): 167.1, 144.4, 133.6, 131.8, 128.4, 128.6 (q, *J* = 31.6 Hz), 127. 8, 127.3, 125.2 (d, *J* = 3.6 Hz), 124.3 (q, *J* = 272.1 Hz), 81.1, 55.4.

^{19}F NMR (376 MHz, DMSO-d_6): 60.88

***N*-[methoxy(4-nitrophenyl)methyl]benzamide (392e)**



The title compound was prepared according to general procedure **G** from benzamide (300 mg, 2.50 mmol), *i*PrMgCl.LiCl (2 mL, 2.60 mmol, 1.3M in THF) and 4-nitrobenzaldehyde (410 mg, 2.70 mmol) in THF (6 mL) to afford the hemiaminal. Transacetalisation in MeOH (6 mL) and PPTS (23 mg, 0.092 mmol) followed by column chromatography (1:9 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (445 mg, 66%)

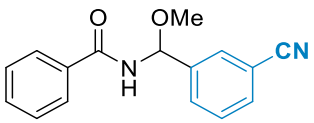
RF (1:3 EtOAc:Hex): 0.23

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 2H), 7.97 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.41 (d, *J* = 8.8 Hz, 1H), 3.45 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.1, 147.2, 147.1, 133.5, 131.9, 128.4, 127.8, 127.8, 123.4, 80.9, 55.5.

*Data in accordance with literature[137]

***N*-[(3-cyanophenyl)(methoxy)methyl]benzamide (392f)**



The title compound was prepared according to general procedure **G** from benzamide (300 mg, 2.50 mmol), *i*PrMgCl.LiCl (2.4 mL, 2.60 mmol, 1.097M in THF) and 3-

Formylbenzonitrile (360 mg, 2.70 mmol) in THF (5 mL) to afford the hemiaminal. Transacetalisation in MeOH (5 mL) and PPTS (20 mg, 0.08 mmol) followed by column chromatography (3:10 EtOAc:Hex, 1% NEt_3) afforded the pure product as a white solid (350 mg, 64%)

RF (3:10 EtOAc:Hex): 0.48

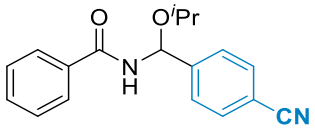
IR ν_{max} (cm^{-1}): 3246, 2950, 2232, 1637, 1515, 1108, 1046

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}N_2O_2Na$ 289.0953; Found 289.0950

^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz,) δ 9.19 (d, *J* = 9.0 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.59 – 7.53 (m, 1H), 7.50 – 7.44 (m, 4H), 7.41 – 7.36 (m, 2H), 7.35 – 7.29 (m, 1H), 6.27 (d, *J* = 9.0 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.0, 141.3, 133.5, 131.9, 131.8, 131.5, 130.1, 129.6, 128.4, 127.8, 118.8, 111.2, 80.9, 55.4.

***N*-{(4-cyanophenyl)[(propan-2-yl)oxy]methyl}benzamide (403a)**



The title compound was prepared according to general procedure **H** from benzamide (250 mg, 2.10 mmol), 4-cyanobenzaldehyde (325 mg, 2.50 mmol) and $Ti(O^iPr)_4$ (880 mg, 3.10 mmol) in DCM (7 mL). Purification by flash column chromatography (0 to 5% EtOAc:CycHex) afforded the pure product as a white solid (299 mg, 59%).

RF (1:5 EtOAc:Hex): 0.26

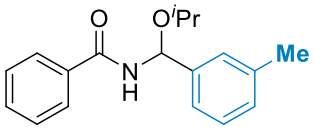
IR ν_{max} (cm^{-1}): 3375, 3267, 2974, 2231, 1645, 1487, 1048

HRMS (ESI) m/z: $[M – C_3H_8O]^+$ Calcd for $C_{15}H_{11}N_2O$ 235.0871; Found 235.0870

^1H NMR (400 MHz, DMSO-d_6): δ 9.30 (d, *J* = 8.9 Hz, 1H), 7.99 – 7.91 (m, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 1H), 3.94 (hept, *J* = 6.1 Hz, 1H), 1.21 (dd, *J* = 9.5, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.7, 145.9, 133.5, 132.2, 131.8, 128.4, 127.7, 127.5, 118.8, 110.6, 77. 5, 68.9, 23.1, 21.6.

***N*-{(3-methylphenyl)[(propan-2-yl)oxy]methyl}benzamide (403b)**



The title compound was prepared according to general procedure **H** from benzamide (250 mg, 2.10 mmol), m-Tolualdehyde (300 mg, 2.50 mmol) and Ti(O^{i}Pr)$_4$ (880 mg, 3.10 mmol) in DCM (8 mL). Purification by flash column chromatography (1:20 EtOAc:Hex) afforded the pure product as a white solid (195 mg, 33%).

RF (1:5 EtOAc:Hex): 0.45

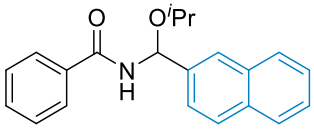
IR ν_{max} (cm^{-1}): 3293, 2970, 1637, 1520, 1276, 1038

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{21}NNaO_2$ 306.1470; Found 306.1468

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 7.1 Hz, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.44 (m, 2H), 7.34 – 7.20 (m, 3H), 7.17 – 7.09 (m, 1H), 6.43 (d, *J* = 8.9 Hz, 1H), 3.89 (hept, *J* = 6.1 Hz, 1H), 2.31 (s, 3H), 1.20 (dd, *J* = 8.9, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5, 140.5, 137.2, 133.8, 131.6, 128.4, 128.3, 128.0, 127.7, 126.9, 123.5, 78.0, 68.3, 23.2, 21.6, 21.1.

***N*-{(naphthalen-2-yl)[(propan-2-yl)oxy]methyl}benzamide (403c)**



The title compound was prepared according to general procedure **H** from benzamide (290 mg, 2.40 mmol), 2-Naphthaldehyde (250 mg, 1.60 mmol) and Ti(O^{i}Pr)$_4$ (910 mg, 3.20 mmol) in DCM (7 mL). Purification by flash column chromatography (1:9 EtOAc:Hex) afforded the pure product as a white solid (128 mg, 25%).

RF (1:5 EtOAc:Hex): 0.39

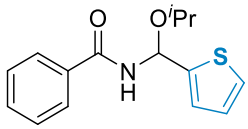
IR ν_{max} (cm^{-1}): 3298, 3056, 2696, 1638, 1517, 1365, 1072

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NNaO_2$ 342.1470; Found 342.1468

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.29 (d, *J* = 8.9 Hz, 1H), 8.01 – 7.87 (m, 6H), 7.62 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.59 – 7.43 (m, 5H), 6.63 (d, *J* = 8.9 Hz, 1H), 3.97 (hept, *J* = 6.1 Hz, 1H), 1.25 (dd, *J* = 9.5, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 66.6, 138.1, 133.8, 132.6, 132.6, 131.7, 128.3, 128.1, 127.8, 127.8, 127.5, 126.3, 126.2, 124.9, 124.8, 78.2, 68.5, 23.2, 21.7.

***N*-{[(propan-2-yl)oxy](thiophen-2-yl)methyl}benzamide (403d)**



The title compound was prepared according to general procedure **H** from benzamide (250 mg, 2.10 mmol), 2-Thiophenecarboxaldehyde (280 mg, 2.50 mmol) and Ti(O^{i}Pr)$_4$ (880 mg, 3.10 mmol) in DCM (8 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (190 mg, 33%).

RF (1:5 EtOAc:Hex): 0.45

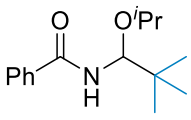
IR ν_{max} (cm^{-1}): 3247, 2970, 1636, 1522, 1362, 1045

HRMS (ESI) m/z: [M + Na]$^{+}$ Calcd for $C_{15}H_{17}NNaO_2S$ 298.0878; Found 298.0881

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (d, *J* = 8.9 Hz, 1H), 7.91 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.38 (m, 3H), 7.00 – 6.98 (m, 1H), 6.95 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 3.87 (hept, *J* = 6.1 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5, 144.5, 133.6, 131.8, 128.3, 127.8, 126.8, 125.7, 124.6, 75.4, 68.9, 23.1, 21.6.

***N*-(1-isopropoxy-2,2-dimethyl-propyl)benzamide (403f)**



The title compound was prepared according to general procedure **H** from benzamide (250 mg, 2.10 mmol), trimethylacetaldehyde (213 mg, 0.27 mL, 2.50 mmol) and Ti(O^{i}Pr)$_4$

(880 mg, 3.10 mmol) in DCM (8 mL). Purification by flash column chromatography (1:9 EtOAc:Hex) afforded the pure product as a white solid (140 mg, 27%).

RF (1:5 EtOAc:Hex): 0.47

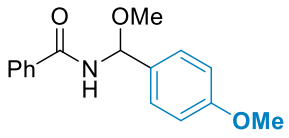
IR ν_{max} (cm^{-1}): 3247, 3060, 1646, 1521, 1363, 1047

HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{12}H_{16}NO$ 192.1388; Found 192.1375

^1H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, *J* = 9.3 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 5.10 (d, *J* = 9.3 Hz, 1H), 3.70 – 3.62 (m, 1H), 1.09 (dd, *J* = 7.0, 6.4 Hz, 6H), 0.91 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.3, 134.4, 131.3, 128.2, 127.7, 84.0, 68.2, 35.5, 25.3, 23.3, 21.3.

***N*-[methoxy(4-methoxyphenyl)methyl]benzamide (392l)**



The title compound was prepared according to general procedure **I** from benzamide (1 g, 8.30 mmol), p-anisaldehyde (1.1 g, 8.30 mmol) and benzotriazole (980 mg, 8.30 mmol) in toluene (4 mL). The product (745 mg, 2.10 mmol) was then stirred in methanol (15 mL) with sodium methoxide (135 mg, 2.50 mmol) overnight to afford the title compound as a white solid (62 mg, 11%).

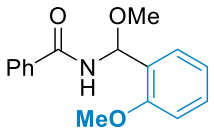
RF (1:5 EtOAc:Hex): 0.24

^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz,) δ 9.12 (d, *J* = 8.9 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 6.21 (d, *J* = 9.0 Hz, 1H), 3.75 (s, 3H), 3.36 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.8, 159.0, 133.8, 131.9, 131.6, 128.3, 127.7, 127.7, 113.5, 81.6, 55.1, 55.1.

*data in accordance with literature[139]

_N_-[methoxy(2-methoxyphenyl)methyl]benzamide (392m)



The title compound was prepared according to general procedure **I** from benzamide (1 g, 8.30 mmol), o-anisaldehyde (1.10 g, 8.30 mmol) and benzotriazole (980 mg, 8.30 mmol) in toluene (4 mL). The product (622 mg, 1.75 mmol) was then stirred in methanol (12 mL) with sodium methoxide (110 mg, 2.10 mmol) overnight to afford the title compound as a white solid (187 mg, 40%).

RF (1:5 EtOAc:Hex): 0.16

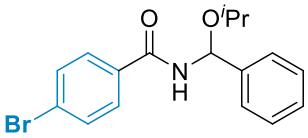
IR ν_{max} (cm^{-1}): 3315, 3073, 2940, 2837, 1638, 1517, 1488, 1242, 1027

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{17}NO_3Na$ 294.1106; Found 294.1101

^1H NMR (400 MHz, DMSO-d_6): δ 8.97 (d, *J* = 8.9 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.06 – 6.90 (m, 2H), 6.47 (d, *J* = 9.0 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 156.5, 134.0, 131.5, 129.4, 128.3, 127.7, 127.4, 127.2, 120.1, 111.0, 77.2, 55.6, 55.3.

4-bromo-_N_-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407a)



The title compound was prepared according to general procedure **H** from 4-bromobenzamide (662 mg, 3.30 mmol), benzaldehyde (421 mg, 4.00 mmol) and $Ti(O^iPr)_4$ (1.40 g, 5.00 mmol) in DCM (10 mL). Purification by flash column chromatography (0 to 10% EtOAc:Hex) afforded the pure product as a white solid (188 mg, 16%).

RF (1:5 EtOAc:Hex): 0.52

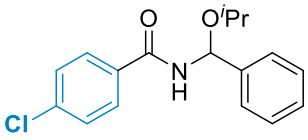
IR ν_{max} (cm^{-1}): 3289, 2971, 1639, 1520, 1482, 1011, 696

HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{14}H_{11}BrNO$ 288.0024; Found 288.0025

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.1 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.34 – 7.28 (m, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 3.90 (hept, *J* = 6.1 Hz, 1H), 1.20 (dd, *J* = 9.3, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 165.7, 140.4, 132.9, 131.4, 129.9, 128.2, 127.9, 126.4, 125.4, 78.1, 68.5, 23.1, 21.6.

4-chloro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407b)



The title compound was prepared according to general procedure **H** from 4-chlorobenzamide (500 mg, 3.20 mmol), benzaldehyde (410 mg, 3.90 mmol) and Ti(O^{i}Pr)$_4$ (1.40 g, 4.80 mmol) in DCM (13 mL). Purification by flash column chromatography (0 to 10% EtOAc:Hex) afforded the pure product as a white solid (222 mg, 23%).

RF (1:5 EtOAc:Hex): 0.54

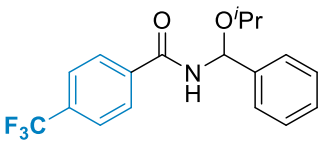
IR ν_{max} (cm^{-1}): 3263, 3064, 2974, 1635, 1532, 1486, 1031,850

HRMS (ESI) m/z: [M + C_3H_8O]$^+$ Calcd for $C_{17}H_{19}ClNO$ 244.0529; Found 244.0534

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (d, *J* = 8.9 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.35 – 7.28 (m, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 3.89 (hept, *J* = 6.1 Hz, 1H), 1.20 (dd, *J* = 10.1, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 165.6, 140.4, 136.5, 132.6, 129.7, 128.4, 128.1, 127.9, 126.4, 78.1, 68.56, 23.1, 21.6.

***N*-{phenyl[(propan-2-yl)oxy]methyl}-4-(trifluoromethyl)benzamide (407c)**



The title compound was prepared according to general procedure **H** from 4-(trifluoromethyl)benzamide (400 mg, 2.10 mmol), benzaldehyde (270 mg, 2.50 mmol) and Ti(O^{i}Pr)$_4$ (900 mg, 3.20 mmol) in DCM (9 mL). Purification by flash column

chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (206 mg, 30%).

RF (1:5 EtOAc:Hex): 0.51

IR ν_{max} (cm^{-1}): 3282, 2977, 1652, 1534, 1326, 1126, 859

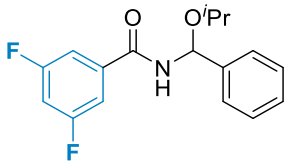
HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{15}H_{11}F_3NO$ 278.0793; Found 278.0792

^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz,) δ 9.48 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.35 – 7.29 (m, 1H), 6.46 (d, *J* = 8.8 Hz, 1H), 3.92 (hept, *J* = 6.0 Hz, 1H), 1.21 (dd, *J* = 9.9, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ ^{13}C NMR (101 MHz,) δ 165.5, 140.3, 137.6, 131.4 (q, *J* = 31.8 Hz), 128.6, 128.2, 127.9, 126.4, 125.3 (d, *J* = 3.7 Hz), 124.0 (q, *J* = 272.9 Hz), 78.2, 68.6, 23.1, 21.6.

^{19}F NMR (376 MHz, DMSO-d_6): 61.27

3,5-difluoro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407d)



The title compound was prepared according to general procedure **H** from 3,5-difluorobenzamide (400 mg, 2.60 mmol), benzaldehyde (324 mg, 3.06 mmol) and $Ti(O^iPr)_4$ (1.10 g, 3.80 mmol) in DCM (10 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (275 mg, 35%).

RF (1:5 EtOAc:Hex): 0.65

IR ν_{max} (cm^{-1}): 3264, 3063, 2970, 1654, 1534, 1330, 1119

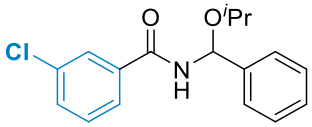
HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{14}H_{10}F_2NO$ 246.0730; Found 246.0729

^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz,) δ 9.39 (d, *J* = 8.7 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.3 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.41 – 7.36 (m, 2H), 7.35 – 7.29 (m, 1H), 6.44 (d, *J* = 8.7 Hz, 1H), 3.89 (hept, *J* = 6.1 Hz, 1H), 1.20 (dd, *J* = 8.5, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 163.9, 163.5 (d, *J* = 12.7 Hz), 161.0 (d, *J* = 12.6 Hz), 140.2, 137.2 (t, *J* = 8.4 Hz), 128.2, 128.0, 126.4, 111.2 (d, *J* = 7.2 Hz), 111.0 (d, *J* = 7.2 Hz), 107.2 (t, *J* = 25.9 Hz), 78.2, 68.6, 23.1, 21.6.

^{19}F NMR (376 MHz, DMSO-d_6): 108.86

3-chloro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407e)



The title compound was prepared according to general procedure **H** from 3-chlorobenzamide (400 mg, 2.60 mmol), benzaldehyde (327 mg, 3.09 mmol) and Ti(O^{i}Pr)$_4$ (1.10 g, 3.90 mmol) in DCM (10 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (136 mg, 17%).

RF (1:5 EtOAc:Hex): 0.46

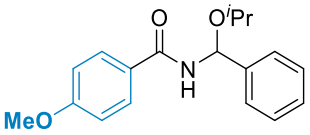
IR ν_{max} (cm^{-1}): 3290, 3031, 2970, 1644, 1523, 1030, 692

HRMS (ESI) m/z: [M – C3H7O] + Calcd for C14H11ClNO 244.0529; Found 244.0533

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (d, *J* = 8.8 Hz, 1H), 8.01 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.56 – 7.44 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 3.90 (hept, *J* = 6.1 Hz, 1H), 1.20 (dd, *J* = 8.4, 6.2 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 165.2, 140.4, 135.7, 133.2, 131.5, 130.4, 128.2, 127.9, 127.5, 126.5, 126.4, 78.1, 68.5, 23.1, 21.6.

4-methoxy-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407f)



The title compound was prepared according to general procedure **H** from 4-methoxybenzamide (400 mg, 2.65 mmol), benzaldehyde (337 mg, 3.20 mmol) and Ti(O^{i}Pr)$_4$ (1.10 g, 4.00 mmol) in DCM (11 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (206 mg, 26%).

RF (1:5 EtOAc:Hex): 0.29

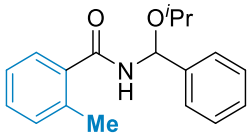
IR ν_{max} (cm^{-1}): 3319, 3065, 2971, 1631, 1495, 1257, 849

HRMS (ESI) m/z: [M – C_3H_8O]$^+$ Calcd for $C_{15}H_{14}NO_2$ 240.1025; Found 240.1024

^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz,) δ 9.04 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.27 (m, 3H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.45 (d, *J* = 9.0 Hz, 1H), 3.89 (hept, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 1.19 (dd, *J* = 11.4, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.0, 161.9, 140.8, 129.6, 128.1, 127.8, 126.4, 125.9, 113.5, 77.9, 68.3, 55.4, 23.2, 21.7.

2-methyl-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (407g)



The title compound was prepared according to general procedure **H** from 2-methylbenzamide (250 mg, 1.85 mmol), benzaldehyde (236 mg, 2.22 mmol) and Ti(O^{i}Pr)$_4$ (790 mg, 2.80 mmol) in DCM (7 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (72 mg, 14%).

RF (1:5 EtOAc:Hex): 0.33

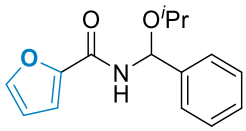
IR ν_{max} (cm^{-1}): 3260, 3065, 2969, 1646, 1516, 1041, 727

HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{15}H_{14}NO$ 224.1075; Found 224.1069

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (d, *J* = 9.1 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.43 – 7.28 (m, 5H), 7.28 – 7.18 (m, 2H), 6.40 (d, *J* = 9.2 Hz, 1H), 4.05 – 3.94 (m, 1H), 2.35 (s, 3H), 1.23 (dd, *J* = 9.3, 6.2 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.4, 140.5, 136.7, 135.1, 130.4, 129. 5, 128.1, 127.8, 127.1, 126.3, 125.5, 77.5, 68.3, 23.2, 21.6, 19.5.

***N*-{phenyl[(propan-2-yl)oxy]methyl}furan-2-carboxamide (407h)**



The title compound was prepared according to general procedure **H** from furan-2carboxamide (400 mg, 3.60 mmol), benzaldehyde (460 mg, 4.32 mmol) and Ti(O^{i}Pr)$_4$ (1.50 g, 5.40 mmol) in DCM (12 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (200 mg, 21%).

RF (1:9 EtOAc:Hex): 0.21

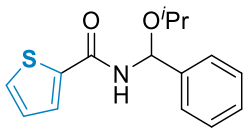
IR ν_{max} (cm^{-1}): 3224, 3047, 2969, 1646, 1531, 1024, 752

HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{12}H_{10}NO_2$ 200.0712; Found 200.0711

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (d, *J* = 9.1 Hz, 1H), 7.87 (s, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.41 – 7.27 (m, 4H), 6.65 – 6.62 (m, 1H), 6.39 (d, *J* = 9.1 Hz, 1H), 3.99 – 3.79 (m, 1H), 1.19 (dd, *J* = 8.3, 6.2 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 157.9, 147.1, 145.7, 140.4, 128.2, 127.9, 126.4, 114.4, 111.9, 77.2, 68.3, 23.1, 21.6.

***N*-{phenyl[(propan-2-yl)oxy]methyl}thiophene-2-carboxamide (407i)**



The title compound was prepared according to general procedure **H** from thiophene-2-carboxamide (400 mg, 3.15 mmol), benzaldehyde (400 mg, 3.80 mmol) and Ti(O^{i}Pr)$_4$

(1.30 g, 4.70 mmol) in DCM (13 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (206 mg, 24%).

RF (1:5 EtOAc:Hex): 0.40

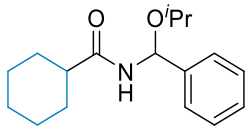
IR ν_{max} (cm^{-1}): 3330, 3090, 2969, 1625, 1533, 1030, 745

HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{15}H_{18}NO_2S$ 216.0483; Found 216.0478

^1H NMR (400 MHz, DMSO-d_6): δ 9.25 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 3.8 Hz, 1H), 7.81 (d, *J* = 5.0 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.41 (d, *J* = 9.0 Hz, 1H), 3.90 (hept, *J* = 6.1 Hz, 1H), 1.20 (dd, *J* = 8.0, 6.2 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 161.4, 140.4, 139.4, 131.8, 129.1, 128.2, 128.1, 127.9, 126.3, 77. 8, 68.4, 23.1, 21.6.

N-[isopropoxy(phenyl)methyl]cyclohexanecarboxamide (407j)



The title compound was prepared according to general procedure **H** from cyclohexanecarboxamide (300 mg, 2.36 mmol), benzaldehyde (300 mg, 2.86 mmol) and Ti(O^{i}Pr)$_4$ (1.01 g, 3.54 mmol) in DCM (10 mL). Purification by flash column chromatography (0 to 5% EtOAc:Hex) afforded the pure product as a white solid (206 mg, 24%).

RF (1:5 EtOAc:Hex): 0.48

IR ν_{max} (cm^{-1}): 3329, 3090, 2969, 2917, 1625, 1533, 1438, 1028

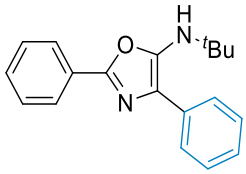
HRMS (ESI) m/z: $[M - C_3H_8O]^+$ Calcd for $C_{14}H_{18}NO$ 216.1388; Found 216.1374

^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, *J* = 9.4 Hz, 1H), 7.48 – 7.17 (m, 5H), 6.17 (d, *J* = 9.3 Hz, 1H), 3.84 – 3.76 (m, 1H), 2.24 (tt, *J* = 11.6, 3.2 Hz, 1H), 1.92 – 1.51 (m, 5H), 1.50 – 1.26 (m, 2H), 1.26 – 0.98 (m, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 175.7, 140.8, 128.1, 127.7, 126.2, 76.8, 67.9, 43.9, 29.3, 29.1, 25.5, 25.3, 25.2, 23.2, 21.6.

9.4.3. Synthesis of 5-aminooxazoles

N-(tert-butyl)-2,4-diphenyloxazol-5-amine (395a)



The title compound was prepared according to general procedure **K**, from 1.130. *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.4 mmol), $Ca(NTf_2)_2$ (12 mg, 0.02 mmol), nBu_4NPF_6 (8 mg, 0.02 mmol) and tert-butyl isocyanide (38 mg, 0.5 mmol) in EtOAc (2 mL).

Following conversion to the product (1h) and column chromatography (1:5 EtOAc:Hex, 1% NEt_3) the pure product was obtained as a white solid (121 mg, 92%)

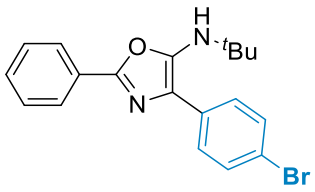
RF (3:1 EtOAc/Hex) = 0.73

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 7.3 Hz, 2H), 7.96 – 7.92 (m, 2H), 7.57 – 7.45 (m, 3H), 7.44 – 7.38 (m, 2H), 7.28 – 7.20 (m, 1H), 5.44 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.9, 148.7, 132.4, 129.8, 129.2, 128.3, 127.4, 126.3, 125.3, 125.1, 124.4, 53.2, 30.1.

*data in accordance with literature[135]

4-(4-bromophenyl)-N-(tert-butyl)-2-phenyloxazol-5-amine (395b)



The title compound was prepared according to general procedure **K**, from *N*-[(4-bromophenyl)(methoxy)methyl]benzamide (100 mg, 0.31 mmol), $Ca(NTf_2)_2$ (9 mg, 0.016 mmol), nBu_4NPF_6 (6 mg, 0.016 mmol) and tert-butyl isocyanide (31 mg, 0.38 mmol) in EtOAc (2 mL).

Following conversion to the product (30 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a white solid (105 mg, 91%)

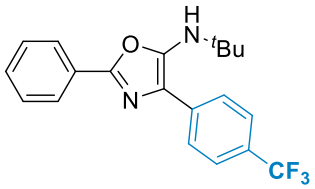
RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.43

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 – 7.90 (m, 4H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.44 (m, 3H), 5.58 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.9, 149.1, 131.7, 131.2, 129.9, 129.2, 127.2, 125.1, 123.0, 118.99, 53.3, 30.0.

*data in accordance with literature[135]

_N_-tert-butyl-2-phenyl-4-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-amine (395c)



The title compound was prepared according to general procedure **K**, from *N*-{methoxy[4-(trifluoromethyl)phenyl]methyl}benzamide (100 mg, 0.32 mmol), $Ca(NTf_2)_2$ (10 mg, 0.016 mmol), nBu$_4$NPF$_6$ (6 mg, 0.016 mmol) and tert-butyl isocyanide (32 mg, 0.39 mmol) in EtOAc (2 mL).

Following conversion to the product (1h 30 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow solid (101 mg, 87%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.38

IR ν_{max} (cm^{-1}): 3259, 2972, 1635, 1323, 1103, 849

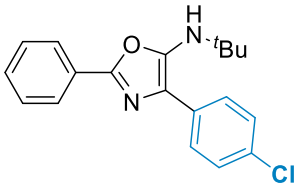
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_3N_2O$ 361.1528; Found 361.1527

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 7.1 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.45 (m, 3H), 5.88 (s, 1H), 1.34 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.5, 150.3, 136.6, 129.9, 129.2, 127.1, 125.9 (q, *J* = 31.8 Hz), 125.3, 125.3 (d, *J* = 3.9 Hz), 125.1, 124.5 (q, *J* = 271.7 Hz), 121.0, 53.3, 30.0.

^{19}F NMR (376 MHz, DMSO-d_6): 60.59

***N*-*tert*-butyl-4-(4-chlorophenyl)-2-phenyl-1,3-oxazol-5-amine (395d)**



The title compound was prepared according to general procedure **K**, from *N*-[(4-chlorophenyl)(methoxy)methyl]benzamide (90 mg, 0.33 mmol), $Ca(NTf_2)_2$ (10 mg, 0.016 mmol), nBu_4NPF_6 (6 mg, 0.016 mmol) and tert-butyl isocyanide (33 mg, 0.39 mmol) in EtOAc (2 mL).

Following conversion to the product (15 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a pale yellow solid (95 mg, 89%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.38

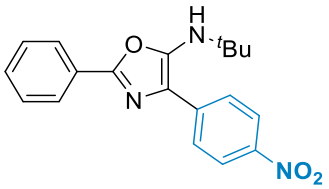
IR ν_{max} (cm^{-1}): 3251, 3055, 2970, 2867, 1634, 1492

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}ClN_2O$ 327.1264; Found 327.1259

^1H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.95 – 7.90 (m, 2H), 7.56 – 7.43 (m, 5H), 5.56 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.9, 149.0, 131.3, 130.5, 129.9, 129.2, 128.4, 127.2, 126.9, 125.1, 123.1, 53.3, 30.0.

***N*-tert-butyl-4-(4-nitrophenyl)-2-phenyl-1,3-oxazol-5-amine (395e)**



The title compound was prepared according to general procedure **K**, from *N*-[methoxy(4-nitrophenyl)methyl]benzamide (100 mg, 0.35 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), nBu_4NPF_6 (7 mg, 0.018 mmol) and tert-butyl isocyanide (35 mg, 0.42 mmol) in EtOAc (2 mL).

Following conversion to the product (1h 15 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a red solid (84 mg, 71%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.18

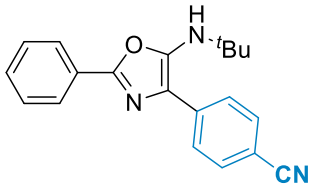
IR ν_{max} (cm^{-1}): 3395, 2980, 2909, 1590, 1321, 1216

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}N_3O_3$ 338.1505; Found 338.1505

^1H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.1 Hz, 2H), 7.93 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.59 – 7.45 (m, 3H), 6.40 (s, 1H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 152.8, 152.0, 144.1, 139. 6, 129.9, 129.3, 126.8, 125.0, 124.9, 123.9, 118.0, 53.4, 29.9.

4-[5-(*tert*-butylamino)-2-phenyl-1,3-oxazol-4-yl]benzonitrile (395f)



The title compound was prepared according to general procedure **K**, from *N*-{(4-cyanophenyl)[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.34 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), nBu_4NPF_6 (7 mg, 0.017 mmol) and tert-butyl isocyanide (34 mg, 0.41 mmol) in EtOAc (2 mL).

Following conversion to the product (30 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a white solid (78 mg, 72%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.16

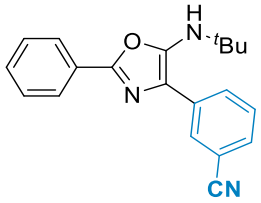
IR ν_{max} (cm^{-1}): 3261, 3060, 2973, 2867, 2230, 1628

HRMS (ESI) m/z: $[M - CH_3]^+$ Calcd for $C_{19}H_{16}F_3N_2O$ 302.1293; Found 302.1227

^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.45 (m, 2H), 6.15 (s, 1H), 1.37 (s, 4H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.0, 151.1, 137.3, 132.3, 129.9, 129.2, 126.9, 125.1, 125.0, 119.4, 119.3, 107.3, 53.3, 29.9.

3-[5-(*tert*-butylamino)-2-phenyl-1,3-oxazol-4-yl]benzonitrile (395g)



The title compound was prepared according to general procedure **K**, from *N*-[(3-cyanophenyl)(methoxy)methyl]benzamide (100 mg, 0.38 mmol), $Ca(NTf_2)_2$ (11 mg, 0.019 mmol), nBu_4NPF_6 (7 mg, 0.019 mmol) and tert-butyl isocyanide (38 mg, 0.45 mmol) in EtOAc (2 mL).

Following conversion to the product (20 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow solid (107 mg, 90%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.15

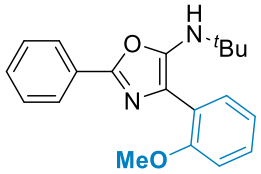
IR ν_{max} (cm^{-1}): 3260, 3067, 2972, 2233, 1636, 1364

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}N_3O$ 318.1606; Found 318.1607

^1H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.69 – 7.59 (m, 2H), 7.58 – 7.45 (m, 3H), 5.92 (s, 1H), 1.34 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.5, 149.9, 133.7, 129.9, 129.7, 129.4, 129.3, 129.2, 128.0, 127.0, 125.1, 120.5, 119.1, 111.5, 53.3, 30.0.

***N*-*tert*-butyl-4-(2-methoxyphenyl)-2-phenyl-1,3-oxazol-5-amine (395h)**



The title compound was prepared according to general procedure **K**, from *N*-[methoxy(2-methoxyphenyl)methyl]benzamide (80 mg, 0.30 mmol), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), nBu_4NPF_6 (6 mg, 0.015 mmol) and tert-butyl isocyanide (29 mg, 0.35 mmol) in EtOAc (1.5 mL).

Following conversion to the product (1h 30 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (86 mg, 90%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.19

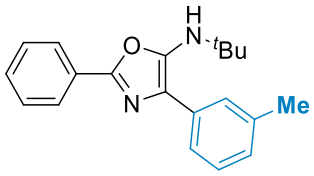
IR ν_{max} (cm^{-1}): 3354, 2963, 1597, 1453, 1233, 750

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O_2$ 323.1760; Found 323.1760

^1H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.67 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 – 7.39 (m, 1H), 7.31 – 7.24 (m, 1H), 7.12 – 7.07 (m, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 5.17 (s, 1H), 3.89 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 154.5, 152.4, 150.4, 129.2, 129.1, 127.8, 127.4, 124.6, 121.6, 121.0, 115.9, 111.9, 55.5, 52.7, 30.0.

***N*-tert-butyl-4-(3-methylphenyl)-2-phenyl-1,3-oxazol-5-amine (395i)**



The title compound was prepared according to general procedure **K**, from **1i** (100 mg, 0.35 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) and tert-butyl isocyanide (35 mg, 0.42 mmol) in EtOAc (2 mL).

Following conversion to the product (20 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil which solidifies on standing (101 mg, 93%)

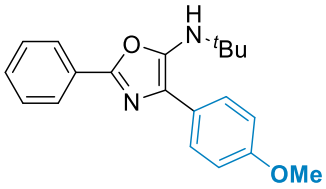
RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.42

^1H NMR (400 MHz, DMSO-d_6): δ 7.97 – 7.90 (m, 2H), 7.84 – 7.77 (m, 2H), 7.56 – 7.45 (m, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 5.41 (s, 1H), 2.35 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.8, 148.6, 137.3, 132.3, 129.7, 129.2, 128.2, 127.4, 127.0, 125.9, 125.1, 124.6, 122.5, 53.3, 30.1, 21.3.

*data in accordance with literature[135]

***N-tert*-butyl-4-(4-methoxyphenyl)-2-phenyl-1,3-oxazol-5-amine (395j)**



The title compound was prepared according to general procedure **K**, from *N*-[methoxy(4-methoxyphenyl)methyl]benzamide (50 mg, 0.18 mmol), $Ca(NTf_2)_2$ (6 mg, 0.009 mmol), nBu_4NPF_6 (4 mg, 0.009 mmol) and tert-butyl isocyanide (18mg, 0.22 mmol) in EtOAc (1 mL).

Following conversion to the product (3h) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a white solid (24 mg, 40%)

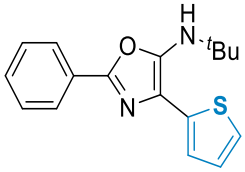
RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.17

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.95 – 7.91 (m, 2H), 7.57 – 7.44 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.19 (s, 1H), 3.78 (s, 3H), 1.25 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 158.0, 154.3, 147.3, 129.8, 129.2, 127.5, 126.8, 126.1, 125.1, 124.8, 113.7, 55.1, 53.3, 30.1.

*data in accordance with literature[135]

***N-tert*-butyl-2-phenyl-4-(thiophen-2-yl)-1,3-oxazol-5-amine (395k)**



The title compound was prepared according to general procedure **K**, from *N*-{[(propan-2-yl)oxy](thiophen-2-yl)methyl}benzamide (73 mg, 0.27 mmol), $Ca(NTf_2)_2$ (8 mg, 0.013 mmol), nBu_4NPF_6 (5 mg, 0.013 mmol) and tert-butyl isocyanide (26 mg, 0.32 mmol) in EtOAc (1 mL).

Following conversion to the product (1h 30 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a brown oil which solidifies (46 mg, 58%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.40

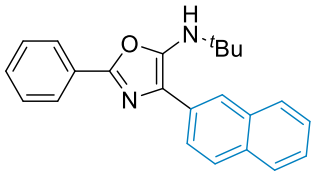
IR ν_{max} (cm^{-1}): 3256, 2968, 1648, 1341, 1202, 830

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2OS$ 299.1218; Found 299.1215

^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz,) δ 7.91 (d, *J* = 6.8 Hz, 2H), 7.56 – 7.46 (m, 4H), 7.43 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.34 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 154.1, 147.2, 134.9, 129.9, 129.2, 127.6, 127.1, 125.2, 124.1, 122.7, 121.9, 53.3, 30.0.

_N_-tert-butyl-4-(naphthalen-2-yl)-2-phenyl-1,3-oxazol-5-amine (395l)



The title compound was prepared according to general procedure **K**, from *N*-{(naphthalen-2-yl)[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.31 mmol), $Ca(NTf_2)_2$ (9 mg, 0.016 mmol), nBu_4NPF_6 (6 mg, 0.016 mmol) and tert-butyl isocyanide (31 mg, 0.38 mmol) in EtOAc (2 mL).

Following conversion to the product (15 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a pale yellow solid (96 mg, 90%)

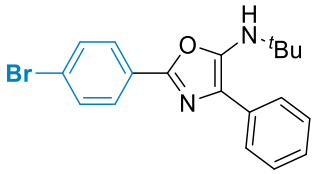
RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.40

^1H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.23 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.01 – 7.92 (m, 4H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.44 (m, 5H), 5.63 (s, 1H), 1.34 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 154.0, 149.2, 133.2, 131.7, 130.0, 129.8, 129.2, 127.9, 127.7, 127.6, 127.4, 126.3, 125.6, 125.2, 124.2, 124.0, 123.4, 53.4, 30.1.

*data in accordance with literature[135]

2-(4-bromophenyl)-*N*-tert-butyl-4-phenyl-1,3-oxazol-5-amine (415a)



The title compound was prepared according to general procedure **K**, from 4-bromo-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.29 mmol), $Ca(NTf_2)_2$ (9 mg, 0.014 mmol), $n$$Bu_4NPF_6$ (6 mg, 0.014 mmol) and tert-butyl isocyanide (29 mg, 0.35 mmol) in EtOAc (2 mL).

Following conversion to the product (15 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a pale-yellow solid (100 mg, 94%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.41

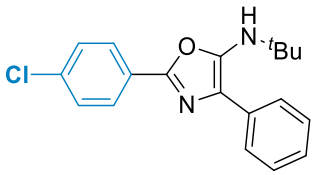
IR ν_{max} (cm^{-1}): 3262, 3057, 2968, 2927, 1631, 1469

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}BrN_2O$ 371.0759; Found 371.0755

^1H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.26 – 7.20 (m, 1H), 5.53 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 152.9, 149.0, 132.2, 128.4, 127.0, 126.5, 126.3, 125.3, 124.1, 123.0, 53.2, 30.1.

***N*-tert-butyl-2-(4-chlorophenyl)-4-phenyl-1,3-oxazol-5-amine (415b)**



The title compound was prepared according to general procedure **K**, from 4-chloro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.33 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), $n$$Bu_4NPF_6$ (6 mg, 0.017 mmol) and tert-butyl isocyanide (33 mg, 0.40 mmol) in EtOAc (2 mL).

Following conversion to the product (10 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a white solid (98 mg, 91%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.45

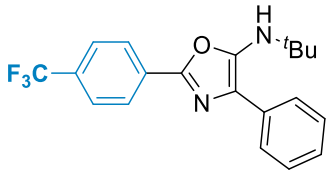
IR ν_{max} (cm^{-1}): 3262, 3058, 2969, 1633, 1392, 1071

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}ClN_2O$ 327.1264; Found 327.1252

^1H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* = 7.1 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.27 – 7.20 (m, 1H), 5.52 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 152.8, 149.0, 134.3, 132.3, 129.3, 128.4, 126.8, 126.3, 126.2, 125.3, 124.1, 53.2, 30.1.

***N*-tert-butyl-4-phenyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-amine (415c)**



The title compound was prepared according to general procedure **K**, from *N*-{phenyl[(propan-2-yl)oxy]methyl}-4-(trifluoromethyl)benzamide (100 mg, 0.30 mmol), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), nBu_4NPF_6 (6 mg, 0.015 mmol) and tert-butyl isocyanide (30 mg, 0.36 mmol) in EtOAc (2 mL).

Following conversion to the product (40 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow solid (91 mg, 85%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.43

IR ν_{max} (cm^{-1}): 3312, 2971, 2920, 1618, 1322, 1124

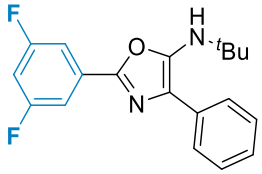
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_3N_2O$ 361.1528; Found 361.1525

^1H NMR (400 MHz, DMSO-d_6): 8.10 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.71 (s, 1H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 152.0, 149.7, 132.2, 130.8, 129.2 (q, *J* = 31.9 Hz), 128.4, 126.3, 126.2 (d, *J* = 3.4 Hz), 125.5, 125.3, 124.1 (q, *J* = 272.1 Hz).123.5, 53.3, 30.0.

^{19}F NMR (376 MHz, DMSO-d_6): 61.10

***N*-tert-butyl-2-(3,5-difluorophenyl)-4-phenyl-1,3-oxazol-5-amine (415d)**



The title compound was prepared according to general procedure **K**, from 3,5-difluoro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.33 mmol), $Ca(NTf_2)_2$ (10 mg, 0.016 mmol), $n$$Bu_4NPF_6$ (6 mg, 0.016 mmol) and tert-butyl isocyanide (33 mg, 0.39 mmol) in EtOAc (2 mL).

Following conversion to the product (45 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange solid (98 mg, 91%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.43

IR ν_{max} (cm^{-1}): 3274, 3084, 2972, 1625, 1356, 1120

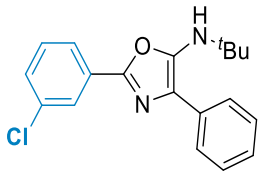
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}F_2N_2O$ 329.1465; Found 329.1460

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.45 – 7.35 (m, 3H), 7.24 (t, *J* = 7.3 Hz, 1H), 5.71 (s, 1H), 1.32 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 164.1 (d, *J* = 13.3 Hz), 161.6 (d, *J* = 12.9 Hz), 151.2 (t, *J* = 3.4 Hz), 149.7, 132.0, 130.3 (t, *J* = 10.6 Hz), 128.4, 126.4, 125.3, 123.5, 108.1 (d, *J* = 7.8 Hz), 107.9 (d, *J* = 7.6 Hz), 105.0 (t, *J* = 26.0 Hz), 53.3, 30.1.

^{19}F NMR (376 MHz, DMSO-d_6): 108.12

***N*-tert-butyl-2-(3-chlorophenyl)-4-phenyl-1,3-oxazol-5-amine (415e)**



The title compound was prepared according to general procedure **K**, from 3-chloro-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.33 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), $n$$Bu_4NPF_6$ (6 mg, 0.017 mmol) and tert-butyl isocyanide (33 mg, 0.40 mmol) in EtOAc (2 mL).

Following conversion to the product (1h) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a pale yellow solid (99 mg, 92%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.38

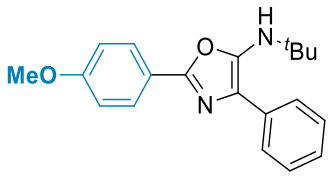
IR ν_{max} (cm^{-1}): 3269, 3066, 2974, 1627, 1492, 1203

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}ClN_2O$ 327.1264; Found 327.1259

^1H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.61 – 7.51 (m, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.58 (s, 1H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 152.2, 149.3, 133.9, 132.2, 131.3, 129.5, 129.2, 128.4, 126.4, 125.3, 124.4, 123.9, 123.6, 53.3, 30.1.

***N*-tert-butyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazol-5-amine (415f)**



The title compound was prepared according to general procedure **K**, from 4-methoxy-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (100 mg, 0.34 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.017 mmol) and tert-butyl isocyanide (34 mg, 0.41 mmol) in EtOAc (2 mL).

Following conversion to the product (30 min) and column chromatography (1:5 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a white solid (105 mg, 97%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.19

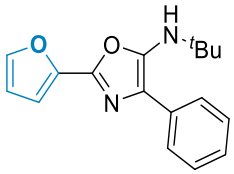
IR ν_{max} (cm^{-1}): 3258, 3010, 2974, 2839, 1614, 1502

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O_2$ 323.1760; Found 323.1759

^1H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 5.27 (s, 1H), 3.82 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 160.6, 154.4, 148.0, 132.5, 128.3, 126.9, 126.3, 125.3, 125.0, 120.2, 114.6, 55.4, 53. 2, 30.1.

***N*-tert-butyl-2-(furan-2-yl)-4-phenyl-1,3-oxazol-5-amine (415g)**



The title compound was prepared according to general procedure **K**, from *N*-{phenyl[(propan-2-yl)oxy]methyl}furan-2-carboxamide (100 mg, 0.39 mmol), $Ca(NTf_2)_2$ (12 mg, 0.019 mmol), nBu_4NPF_6 (7 mg, 0.019 mmol) and tert-butyl isocyanide (39 mg, 0.46 mmol) in EtOAc (2 mL).

Following conversion to the product (20 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an off-white solid (71 mg, 65%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.26

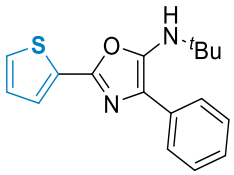
IR ν_{max} (cm^{-1}): 3287, 3118, 2973, 1633, 1497, 1206

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2O_2$ 283.1447; Found 283.1447

^1H NMR (400 MHz, DMSO-d_6): δ 7.98 (d, *J* = 7.3 Hz, 2H), 7.93 – 7.88 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.05 – 7.03 (m, 1H), 6.70 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.39 (s, 1H), 1.25 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 148.0, 147.6, 144.9, 142.6, 132.1, 128.3, 126.5, 125.4, 124.7, 112.2, 110.4, 53.4, 30.0.

***N*-tert-butyl-4-phenyl-2-(thiophen-2-yl)-1,3-oxazol-5-amine (415h)**



The title compound was prepared according to general procedure **K**, from *N*-{phenyl[(propan-2-yl)oxy]methyl}thiophene-2-carboxamide (100 mg, 0.36 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), nBu_4NPF_6 (7 mg, 0.018 mmol) and tert-butyl isocyanide (36 mg, 0.44 mmol) in EtOAc (2 mL).

Following conversion to the product (2.5 h) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow solid (96 mg, 86%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.37

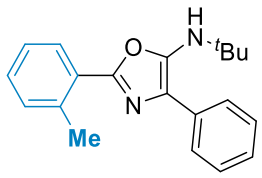
IR ν_{max} (cm^{-1}): 3268, 3104, 2974, 1633, 1498, 1364

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2OS$ 299.1218; Found 299.1218

^1H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.72 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.59 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.20 (dd, *J* = 4.9, 3.7 Hz, 1H), 5.40 (s, 1H), 1.26 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 150.7, 148.0, 132.1, 130. 0, 128.5, 128.4, 128.3, 126.6, 126.4, 125.4, 124.8, 53.3, 30.0.

***N*-tert-butyl-2-(2-methylphenyl)-4-phenyl-1,3-oxazol-5-amine (415i)**



The title compound was prepared according to general procedure **K**, from 2-methyl-*N*-{phenyl[(propan-2-yl)oxy]methyl}benzamide (90 mg, 0.33 mmol), $Ca(NTf_2)_2$ (10 mg, 0.016 mmol), nBu_4NPF_6 (6 mg, 0.016 mmol) and tert-butyl isocyanide (32 mg, 0.44 mmol) in EtOAc (2 mL).

Following conversion to the product (20 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an off-white solid (95 mg, 95%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.42

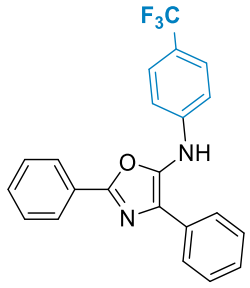
IR ν_{max} (cm^{-1}): 3327, 3065, 2969, 1601, 1447, 1365

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O$ 307.1810; Found 307.1807

^1H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 7.3 Hz, 2H), 7.93 – 7.87 (m, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.23 (t, *J* = 7.4 Hz, 1H), 5.41 (s, 1H), 2.70 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 154.3, 148.2, 136.0, 132.6, 131.7, 129.4, 128.3, 127.5, 126.3, 126.2, 126.2, 125.3, 124.0, 53.2, 30.1, 21.9.

2,4-diphenyl-*N*-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-amine (418a)



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), nBu$_4$NPF$_6$ (8 mg, 0.021 mmol) and 1-isocyano-4-(trifluoromethyl)benzene (85 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (20 min) and column chromatography (1:20 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (129 mg, 82%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.48

IR ν_{max} (cm^{-1}): 3369, 3061, 2973, 1613, 1320, 830

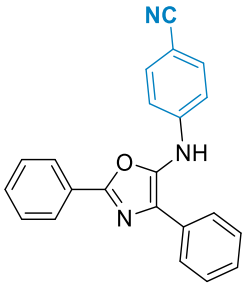
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}F_3N_2O$ 381.1215; Found 381.1215

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (s, 1H), 8.09 – 7.96 (m, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.62 – 7.52 (m, 5H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ ^{13}C NMR (101 MHz,) δ 157.2, 148.3, 141.8, 131.2, 131.2, 130.1, 129.7, 129.3, 128.3, 127.3, 126.3, 126.2, 125.3 (q, *J* = 270.8 Hz), 120.2 (q, *J* = 32.3 Hz), 114.5, 46.2.

^{19}F NMR (376 MHz, DMSO-d_6): 59.56

4-[(2,4-diphenyl-1,3-oxazol-5-yl)amino]benzonitrile (418b)



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), nBu_4NPF_6 (8 mg, 0.021 mmol) and 4-isocyanobenzonitrile (64 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (30 min) and column chromatography (10 to 20% EtOAc/Hex, 1% NEt_3) the pure product was obtained as an off-white solid (120 mg, 86%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.27

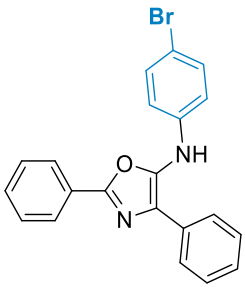
IR ν_{max} (cm^{-1}): 3287, 3060, 2219, 1601, 1512, 1328, 1173, 690

HRMS (ESI) m/z: [M - H]+ Calcd for $C_{22}H_{14}N_3O$ 336.1137; Found 336.1149

^1H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 8.06 – 7.98 (m, 2H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 156.9, 148.5, 140.7, 134.0, 130.8, 130.5, 129.7, 129.2, 128.8, 127.9, 126.8, 125.9, 125.7, 119.7, 114.5, 100.9.

***N*-(4-bromophenyl)-2,4-diphenyl-1,3-oxazol-5-amine (418c)**



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (60 mg, 0.24 mmol), $Ca(NTf_2)_2$ (7 mg, 0.012 mmol),

nBu_4NPF_6 (5 mg, 0.012 mmol) and 1-bromo-4-isocyanobenzene (53 mg, 0.29 mmol) in EtOAc (1 mL).

Following conversion to the product (45 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (77 mg, 82%)

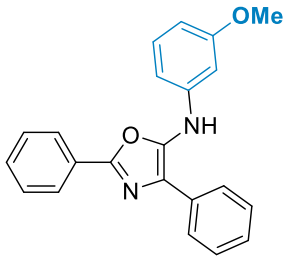
RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.42

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.03 – 7.98 (m, 2H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.53 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 156.3, 143.6, 142.2, 132.1, 130.8, 130.6, 129.2, 128.9, 128.7, 127.6, 126.9, 125.7, 125.6, 116.2, 110.7.

*data in accordance with literature[135]

_N_-(3-methoxyphenyl)-2,4-diphenyl-1,3-oxazol-5-amine (418d)



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), *n*Bu_4NPF_6 (8 mg, 0.021 mmol) and 1-isocyano-3-methoxybenzene (64 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (15 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (72 mg, 51%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.37

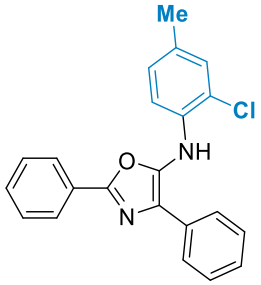
IR ν_{max} (cm^{-1}): 3298, 2922, 1595, 1331, 1202, 840

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$ 343.1447; Found 343.1440

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.03 – 7.97 (m, 2H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.59 – 7.50 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.46 – 6.28 (m, 1H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 160.4, 156.2, 145.5, 142.6, 131.0, 130.6, 130.3, 129.2, 128.7, 128.6, 127.5, 127.0, 125.7, 106.8, 105.0, 100.2, 54.9.

***N*-(2-chloro-4-methylphenyl)-2,4-diphenyl-1,3-oxazol-5-amine (418e)**



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), $n$$Bu_4NPF_6$ (8 mg, 0.021 mmol) and 2-chloro-1-isocyano-4-methylbenzene (75 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (15 min) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (139 mg, 93%)

RF (1:5 EtOAc/Hex, 1% NEt_3) = 0.56

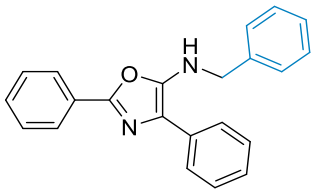
IR ν_{max} (cm^{-1}): 3300, 2920, 1640, 1506, 1283, 810

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}ClN_2O$ 361.1108; Found 361.1109

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 8.02 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.59 – 7.51 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.25 (s, 1H), 6.92 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 156.9, 142.2, 138.3, 130.8, 130.7, 130.5, 130.1, 130.0, 129.2, 128.8, 128.6, 127.7, 126.9, 125.8, 125.6, 119.0, 115.0, 19.7.

***N*-benzyl-2,4-diphenyl-1,3-oxazol-5-amine (418f)**



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), nBu_4NPF_6 (8 mg, 0.021 mmol) and benzyl isocyanide (58 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (1h 15 min) and column chromatography (1:20 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (75 mg, 55%)

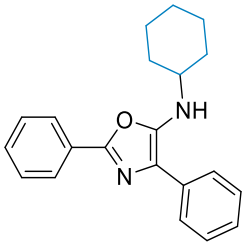
RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.53

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.50 – 7.43 (m, 4H), 7.43 – 7.36 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 150.6, 150.3, 140.2, 132.8, 129.0, 129.0, 128.5, 128.4, 127.5, 127.2, 127.0, 125.0, 124.5, 124.2, 113.9, 47.4.

*data in accordance with literature[135]

***N*-cyclohexyl-2,4-diphenyl-1,3-oxazol-5-amine (418g)**



The title compound was prepared according to general procedure **K**, from *N*-(Methoxy(phenyl)methyl)benzamide (100 mg, 0.41 mmol), $Ca(NTf_2)_2$ (12 mg, 0.021 mmol), nBu_4NPF_6 (8 mg, 0.021 mmol) and cyclohexyl isocyanide (54 mg, 0.50 mmol) in EtOAc (2 mL).

Following conversion to the product (5h) and column chromatography (1:9 EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (82 mg, 62%)

RF (1:9 EtOAc/Hex, 1% NEt_3) = 0.42

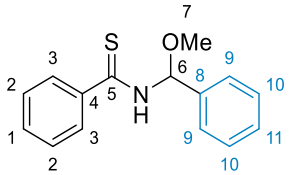
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.47 – 7.36 (m, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.07 (d, *J* = 7.2 Hz, 1H), 3.47 – 3.37 (m, 1H), 2.00 – 1.90 (m, 2H), 1.80 – 1.68 (m, 2H), 1.64 – 1.52 (m, 1H), 1.46 – 1.24 (m, 4H), 1.23 – 1.08 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 151.2, 150.1, 132.8, 129.2, 129.1, 128.4, 127.4, 125.3, 124.7, 124.6, 116.5, 53.9, 33.4, 25.4, 24.8.

*data in accordance with literature[135]

9.4.4. Synthesis of *N*-thioacyl-*N*,*O*-acetals

N-[methoxy(phenyl)methyl]benzenecarbothioamide (427a)



Title compound was prepared according to general procedure **J** from thiobenzamide (300 mg, 2.20 mmol), benzaldehyde dimethyl acetal (670 mg, 4.40 mmol) and MsOH (21 mg, 0.22 mmol) in Et_2O (11 mL). Work up and purification by FCC (Hex to 5% Et_2O/Hex) afforded the pure product as a yellow solid (136 mg, 24%).

RF (1:5 EtOAc/Hex) = 0.52

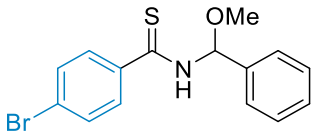
IR ν_{max} (cm^{-1}): 3240, 2990, 2834, 1512, 1446, 1352, 1066, 743

HRMS (ESI) m/z: $[M - CH_4O]^+$ Calcd for $C_{14}H_{12}NS$ 226.0690; Found 226.0693

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (d, *J* = 7.8 Hz, 1H, **NH**), 7.77 (d, *J* = 7.4 Hz, 2H, **H3**), 7.58 – 7.46 (m, 3H, **ArH**), 7.46 – 7.28 (m, 5H, **ArH**), 6.88 (d, *J* = 7.9 Hz, 1H, **H6**), 3.51 (s, 3H, **H7**).

^{13}C NMR (101 MHz, DMSO-d_6): δ 199.5 (**C5**), 141.0 (**C4**), 138.5 (**C8**), 131.0 (**ArC**), 128.5 (**ArC**), 128.3 (**ArC**), 128.0 (**ArC**), 127.6 (**ArC**), 126.4 (**ArC**), 87.5 (**C6**), 56.2 (**C7**).

4-bromo-*N*-[methoxy(phenyl)methyl]benzene-1-carbothioamide (427b)



Title compound was prepared according to general procedure **J** from 4-bromothiobenzamide (514 mg, 2.40 mmol), benzaldehyde dimethyl acetal (724 mg, 4.80 mmol) and MsOH (23 mg, 0.024 mmol) in Et_2O (12 mL). Work up and purification by FCC (1% EtOAc/Hex, 1% NEt_3) afforded the pure product as a yellow oil which solidifies to a yellow solid (289 mg, 36%).

RF (1:5 EtOAc/Hex) = 0.52

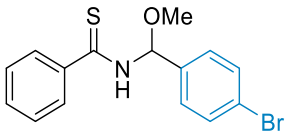
IR ν_{max} (cm^{-1}): 3248, 3027, 2927, 1585, 1395, 1246, 1060, 827

HRMS (ES) m/z: $[M - CH_4O]^+$ Calcd for $C_{14}H_{11}BrNS$ 303.9796; Found 303.9801

^1H NMR (400 MHz, DMSO-d_6): δ 11.09 (d, *J* = 6.9 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.44 – 7.31 (m, 3H), 6.83 (d, *J* = 7.1 Hz, 1H), 3.50 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 198.0, 139.9, 138.3, 130.9, 129.6, 128.5, 128.3, 126.4, 124.7, 87.6, 56.3.

***N*-[(4-bromophenyl)(methoxy)methyl]benzenecarbothioamide (427c)**



Title compound was prepared according to general procedure **J** from thiobenzamide (300 mg, 2.20 mmol), benzaldehyde dimethyl acetal (1.00 g, 4.40 mmol) and MsOH (21 mg, 0.022 mmol) in Et_2O (11 mL). Work up and purification by FCC (5% EtOAc/Hex, 1% NEt_3) afforded the pure product as a yellow solid (247 mg, 34%).

RF (1:5 EtOAc/Hex) = 0.43

IR ν_{max} (cm^{-1}): 3275, 3059, 3024, 1593, 1504, 1484, 1352, 1067, 688

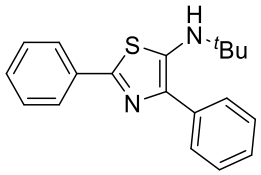
HRMS (ESI) m/z: $[M - CH_3O]$ + Calcd for $C_{14}H_{11}BrNS$ 303.9796; Found 303.9814

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (d, *J* = 7.7 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.49 – 7.39 (m, 4H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.51 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 199.6, 140.8, 137.9, 131.3, 131.1, 128.7, 128.0, 127.6, 121.6, 86.9, 56.3.

9.4.5. Synthesis of 5-aminothiazoles

_N_-tert-butyl-2,4-diphenyl-1,3-thiazol-5-amine (436a)



The title compound was prepared according to general procedure **L**, from *N*-[methoxy(phenyl)methyl]benzenecarbothioamide (50 mg, 0.19 mmol), $Ca(NTf_2)_2$ (12 mg, 0.019 mmol), $n$$Bu_4NPF_6$ (8 mg, 0.019 mmol) and tert-butyl isocyanide (19 mg, 0.23 mmol) in EtOAc (1 mL).

Following conversion to the product (30 min) and column chromatography (1:20 EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (50 mg, 83%)

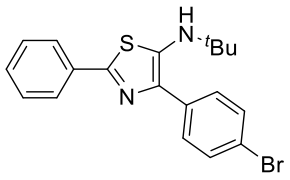
RF (1:5 EtOAc/Hex) = 0.57

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 6.9 Hz, 2H), 7.53 – 7.36 (m, 5H), 7.28 (t, *J* = 7.4 Hz, 1H), 4.97 (s, 1H), 1.22 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 155.9, 142.2, 142.1, 135.2, 133.7, 129.4, 129.1, 128.2, 127.6, 126.9, 125.3, 53.2, 28.9.

*data in accordance with literature[135]

4-(4-bromophenyl)-*N*-tert-butyl-2-phenyl-1,3-thiazol-5-amine (436b)



The title compound was prepared according to general procedure **L**, from *N*-[(4-bromophenyl)(methoxy)methyl]benzenecarbothioamide (50 mg, 0.15 mmol), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), nBu_4NPF_6 (6 mg, 0.015 mmol) and tert-butyl isocyanide (15 mg, 0.18 mmol) in EtOAc (0.8 mL).

Following conversion to the product (15 min) and column chromatography (2% EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (44 mg, 76%)

RF (1:5 EtOAc/Hex) = 0.70

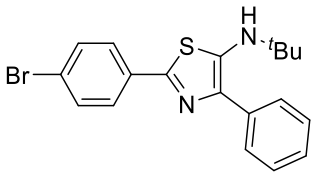
IR ν_{max} (cm^{-1}): 3326, 3063, 2968, 1520, 1479, 1384, 1200, 1069, 829

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}BrN_2S$ 387.0531; Found 387.0532

^1H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.93 – 7.87 (m, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.39 (m, 3H), 5.08 (s, 1H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 156.4, 142.7, 141.2, 134.4, 133.6, 131.1, 129.6, 129.6, 129.2, 125.4, 119.7, 53.3, 28.8.

2-(4-bromophenyl)-*N*-tert-butyl-4-phenyl-1,3-thiazol-5-amine (436c)



The title compound was prepared according to general procedure **L**, from 4-bromo-*N*-[methoxy(phenyl)methyl]benzene-1-carbothioamide (50 mg, 0.15 mmol), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), nBu_4NPF_6 (6 mg, 0.015 mmol) and tert-butyl isocyanide (15 mg, 0.18 mmol) in EtOAc (0.8 mL).

Following conversion to the product (15 min) and column chromatography (2% EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (51 mg, 89%)

RF (1:5 EtOAc/Hex) = 0.59

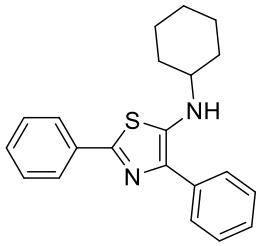
IR ν_{max} (cm^{-1}): 3373, 3057, 2968, 1523, 1487, 1384, 1202, 1069, 826

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}BrN_2S$ 387.0531; Found 387.0539

^1H NMR (400 MHz, DMSO-d_6): δ 8.11 – 8.03 (m, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 5.09 (s, 1H), 1.22 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 154.2, 142.7, 141.9, 135.1, 132.9, 132.1, 128.3, 127.6, 127.1, 126.9, 122.4, 53.2, 28.9.

***N*-cyclohexyl-2,4-diphenyl-1,3-thiazol-5-amine (436d)**



The title compound was prepared according to general procedure **L**, from *N*-[methoxy(phenyl)methyl]benzenecarbothioamide (50 mg, 0.19 mmol), $Ca(NTf_2)_2$ (12 mg, 0.019 mmol), nBu_4NPF_6 (8 mg, 0.019 mmol) and cyclohexyl isocyanide (26 mg, 0.23 mmol) in EtOAc (1 mL).

Following conversion to the product (1 h) and column chromatography (2% EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (41 mg, 63%)

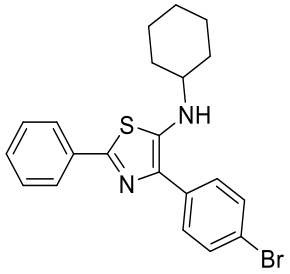
RF (1:5 EtOAc/Hex) = 0.46

^1H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.47 – 7.40 (m, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.10 – 1.93 (m, 2H), 1.80 – 1.67 (m, 2H), 1.61 – 1.53 (m, 1H), 1.44 – 1.08 (m, 5H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 150.0, 146.9, 135.3, 133.9, 133.3, 129.1, 128.7, 128.4, 126.8, 126.1, 124.8, 59.1, 32.4, 25.4, 24.6.

*data in accordance with literature[135]

4-(4-bromophenyl)-*N*-cyclohexyl-2-phenyl-1,3-thiazol-5-amine (436e)



The title compound was prepared according to general procedure **L**, from *N*-[(4-bromophenyl)(methoxy)methyl]benzenecarbothioamide (50 mg, 0.15 mmol), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), nBu_4NPF_6 (6 mg, 0.015 mmol) and cyclohexyl isocyanide (20 mg, 0.18 mmol) in EtOAc (0.8 mL).

Following conversion to the product (45 min) and column chromatography (2% EtOAc/Hex, 1% NEt_3) the pure product was obtained as an orange oil (37 mg, 60%)

RF (1:5 EtOAc/Hex) = 0.59

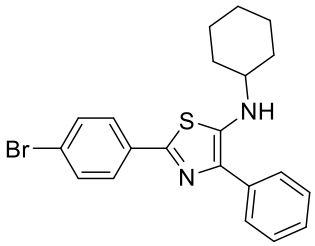
IR ν_{max} (cm^{-1}): 3276, 3060, 2927, 2952, 1590, 1481, 1347, 1068, 827

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}BrN_2S$ 413.0687; Found 413.0681

^1H NMR (400 MHz, DMSO-d_6): δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.83 – 7.78 (m, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 6.04 (d, *J* = 6.8 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.06 – 1.97 (m, 2H), 1.77 – 1.69 (m, 2H), 1.65 – 1.51 (m, 1H), 1.41 – 1.14 (m, 5H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 150.3, 147.6, 134.5, 133.7, 132.1, 131.3, 129.1, 128.8, 128.7, 124.9, 118.7, 59.2, 32.3, 25.3, 24.6.

2-(4-bromophenyl)-*N*-cyclohexyl-4-phenyl-1,3-thiazol-5-amine (436f)



The title compound was prepared according to general procedure **L**, from 4-bromo-*N*-[methoxy(phenyl)methyl]benzene-1-carbothioamide (50 mg, 0.15 mmol), $Ca(NTf_2)_2$ (9

mg, 0.015 mmol), *n*Bu_4NPF_6 (6 mg, 0.015 mmol) and cyclohexyl isocyanide (20 mg, 0.18 mmol) in EtOAc (0.8 mL).

Following conversion to the product (30 min) and column chromatography (2% EtOAc/Hex, 1% NEt_3) the pure product was obtained as a yellow oil (40 mg, 65%)

RF (1:5 EtOAc/Hex) = 0.68

IR ν_{max} (cm^{-1}): 3369, 2927, 2851, 1252, 1487, 1361, 1088, 971

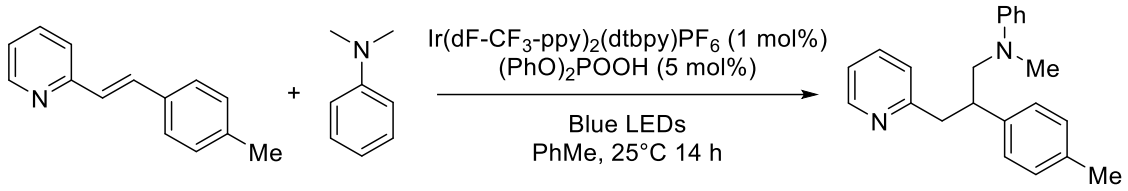
HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}BrN_2S$ 413.0687; Found 413.0698

^1H NMR (400 MHz, DMSO-d_6): δ 7.89 – 7.85 (m, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 6.01 (d, *J* = 7.0 Hz, 1H), 3.01 – 2.90 (m, 1H), 2.05 – 1.91 (m, 2H), 1.80 – 1.66 (m, 2H), 1.62 – 1.51 (m, 1H), 1.45 – 1.08 (m, 5H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 148.3, 147.5, 135.1, 133.2, 133.1, 132.0, 128.4, 126.8, 126.6, 126.2, 121.5, 59.2, 32.3, 25.3, 24.6.

9.5. Chapter 5 Experimental

Synthesis of N-Methyl-N-(3-(pyridin-2-yl)-2-(p-tolyl)propyl)aniline (539)



(E)-2-(p-Tolylstyryl)pyridine (30 mg, 0.15 mmol), Ir(dF-CF_3-ppy)$_2$(dtbpy)PF_6 (1.7 mg, 0.0015 mmol) and diphenyl phosphate (1.9 mg, 0.0077 mmol) were added to a Schlenk tube, which was then sealed, evacuated and backfilled with nitrogen three times. Toluene (1.5 mL) followed by N,N-dimethylaniline (37 mg, 0.31 mmol) was then added and the solution was subjected to three freeze-pump-thaw cycles. The flask was then irradiated with blue LED's overnight. Upon completion of the reaction, the solution was diluted with EtOAc and 1M NaOH was added. The aqueous layer was then extracted into EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was purified by FCC (10% EtOAc:Hex) to afford the pure product as an off-white solid (11 mg, 23%).

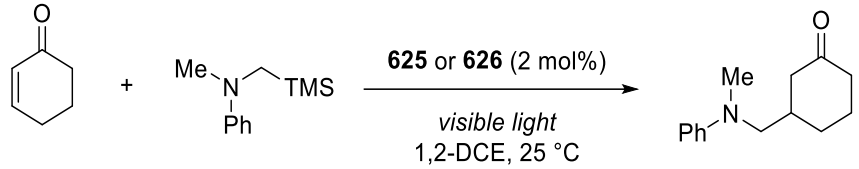
RF (1:3 EtOAc:Hex): 0.19

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.4 Hz, 1H), 7.49 (td, *J* = 7.7, 1.8 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.11 – 7.01 (m, 5H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 3.73 (dd, *J* = 14.5, 6.3 Hz, 1H), 3.64 – 3.51 (m, 1H), 3.38 (dd, *J* = 14.4, 8.1 Hz, 1H), 3.24 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.12 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.65 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.2, 149.2, 139.9, 136.5, 136.1, 129.8, 129.3, 129.2, 128.0, 123.8, 121.3, 115.9, 112.0, 59.4, 44.2, 42.2, 39.5, 21.2.

Data in accordance with literature[169]

Synthesis of 3-[(N-methylanilino)methyl]cyclohexanone (548)



To a Schlenk tube containing 1,2-DCE (2 mL) was added cyclohex-2-en-1-one (20 mg, 0.21 mmol) and **625** (3 mg, 0.0042 mmol) or **626** (2.5 mg, 0.0042 mmol) and N-methyl-N-(trimethylsilylmethyl)aniline (60 mg, 0.31 mmol). The flask was evacuated and backfilled three times with nitrogen and then subjected to three freeze-pump-thaw cycles. The flask was then irradiated with visible light overnight. Upon completion of the reaction, the reaction was quenched with sat. aq. $NaHCO_3$ and transferred to a separating funnel. The aqueous layer was extracted into DCM (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was purified by FCC (1:3 EtOAc:Hex) to afford the pure product as a colourless oil (14 mg, 31% using **625** and 6.5mg 14% using **626**).

RF (1:3 EtOAc:Hex): 0.52

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.19 (m, 2H), 6.87 – 6.54 (m, 3H), 3.39 – 3.16 (m, 2H), 2.97 (s, 3H), 2.50 – 2.18 (m, 4H), 2.15 – 2.00 (m, 2H), 2.02 – 1.89 (m, 1H), 1.70 – 1.57 (m, 1H), 1.48 – 1.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.1, 149.3, 129.4, 116.4, 112.1, 58.8, 46.1, 41.6, 38.5, 29.6, 25.3.

Data in accordance with literature[170]

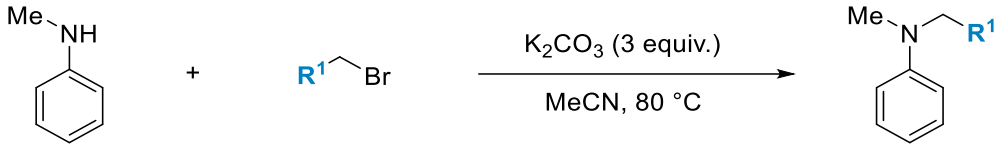
9.6. Chapter 6 Experimental

9.6.1. Chapter 6 General Procedures

General Procedure M

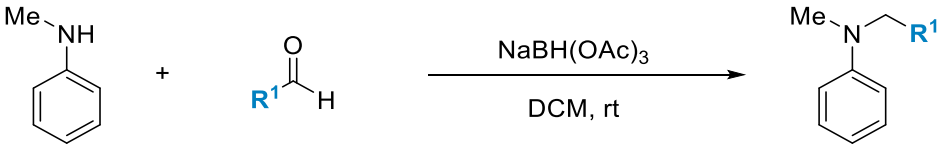
To a 4 mL vial capped with a capped with teflon cap was added 3-hydroxyisoindolinone or *N*-acyl-*N,O*-acetal (1 equiv.), aniline derivative (1.5 equiv.), $Ca(NTf_2)_2$ (5 mol%) and $n Bu_4NPF_6$ (5 mol%) in 1,2-DCE (0.2 M). The reaction was stirred at 80 °C until TLC analysis indicated full conversion to the product (typically 12 h). The solution was then concentrated and purified by FCC (EtOAc:Hept) to afford the pure compound.

General Procedure N



To a solution of N-methyl-aniline (1.0 equiv.) and K_2CO_3 (3.0 equiv.) in MeCN (0.2 M) was added alkyl bromide (1.1 equiv.). The suspension was heated to reflux overnight. Upon completion of the reaction (indicated by TLC), the reacted was cooled and quenched with water. The solution was then transferred to a separating funnel and the aqueous layer was extracted into DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC (DCM:Petrol) to afford the pure N,N-disubstituted anilines.

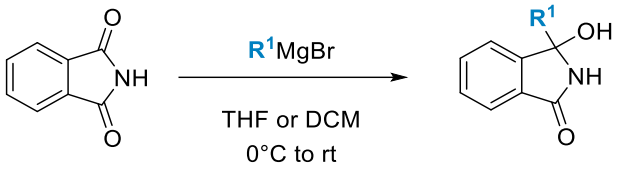
General Procedure O



To a solution of N-methyl-aniline (1.0 equiv.) and aldehyde (1.1 equiv.) in DCM (0.3 M) was added $NaBH(OAc)_3$ (1.5 equiv.) portion wise at 0 °C. The reaction was warmed to room temperature and stirred until TLC indicated full consumption of starting material. The reaction was then quenched with sat. aq. NaHCO3 and transferred to a separating funnel. The aqueous layer was extracted into DCM (3 x 15 mL) and the combined organic

layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC (DCM:Petrol) to afford the pure N,N-disubstituted anilines.

General Procedure P – Synthesis of 3-hydroxyisoindolinones by Grignard Addition

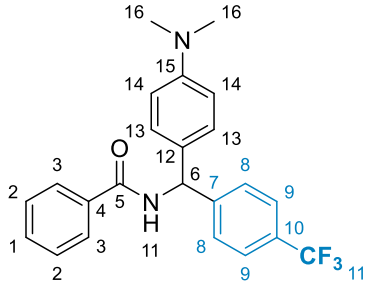


Phthalimide (1.0 equiv.) was added to a flame dried RBF and purged with argon. Dry THF or DCM (0.25 M) was added, and the solution was cooled to 0°C. The Grignard reagent* (3.0 equiv.) was then added dropwise, and the reaction was warmed to room temperature. Upon completion of the reaction (30 mins) which was indicated by the TLC, the reaction was quenched with NH_4Cl, and extracted into DCM (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The product was then purified by FCC (EtOAc:Hex) to afford the pure compound.

*Grignard reagents were either purchased or freshly prepared by suspending magnesium turnings (3.10 equiv.) in dry THF (1.0 M) under argon with 1,2-dibromoethane (0.1 equiv.) as an initiator. Dropwise addition of aryl halide (3.0 equiv.) and stirring for 2 h afforded the Grignard reagent which was then diluted to 0.5 M before being added to the electrophile.

9.6.2. aza-Freidel-Crafts Products – N-acyl-*N,O*-acetal Variation

N-[[4-(dimethylamino)phenyl]-[4-(trifluoromethyl)phenyl]methyl]benzamide (594a)



The title compound was prepared according to general procedure **M** from N-[(4-bromophenyl)(methoxy)methyl]benzamide (50 mg, 0.162 mmol), *N,N*-dimethylaniline (31 µL, 0.242 mmol), $Ca(NTf_2)_2$ (5 mg, 0.0081 mmol), nBu_4NPF_6 (3 mg, 0.0081 mmol) in 1,2-DCE (0.8 mL). Following completion of the reaction (12 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (56 mg, 87 %).

RF (1:3 EtOAc:Hept): 0.14

IR ν_{max} (cm^{-1}): 3219, 30432, 2801, 1633, 1519, 1321, 1111, 818

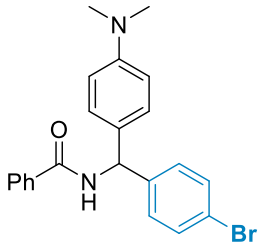
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}F_3N_2O$ 399.1684; Found 399.1680

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.78 (m, 2H, **H3**), 7.59 (d, *J* = 8.2 Hz, 2H, **H9**), 7.54 – 7.49 (m, 1H, **H1**), 7.48 – 7.40 (m, 4H, **H8, H2**), 7.11 (d, *J* = 8.6 Hz, 2H, **H13**), 6.69 (d, *J* = 8.9 Hz, 2H, **H14**), 6.64 (d, *J* = 7.1 Hz, 1H, **NH**), 6.36 (d, *J* = 7.1 Hz, 1H, **H6**), 2.95 (s, 6H, **H16**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.67 (**C5**), 150.39 (**C15**), 146.20 (**C7**), 134.19 (**C4**), 131.92 (**C1**), 128.87 (**C8**), 129.47 (q, *J* = 32.4 Hz, **C10**), 128.80 (**C12**), 128.30 (**C2**), 127.46 (**C3**), 127.18 (**C13**), 125.64 (q, *J* = 3.7 Hz, **C9**), 124.3 (q, *J* = 273.2 Hz, **C11**), 112.75 (**C14**), 57.17 (**C6**), 40.58 (**C16**).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4.

N-[(4-bromophenyl)-[4-(dimethylamino)phenyl]methyl]benzamide (594b)



The title compound was prepared according to general procedure **M** from N-[(4-bromophenyl)(methoxy)methyl]benzamide (50 mg, 0.156 mmol), *N,N*-dimethylaniline (30 µL, 0.234 mmol), $Ca(NTf_2)_2$ (5 mg, 0.0078 mmol), $n$$Bu_4NPF_6$ (3 mg, 0.0078 mmol) in 1,2-DCE (0.8 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (56 mg, 88 %).

RF (1:3 EtOAc:Hept): 0.16

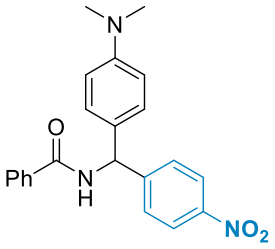
IR ν_{max} (cm^{-1}): 3317, 3055, 2883, 1631, 1519, 1484, 1010, 788

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}BrN_2O$ 409.0916; Found 409.0913

^1H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.77 (m, 2H), 7.54 – 7.48 (m, 1H), 7.48 – 7.39 (m, 4H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 7.3 Hz, 1H), 6.28 (d, *J* = 7.4 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 150.3, 141.2, 134.3, 131.8, 131.7, 129.0, 128.8, 128.7, 127.2, 121.2, 112.7, 56.8, 40.6.

N-[[4-(dimethylamino)phenyl]-(4-nitrophenyl)methyl]benzamide (594c)



The title compound was prepared according to general procedure **M** from N-[methoxy(4-nitrophenyl)methyl]benzamide (46 mg, 0.161 mmol), *N,N*-dimethylaniline (31 µL, 0.241 mmol), $Ca(NTf_2)_2$ (5 mg, 0.0080 mmol), $n$$Bu_4NPF_6$ (3 mg, 0.0080 mmol) in 1,2-DCE (0.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (50 mg, 83 %).

RF (1:1 EtOAc:Hept): 0.20

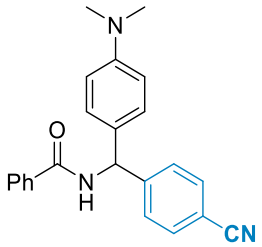
IR ν_{max} (cm^{-1}): 3293, 3056, 2920, 1631, 1515, 1342, 790

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}N_3O_3$ 376.1661; Found 376.1556

^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.84 – 7.79 (m, 2H), 7.57 – 7.41 (m, 5H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.64 (d, *J* = 6.6 Hz, 1H), 6.34 (d, *J* = 6.7 Hz, 1H), 2.95 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 150.5, 149.7, 147.2, 133.9, 132.1, 128.9, 128.9, 127.9, 127.5, 127.2, 123.9, 112.8, 57.4, 40.5.

N-[(4-cyanophenyl)-[4-(dimethylamino)phenyl]methyl]benzamide (594d)



The title compound was prepared according to general procedure **M** from N-{(4-cyanophenyl)[(propan-2-yl)oxy]methyl}benzamide (30 mg, 0.102 mmol), *N,N*-dimethylaniline (19 µL, 0.153 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0051 mmol), $n Bu_4NPF_6$ (2 mg, 0.0051 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (12 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (30 mg, 83 %).

RF (1:1 EtOAc:Hept): 0.11

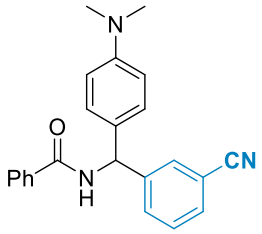
IR ν_{max} (cm^{-1}): 3299, 3032, 2883, 2227, 1631, 1521, 1353, 811

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}N_3O$ 356.1763; Found 356.1758

^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.77 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.48 – 7.40 (m, 4H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 6.9 Hz, 1H), 6.31 (d, *J* = 6.8 Hz, 1H), 2.95 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 150.5, 147.7, 134.0, 132.5, 132.1, 128.9, 128.8, 127.8, 127.7, 127.2, 119.0, 112.8, 111.1, 57.4, 40.5.

N-[(3-cyanophenyl)-[4-(dimethylamino)phenyl]methyl]benzamide (594e)



The title compound was prepared according to general procedure **M** from N-[(3-cyanophenyl)(methoxy)methyl]benzamide (50 mg, 0.188 mmol), *N,N*-dimethylaniline (36 µL, 0.282 mmol), $Ca(NTf_2)_2$ (6 mg, 0.0094 mmol), nBu_4NPF_6 (4 mg, 0.0094 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (3 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (58 mg, 87 %).

RF (1:1 EtOAc:Hept): 0.10

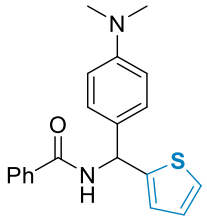
IR ν_{max} (cm^{-1}): 3338, 3038, 2922, 2225, 1631, 1519, 1484, 1157, 803

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}N_3O$ 356.1763; Found 356.1759

^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.79 (m, 2H), 7.64 – 7.39 (m, 7H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 6.9 Hz, 1H), 6.30 (d, *J* = 7.0 Hz, 1H), 2.96 (s, 6H).

^{13}C NMR (101 MHz, CDCl3) δ 166.7, 150.5, 143.9, 133.9, 132.0, 131.8, 130.9, 130.5, 129.4, 128.9, 128.8, 127.8, 127.2, 119.0, 112.8, 112.7, 57.0, 40.5.

N-[[4-(dimethylamino)phenyl]-(2-thienyl)methyl]benzamide (594f)



The title compound was prepared according to general procedure **M** from N-{[(propan-2-yl)oxy](thiophen-2-yl)methyl}benzamide (30 mg, 0.121 mmol), *N,N*-dimethylaniline (23 µL, 0.182 mmol), $Ca(NTf_2)_2$ (4 mg, 0.0061 mmol), nBu_4NPF_6 (3 mg, 0.0061 mmol) in 1,2-DCE (0.6 mL). Following completion of the reaction (3 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a white solid (26 mg, 64%).

RF (1:1 EtOAc:Hept): 0.21

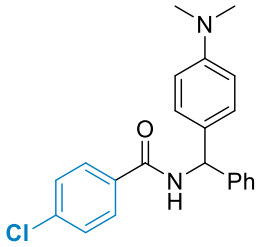
IR ν_{max} (cm^{-1}): 3258, 2881, 2797, 1629, 1519, 1226, 818

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2OS$ 337.1375; Found 337.1377

^1H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.76 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.30 – 7.26 (m, 2H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.91 (dt, *J* = 3.5, 1.1 Hz, 1H), 6.76 – 6.66 (m, 3H), 6.58 (d, *J* = 8.0 Hz, 1H), 2.95 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 150.4, 146.9, 134.5, 131.8, 129.0, 128.7, 128.3, 127.2, 127.0, 125.6, 125.0, 112.6, 53.2, 40.7.

4-chloro-N-[[4-(dimethylamino)phenyl]-phenyl-methyl]benzamide (595a)



The title compound was prepared according to general procedure **M** from 4-chloro-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (30 mg, 0.099 mmol), *N,N*-dimethylaniline (19 µL, 0.148 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0049 mmol), $n Bu_4NPF_6$ (2 mg, 0.0049 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (3 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a white solid (31 mg, 86 %).
RF (1:3 EtOAc:Hept): 0.20

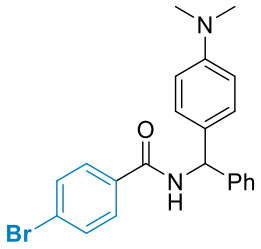
IR ν_{max} (cm^{-1}): 3293, 3029, 2801, 1631, 1519, 1483, 1016, 721

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}ClN_2O$ 365.1421; Found 365.1418

^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.26 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 7.4 Hz, 1H), 6.34 (d, *J* = 7.6 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 150.2, 141.9, 137.9, 133.0, 129.2, 129.0, 128.7, 128.7, 128.6, 127.4, 127.3, 112.7, 57.2, 40.7.

4-bromo-N-[[4-(dimethylamino)phenyl]-phenyl-methyl]benzamide (595b)



The title compound was prepared according to general procedure **M** from 4-bromo-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (30 mg, 0.086 mmol), *N,N*-dimethylaniline (16 µL, 0.129 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0043 mmol), $n Bu_4NPF_6$ (2 mg, 0.0043 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (3 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a white solid (30 mg, 85 %).
RF (1:3 EtOAc:Hept): 0.23

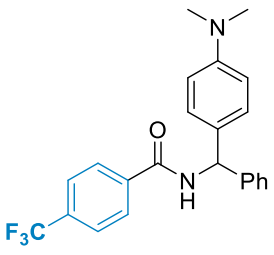
IR ν_{max} (cm^{-1}): 3293, 2887, 2801, 1631, 1519, 1479, 1012, 757

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}BrN_2O$ 409.0916; Found 409.0920

^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.27 (m, 5H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.34 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 150.2, 141.9, 133.4, 131.9, 129.1, 128.8, 128.7, 128.7, 127.4, 127.3, 126.4, 112.7, 57.2, 40.7.

N-[[4-(dimethylamino)phenyl]-phenyl-methyl]-4-(trifluoromethyl)benzamide (595c)



The title compound was prepared according to general procedure **M** from N-{phenyl[(propan-2-yl)oxy]methyl}-4-(trifluoromethyl)benzamide (30 mg, 0.089 mmol), *N,N*-dimethylaniline (17 µL, 0.133 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0045 mmol), $n Bu_4NPF_6$ (2 mg, 0.0045 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (5 h),

purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a white solid (32 mg, 90 %).

RF (1:3 EtOAc:Hept): 0.11

IR ν_{max} (cm^{-1}): 3286, 2922, 2809, 1643, 1522, 1323, 1120, 859

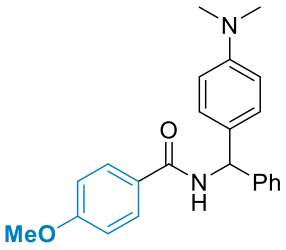
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}F_3N_2O$ 399.1684; Found 399.1685

^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.26 (m, 5H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.74 – 6.64 (m, 3H), 6.36 (d, *J* = 7.7 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 150.2, 141.7, 137.9, 133.4 (q, *J* = 32.7 Hz), 128.9, 128.8, 128.7, 127.7, 127.5, 127.3, 125.8 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.5 Hz), 112.7, 57.4, 40.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9.

N-[[4-(dimethylamino)phenyl]-phenyl-methyl]-4-methoxy-benzamide (595d)



The title compound was prepared according to general procedure **M** from 4-methoxy-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (30 mg, 0.100 mmol), *N,N*-dimethylaniline (19 µL, 0.150 mmol), $Ca(NTf_2)_2$ (3 mg, 0.005 mmol), $n$$Bu_4NPF_6$ (2 mg, 0.005 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (5 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (31 mg, 86 %).

RF (1:1 EtOAc:Hept): 0.23

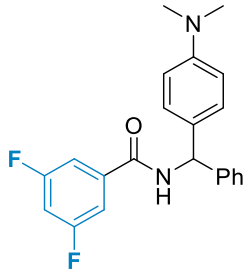
IR ν_{max} (cm^{-1}): 3325, 2922, 2797, 1627, 1495, 1249, 1025, 762

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_2$ 361.1916; Found 361.1913

^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.37 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 2.93 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 162.4, 150.1, 142.3, 129.7, 129.0, 128.7, 128.7, 127.4, 127.3, 126.9, 113.9, 112.7, 57.0, 55.6, 40.7.

N-[[4-(dimethylamino)phenyl]-phenyl-methyl]-3,5-difluoro-benzamide (595e)



The title compound was prepared according to general procedure **M** from 3,5-difluoro-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (30 mg, 0.098 mmol), *N,N*-dimethylaniline (19 µL, 0.150 mmol), $Ca(NTf_2)_2$ (3 mg, 0.0049 mmol), $n$$Bu_4NPF_6$ (2 mg, 0.0049 mmol) in 1,2-DCE (0.5 mL). Following completion of the reaction (5 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (32 mg, 89 %).

RF (1:3 EtOAc:Hept): 0.16

IR ν_{max} (cm^{-1}): 3286, 3094, 2920, 2853, 1638, 1598, 1520, 1318, 982

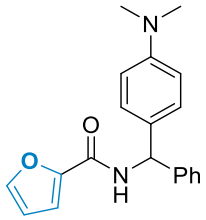
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}F_2N_2O$ 367.1622; Found 367.1618

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 7H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.94 (tt, *J* = 8.6, 2.3 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 6.7 Hz, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.35 (d, *J* = 12.0 Hz), 164.10 (t, *J* = 2.8 Hz), 161.86 (d, *J* = 12.0 Hz), 150.3, 141.6, 138.00 (t, *J* = 8.1 Hz), 128.8, 128.8, 128.7, 127.5, 127.3, 112.7, 110.46 (d, *J* = 11.2 Hz), 110.46 (d, *J* = 26.4 Hz), 107.03 (t, *J* = 25.3 Hz), 57.4, 40.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -108.0.

N-[[4-(dimethylamino)phenyl]-phenyl-methyl]furan-2-carboxamide (595f)



The title compound was prepared according to general procedure **M** from N-{phenyl[(propan-2-yl)oxy]methyl}furan-2-carboxamide (40 mg, 0.154 mmol), *N,N*-dimethylaniline (29 µL, 0.231 mmol), $Ca(NTf_2)_2$ (5 mg, 0.0077 mmol), $n$$Bu_4NPF_6$ (3 mg, 0.0077 mmol) in 1,2-DCE (0.8 mL). Following completion of the reaction (5 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a white solid (33 mg, 67 %).

RF (1:3 EtOAc:Hept): 0.23

IR ν_{max} (cm^{-1}): 3284, 3058, 2920, 1638, 1515, 1174, 1008, 747

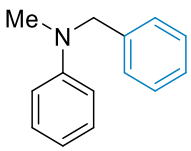
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1603; Found 321.1599

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.30 – 7.26 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.50 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.5, 150.1, 148.1, 143.9, 142.0, 129.3, 128.7, 128.6, 127.4, 127.3, 114.6, 112.7, 112.3, 56.1, 40.7.

9.6.3. Synthesis of N-substituted anilines

***N*-benzyl-*N*-methyl-aniline (598a)**



The title compound was prepared according to general procedure **N** from *N*-methyl-aniline (500 mg, 4.7 mmol), benzyl bromide (878 mg, 5.1 mmol) and K_2CO_3 (1.9 g, 14 mmol) in MeCN (23 mL). Following completion of the reaction (12 h) and subsequent work-up, the product was purified by FCC (1:1 DCM:Petrol) to afford the pure product as a yellow oil (350 mg, 38%).

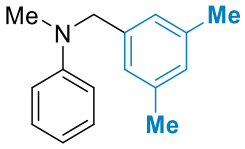
RF (1:1 DCM:Petrol) = 0.68

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.33 (m, 2H), 7.32 – 7.22 (m, 5H), 6.81 (d, *J* = 7.9 Hz, 2H), 6.77 (dt, *J* = 8.1, 4.1 Hz, 1H), 4.59 (s, 2H), 3.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 139.2, 129.3, 128.7, 127.0, 126.9, 116.7, 112.5, 56.8, 38.6.

*Data in accordance with literature[203]

***N*-[(3,5-dimethylphenyl)methyl]-*N*-methyl-aniline (598b)**



The title compound was prepared according to general procedure **N** from *N*-methyl-aniline (200 mg, 1.9 mmol), 3,5-dimethylbenzyl bromide (409 mg, 2.1 mmol) and K_2CO_3 (775 mg, 5.6 mmol) in MeCN (4 mL). Following completion of the reaction (12 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (374 mg, 89%).

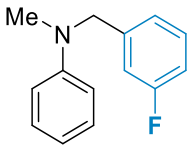
RF (1:3 DCM:Petrol) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 2H), 6.95 – 6.85 (m, 2H), 6.78 (d, *J* = 7.9 Hz, 2H), 6.76 – 6.68 (m, 1H), 4.47 (s, 2H), 3.02 (s, 3H), 2.31 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.1, 139.3, 138.3, 129.3, 128. 7, 124.6, 116.5, 112.5, 56.9, 38.6, 21.5.

Data in accordance with literature[204]

***N*-[(3-fluorophenyl)methyl]-*N*-methyl-aniline (598c)**



The title compound was prepared according to general procedure **N** from *N*-methyl-aniline (200 mg, 1.9 mmol), 3-fluorobenzyl bromide (388 mg, 2.1 mmol) and K_2CO_3 (775 mg, 5.6 mmol) in MeCN (4 mL). Following completion of the reaction (12 h) and

subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (420 mg, 95%).

RF (1:3 DCM:Petrol) = 0.24

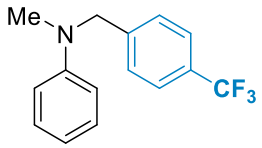
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.19 (m, 3H), 7.09 – 7.00 (m, 1H), 7.00 – 6.88 (m, 2H), 6.80 – 6.69 (m, 3H), 4.53 (s, 2H), 3.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.6, 162.1, 149.7, 142.2 (d, *J* = 6.5 Hz), 130.2 (d, *J* = 8.2 Hz), 129.4, 122.3 (d, *J* = 2.8 Hz), 117.0, 113.8 (t, *J* = 21.3 Hz), 112.5, 56.5, 56.5, 38.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.0

*Data in accordance with literature[205]

_N_-methyl-_N_-[[4-(trifluoromethyl)phenyl]methyl]aniline (598d)



The title compound was prepared according to general procedure **N** from *N*-methyl-aniline (200 mg, 1.9 mmol), 4-(trifluoromethyl)benzyl bromide (491 mg, 2.1 mmol) and K_2CO_3 (775 mg, 5.6 mmol) in MeCN (4 mL). Following completion of the reaction (12 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (468 mg, 94%).

RF (1:3 DCM:Petrol) = 0.31

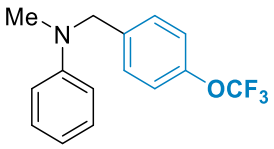
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 6.80 – 6.69 (m, 3H), 4.59 (s, 2H), 3.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 143.4, 129.3, 129.3 (q, *J* = 32.4 Hz), 127.0, 125.6 (q, *J* = 3.7 Hz), 117.0, 112.4, 56.5, 38.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4

Data in accordance with literature[204]

***N*-methyl-*N*-[[4-(trifluoromethoxy)phenyl]methyl]aniline (598e)**



The title compound was prepared according to general procedure **N** from *N*-methyl-aniline (200 mg, 1.9 mmol), 4-(trifluoromethoxy)benzyl bromide (524 mg, 2.1 mmol) and K_2CO_3 (775 mg, 5.6 mmol) in MeCN (4 mL). Following completion of the reaction (12 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (501 mg, 95%).

RF (1:3 DCM:Petrol) = 0.27

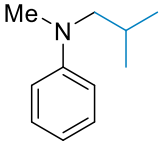
HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}F_3NO$ 282.1106; Found 282.1115

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.21 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.97 – 6.59 (m, 3H), 4.53 (s, 2H), 3.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7, 148.3, 137.9, 129.4, 128.1, 121.3, 120.6 (q, *J* = 256.8 Hz), 117.1, 112.6, 56.3, 38.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -57.9

***N*-isobutyl-*N*-methyl-aniline (598f)**



The title compound was prepared according to general procedure **O** from *N*-methyl-aniline (262 mg, 2.45 mmol), isobutyraldehyde (212 mg, 2.93 mmol) and $NaBH(OAc)_3$ (774 mg, 3.67 mmol) in DCM (8 mL). Following completion of the reaction (3 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (432 mg, 93%).

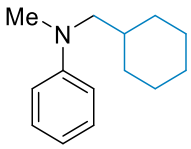
RF (1:3 DCM:Petrol) = 0.47

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.3 Hz, 2H), 6.75 – 6.63 (m, 3H), 3.12 (d, *J* = 7.3 Hz, 2H), 2.98 (s, 3H), 2.08 (hept, *J* = 6.7 Hz, 1H), 0.95 (d, *J* = 2.9 Hz, 3H), 0.94 (d, *J* = 2.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.8, 129.2, 115.7, 111.9, 61.1, 39.6, 27.5, 20.6.

*Data in accordance with literature[206]

_N_-(cyclohexylmethyl)-_N_-methyl-aniline (598g)



The title compound was prepared according to general procedure **O** from *N*-methyl-aniline (300 mg, 2.80 mmol), cyclohexane carboxaldehyde (345 mg, 3.08 mmol) and $NaBH(OAc)_3$ (886 mg, 4.20 mmol) in DCM (9 mL). Following completion of the reaction (12 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (527 mg, 93%).

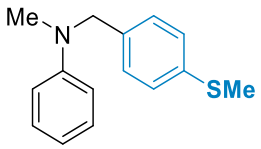
RF (1:3 DCM:Petrol) = 0.44

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.18 (m, 2H), 6.78 – 6.64 (m, 3H), 3.16 (d, *J* = 6.7 Hz, 2H), 2.99 (s, 3H), 1.94 – 1.62 (m, 6H), 1.41 – 1.11 (m, 3H), 1.11 – 0.87 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7, 129.2, 115.5, 111.8, 59.9, 39.7, 37.0, 31.5, 26.7, 26.2.

*Data in accordance with literature[207]

_N_-methyl-_N_-[(4-methylsulfanylphenyl)methyl]aniline (598h)



The title compound was prepared according to general procedure **O** from N-methyl-aniline (262 mg, 2.45 mmol), 4-(methylthio)benzaldehyde (447 mg, 2.93 mmol) and $NaBH(OAc)_3$ (774 mg, 3.67 mmol) in DCM (8 mL). Following completion of the reaction (1 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (501 mg, 86%).

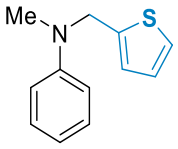
RF (1:3 DCM:Petrol) = 0.44

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.22 (m, 4H), 7.20 (d, *J* = 6.6 Hz, 2H), 6.79 (d, *J* = 6.5 Hz, 2H), 6.77 – 6.73 (m, 1H), 4.53 (s, 2H), 3.04 (d, *J* = 2.6 Hz, 3H), 2.51 (d, *J* = 2.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.8, 136.8, 136.2, 129.3, 127.5, 127.2, 116.8, 112.6, 56.4, 38.6, 16.2.

*Data in accordance with literature[208]

_N_-methyl-_N_-(2-thienylmethyl)aniline (598i)



The title compound was prepared according to general procedure **O** from *N*-methyl-aniline (262 mg, 2.45 mmol), 2-thiophenecarboxaldehyde (302 mg, 2.69 mmol) and $NaBH(OAc)_3$ (774 mg, 3.67 mmol) in DCM (8 mL). Following completion of the reaction (1 h) and subsequent work-up, the product was purified by FCC (1:3 DCM:Petrol) to afford the pure product as a yellow oil (428 mg, 93%).

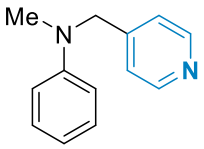
RF (1:3 DCM:Petrol) = 0.44

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.1 Hz, 3H), 7.18 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 4.68 (s, 2H), 2.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 142.3, 129.3, 126.8, 125.0, 124.4, 117.4, 113.3, 52.2, 38.3.

*Data in accordance with literature[209]

_N_-methyl-_N_-(4-pyridylmethyl)aniline (598j)



The title compound was prepared according to general procedure **O** from *N*-methyl-aniline (262 mg, 2.45 mmol), 4-pyridinecarboxaldehyde (314 mg, 2.93 mmol) and $NaBH(OAc)_3$ (774 mg, 3.67 mmol) in DCM (8 mL). Following completion of the reaction

(12 h) and subsequent work-up, the product was purified by FCC (1:1 EtOAc:Petrol) to afford the pure product as a yellow oil (362 mg, 75%).

RF (1:1 EtOAc:Petrol) = 0.27

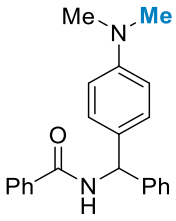
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.21 (d, *J* = 6.0 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 4.57 (s, 2H), 3.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2, 149.3, 148.6, 129.4, 121.9, 117.3, 112.5, 56.1, 39.0.

Data in accordance with literature[204]

9.6.4. aza-Friedel-Crafts Products – Amine Variation

N-[[4-(dimethylamino)phenyl]-phenyl-methyl]benzamide (601a)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), N,N-dimethylaniline (39 µL, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (58 mg, 82 %).

RF (1:3 EtOAc:Hept): 0.21

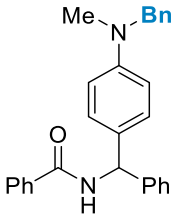
IR ν_{max} (cm^{-1}): 3327, 3058, 2883, 2799, 1631, 1519, 1489, 1349, 794

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O$ 331.1810; Found 331.1805

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.76 (m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 7.38 – 7.26 (m, 6H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 7.4 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 150.2, 142.1, 134.6, 131.7, 129.4, 128.7, 128.7, 127.4, 127.3, 127.2, 112.7, 57.1, 40.7.

N-[[4-[benzyl(methyl)amino]phenyl]-phenyl-methyl]benzamide (601b)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-benzyl-*N*-methyl-aniline (61 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (3 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (72 mg, 85 %).

RF (1:3 EtOAc:Hept): 0.23

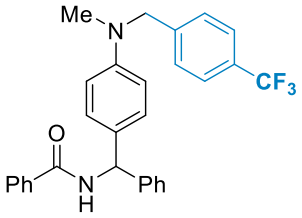
IR ν_{max} (cm^{-1}): 3316, 3032, 2920, 1634, 1519, 1319, 790

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}N_2O$ 407.2123; Found 407.2129

^1H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.78 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 7.37 – 7.27 (m, 7H), 7.25 – 7.20 (m, 3H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 4.52 (s, 2H), 3.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.2, 142.1, 139.0, 134.6, 131.7, 129.4, 128.8, 128.7, 128.7, 128.7, 127.4, 127.3, 127.2, 127.1, 126.8, 112. 5, 57.1, 56.7, 38.8.

N-[[4-[methyl-[[4-(trifluoromethyl)phenyl]methyl]amino]phenyl]-phenyl-methyl]benzamide (601c)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-methyl-N-[[4-(trifluoromethyl)phenyl]methyl]aniline (83 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the

reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (77 mg, 77 %).

RF (1:3 EtOAc:Hept): 0.14

IR ν_{max} (cm^{-1}): 3299, 3029, 2823, 1638, 1517, 1325, 1064, 736

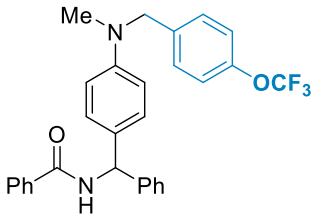
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{26}F_3N_2O$ 475.1997; Found 475.1992

^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.78 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.29 (m, 6H), 7.29 – 7.26 (m, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 4.56 (s, 2H), 3.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.9, 143.3, 143.3, 142.0, 134.6, 131.7, 130.0, 129.9, 129.5 (q, J = 32.4 Hz), 128.7, 127.4, 127.4, 127.2, 127.0, 125.7 (q, J = 3.8 Hz), 124.4 (q, J = 273.2 Hz), 112.5, 57.1, 56.6, 39.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4.

N-[[4-[methyl-[[4-(trifluoromethoxy)phenyl]methyl]amino]phenyl]-phenyl-methyl]benzamide (601d)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-methyl-N-[[4-(trifluoromethoxy)phenyl]methyl]aniline (87 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (1.5 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (77 mg, 76 %).

RF (1:3 EtOAc:Hept): 0.10

IR ν_{max} (cm^{-1}): 3325, 3032, 2920, 1631, 1519, 1262, 1172, 740

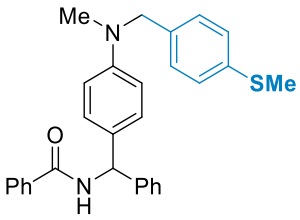
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{26}F_3N_2O_2$ 491.1946; Found 491.1942

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.78 (m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 7.37 – 7.30 (m, 4H), 7.28 (dd, *J* = 3.6, 2.7 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.19 – 7.10 (m, 4H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 4.50 (s, 2H), 3.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.0, 148.3 (d, *J* = 1.8 Hz), 142.0, 137.7, 134.6, 131.7, 129.8, 128.8, 128.7, 128.1, 127.4, 127.2, 121.3, 120.6 (q, *J* = 256.9 Hz), 112.5, 57.0, 56.2, 38.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -57.9.

N-[[4-[methyl-[(4-methylsulfanylphenyl)methyl]amino]phenyl]-phenyl-methyl]benzamide (601e)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-methyl-N-[(4-methylsulfanylphenyl)methyl]aniline (76 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (1.5 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (76 mg, 81 %).

RF (1:3 EtOAc:Hept): 0.12

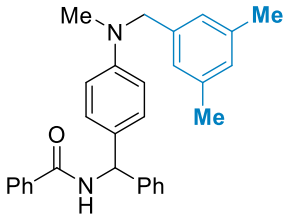
IR ν_{max} (cm^{-1}): 3299, 3058, 2919, 1634, 1515, 1180, 796

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}N_2OS$ 453.2001; Found 453.2009

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.79 (m, 2H), 7.53 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.30 (m, 4H), 7.30 – 7.26 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.17 – 7.09 (m, 4H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 4.47 (s, 2H), 3.00 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.2, 142.1, 136.9, 136.0, 134.6, 131.7, 129.5, 128.8, 128.7, 128.7, 127.4, 127.4, 127.4, 127.2, 127.2, 112.5, 57.1, 56.3, 38.8, 16.2.

N-[[4-[(3,5-dimethylphenyl)methyl-methyl-amino]phenyl]-phenyl-methyl]benzamide (601f)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-[(3,5-dimethylphenyl)methyl]-N-methyl-aniline (70 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (82 mg, 91 %).

RF (1:3 EtOAc:Hept): 0.20

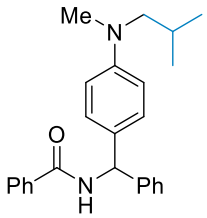
IR ν_{max} (cm^{-1}): 3332, 3025, 2917, 1638, 1510, 1336, 1120, 790

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{31}N_2O$ 435.2436; Found 435.2442

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.78 (m, 2H), 7.55 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 7.37 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.88 (s, 1H), 6.84 (s, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 4.43 (s, 2H), 3.01 (s, 3H), 2.29 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.5, 142.1, 139.1, 138.3, 134.6, 131.7, 129.3, 128.8, 128.7, 128.7, 127.4, 127.3, 127.2, 124.5, 112.4, 57.1, 56.8, 38.7, 21.5.

N-[[4-[isobutyl(methyl)amino]phenyl]-phenyl-methyl]benzamide (601g)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (80 mg, 0.332 mmol), *N*-isobutyl-*N*-methyl-aniline (82 mg, 0.497 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), $n Bu_4NPF_6$ (6 mg, 0.017 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (102 mg, 83 %).

RF (1:3 EtOAc:Hept): 0.27

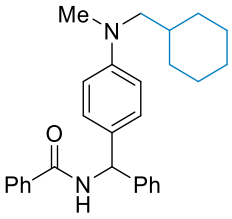
IR ν_{max} (cm^{-1}): 3340, 3060, 2948, 2865, 1636, 1515, 1254, 1152, 794

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}N_2O$ 373.2280; Found 373.2286

^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.78 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.69 – 6.58 (m, 3H), 6.35 (d, *J* = 7.7 Hz, 1H), 2.04 (hept, *J* = 6.9 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.2, 142.2, 134.7, 131.6, 128.8, 128.7, 128.7, 128.4, 127.3, 127.3, 127.2, 111.9, 61.0, 57.1, 39.6, 27.5, 20.5.

N-[[4-[cyclohexylmethyl(methyl)amino]phenyl]-phenyl-methyl]benzamide (601h)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-(cyclohexylmethyl)-*N*-methyl-aniline (63 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (1.5 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (74 mg, 87 %).

RF (1:3 EtOAc:Hept): 0.16

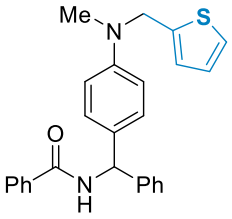
IR ν_{max} (cm^{-1}): 3323, 3058, 2917, 2846, 1635, 1519, 1206, 790

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}N_2O$ 413.2593; Found 413.2596

^1H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.80 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 7.37 – 7.30 (m, 4H), 7.30 – 7.27 (m, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.66 – 6.57 (m, 3H), 6.35 (d, *J* = 7.7 Hz, 1H), 3.10 (d, *J* = 6.7 Hz, 2H), 2.94 (s, 3H), 1.81 – 1.61 (m, 6H), 1.32 – 1.09 (m, 3H), 1.05 – 0.84 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 149.1, 142.2, 134.7, 131.6, 128.8, 128.7, 128.7, 128.3, 127.3, 127.3, 127.2, 111.7, 59.8, 57.1, 39.9, 37.0, 31.4, 26.7, 26.1.

N-[[4-[methyl(2-thienylmethyl)amino]phenyl]-phenyl-methyl]benzamide (601i)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-methyl-N-(2-thienylmethyl)aniline (63 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), nBu_4NPF_6 (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (69 mg, 81 %).

RF (1:3 EtOAc:Hept): 0.20

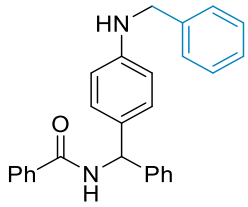
IR ν_{max} (cm^{-1}): 3342, 3055, 2932, 1634, 1515, 1254, 790

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2OS$ 413.1688; Found 413.1685

^1H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.76 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.39 (m, 2H), 7.37 – 7.30 (m, 4H), 7.29 – 7.27 (m, 1H), 7.17 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.90 (dd, *J* = 3.4, 1.0 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 4.65 (s, 2H), 2.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 148.7, 142.2, 142.0, 134.6, 131.7, 130.1, 128.8, 128.7, 128.7, 127.4, 127.4, 127.2, 126.9, 125.0, 124.5, 113.2, 57.1, 52.1, 38.4.

N-[[4-(benzylamino)phenyl]-phenyl-methyl]benzamide (604a)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-benzylaniline (57 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (2 h), purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (59mg, 73 %).

RF (1:3 EtOAc:Hept): 0.24

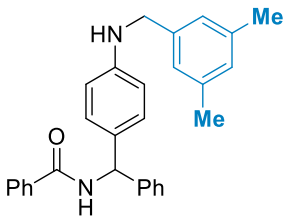
IR ν_{max} (cm^{-1}): 3401, 3338, 3060, 2850, 1634, 1515, 1314, 691

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{25}N_2O$ 393.1967; Found 393.1969

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.76 (m, 2H), 7.55 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 7.38 – 7.26 (m, 10H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.68 – 6.56 (m, 3H), 6.34 (d, *J* = 7.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.51, 147.73, 142.03, 139.36, 134.58, 131.68, 130.56, 128.89, 128.79, 128.71, 128.69, 127.58, 127.43, 127.37, 127.36, 127.16, 113.04, 57.14, 48.42.

N-[[4-[(3,5-dimethylphenyl)methylamino]phenyl]-phenyl-methyl]benzamide (604b)



The title compound was prepared according to general procedure **M** from *N*-(Methoxy(phenyl)methyl)benzamide (50 mg, 0.207 mmol), *N*-[(3,5-dimethylphenyl)methyl]aniline (66 mg, 0.311 mmol), $Ca(NTf_2)_2$ (6 mg, 0.010 mmol),

nBu_4NPF_6 (4 mg, 0.010 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (2 h), purification by FCC (1:9 EtOAc:Heptane) afforded the pure compound as an orange oil (46 mg, 53 %).

RF (1:3 EtOAc:Hept): 0.25

IR ν_{max} (cm^{-1}): 3401, 3338, 2920, 1629, 1517, 1321, 798

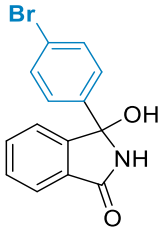
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}N_2O$ 421.2280; Found 421.2287

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 7.37 – 7.29 (m, 4H), 7.29 – 7.26 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.97 (s, 2H), 6.92 (s, 1H), 6.66 – 6.56 (m, 3H), 6.35 (d, *J* = 7.7 Hz, 1H), 4.22 (s, 2H), 4.05 (s, 1H), 2.31 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 147.9, 142.1, 139.3, 138.4, 134.6, 131.7, 130.5, 129.1, 128.9, 128.7, 128.7, 127.4, 127.4, 127.2, 125.5, 113.0, 57.2, 48.5, 21.4.

9.6.5. Synthesis of Starting Materials – 3-hydroxyisoindolinones

3-(4-bromophenyl)-3-hydroxy-isoindolin-1-one (198n)



The title compound was prepared according to general procedure **P** from phthalimide (300 mg, 2.04 mmol), (4-bromo-phenyl)magnesium bromide (0.5 M in THF, 14 mL, 6.32 mmol) in DCM (8 mL). The Grignard reagent was freshly prepared from magnesium turnings (154 mg, 6.32 mmol), 1,4-dibromobenzene (1.68 g, 1.13 mL, 7.14 mmol) and 1,2-dibromoethane (18 µL, 0.204 mmol) in THF (7 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (322 mg, 52%).

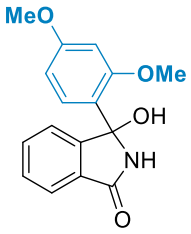
RF (1:1 EtOAc:Petrol) = 0.23

^1H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 1H), 7.67 – 7.62 (m, 1H), 7.57 – 7.52 (m, 3H), 7.48 (td, *J* = 7.4, 1.1 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.01 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.4, 141.7, 132.5, 131.2, 130.6, 129.1, 127.9, 122.7, 122.6, 121.0, 87.0.

*Data in accordance with literature[196]

3-(2,4-dimethoxyphenyl)-3-hydroxy-isoindolin-1-one (198o)



The title compound was prepared according to general procedure **P** from phthalimide (300 mg, 2.04 mmol), (4-bromo-phenyl)magnesium bromide (0.5 M in THF, 14 mL, 6.32 mmol) in DCM (8 mL). The Grignard reagent was freshly prepared from magnesium turnings (154 mg, 6.32 mmol), 1-bromo-2,4-dimethoxybenzene (1.55 g, 0.91 mL, 7.14 mmol) and 1,2-dibromoethane (18 µL, 0.204 mmol) in THF (7 mL). Following completion of the reaction (1 h), purification by FCC (1:1 EtOAc:Hex) afforded the pure product as a white solid (113 mg, 19%).

RF (1:1 EtOAc:Petrol) = 0.15

IR ν_{max} (cm^{-1}): 3278, 2939, 1682, 1621

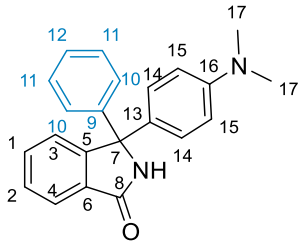
HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO_4$ 286.1074; Found 286.1071

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.46 (td, *J* = 7.4, 1.5 Hz, 1H), 7.42 (td, *J* = 7.3, 1.3 Hz, 1H), 7.15 (d, *J* = 6.7 Hz, 1H), 6.58 – 6.53 (m, 2H), 6.43 (d, *J* = 2.4 Hz, 1H), 3.74 (s, 3H), 3.31 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.74, 160.54, 157.46, 151.04, 132.25, 131.55, 128.35, 128.20, 121.83, 121.78, 121.54, 104.18, 99.51, 85.22, 55.53, 55.18.f

9.6.6. Functionalised Isoindolinones – 3-hydroxyisoindolinone Variation

3-[4-(dimethylamino)phenyl]-3-phenyl-isoindolin-1-one (609a)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.222 mmol), N,N-dimethylaniline (42 µL, 0.333 mmol), $Ca(NTf_2)_2$ (6 mg, 0.011 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.011 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (67 mg, 92 %).

RF (1:1 EtOAc:Hept): 0.28

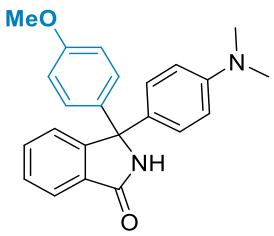
IR ν_{max} (cm^{-1}): 3190, 3047, 2928, 1687, 1519, 1347, 1171.

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2O$ 329.1654; Found 329.1658

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 1H, **H4**), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H, **H1**), 7.46 (td, *J* = 7.4, 1.0 Hz, 1H, **H1**), 7.43 – 7.40 (m, 1H, **H2**), 7.35 – 7.27 (m, 5H, **ArH**), 7.09 (d, *J* = 9.0 Hz, 2H, **H14**), 6.71 – 6.60 (m, 3H, **H15**, **NH**), 2.94 (s, 6H, **H17**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9 (**C8**), 151.0 (**C16**), 149.8 (**ArC**), 149.8 (**ArC**), 143.3 (**ArC**), 132.4 (**ArC**), 130.7 (**ArC**), 128.4 (**ArC**), 128.4 (**ArC**), 128.2 (**ArC**), 127.9 (**ArC**), 127.2 (**ArC**), 124.6 (**ArC**), 124.3 (**ArC**), 112.6 (**C15**), 70.7 (**C7**), 40.8 (**C17**).

3-[4-(dimethylamino)phenyl]-3-(4-methoxyphenyl)isoindolin-1-one (609b)



The title compound was prepared according to general procedure **M** from 3-(4-methoxyphenyl)-3-hydroxyisoindolin-1-one (100 mg, 0.392 mmol), N,N-dimethylaniline

(75 µL, 0.588 mmol), $Ca(NTf_2)_2$ (12 mg, 0.0196 mmol), nBu$_4$NPF$_6$ (8 mg, 0.0196 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (134 mg, 95 %).

RF (3:1 EtOAc:Hept): 0.26

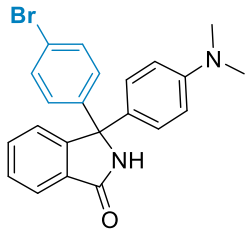
IR ν_{max} (cm^{-1}): 3215, 2928, 2835, 1687, 1607, 1508, 1347, 1172.

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O_2$ 359.1760; Found 359.1765

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.82 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.44 (td, *J* = 7.5, 1.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.76 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 3H), 2.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 159.2, 151.4, 150.1, 135.4, 132.3, 130.6, 130.1, 128.5, 128.2, 128.1, 124.4, 124.2, 113.9, 112.3, 70.4, 55.4, 40.5.

3-(4-bromophenyl)-3-[4-(dimethylamino)phenyl]isoindolin-1-one (609c)



The title compound was prepared according to general procedure **M** from 3-(4-bromophenyl)-3-hydroxyisoindolin-1-one (100 mg, 0.329 mmol), N,N-dimethylaniline (65 µL, 0.493 mmol), $Ca(NTf_2)_2$ (10 mg, 0.0164 mmol), nBu$_4$NPF$_6$ (6 mg, 0.0164 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (129 mg, 96 %).

RF (3:1 EtOAc:Hept): 0.59

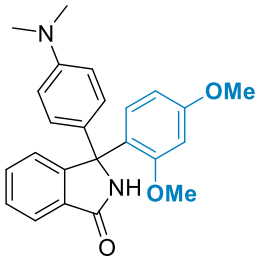
IR ν_{max} (cm^{-1}): 3193, 3047, 1799, 1687, 1519, 1343, 747.

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}BrN_2O$ 407.0759; Found 407.0765

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.82 (m, 1H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 (td, *J* = 7.4, 1.0 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.36 (m, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.51 (s, 1H), 2.93 (s, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 150.6, 150.2, 142.7, 132.4, 131.7, 130.7, 129.3, 129.0, 128.5, 128.1, 124.4, 124.4, 122.0, 112.3, 70.4, 40.5.

3-(2,4-dimethoxyphenyl)-3-[4-(dimethylamino)phenyl]isoindolin-1-one (609d)



The title compound was prepared according to general procedure **M** from 3-(2,4-dimethoxyphenyl)-3-hydroxy-isoindolin-1-one (50 mg, 0.175 mmol), N,N-dimethylaniline (33 µL, 0.263 mmol), $Ca(NTf_2)_2$ (5 mg, 0.00876 mmol), $n$$Bu_4NPF_6$ (3 mg, 0.00876 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (62 mg, 91 %).

RF (3:1 EtOAc:Hept): 0.40

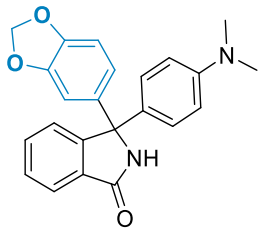
IR ν_{max} (cm^{-1}): 3407, 3038, 2932, 2835, 1685, 1607, 1206, 1156.

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}N_2O_3$ 389.1865; Found 389.1871

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 (td, *J* = 7.4, 0.9 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 2.88 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 160.9, 158.8, 150.7, 149.6, 131.7, 131.2, 130.9, 128.6, 128.1, 125.9, 125.7, 124.4, 122.4, 112.3, 103.4, 100.5, 68.9, 55.8, 55.5, 40.6.

3-(1,3-benzodioxol-5-yl)-3-[4-(dimethylamino)phenyl]isoindolin-1-one (609e)



The title compound was prepared according to general procedure **M** from 3-(1,3-benzodioxol-5-yl)-3-hydroxy-isoindolin-1-one (50 mg, 0.186 mmol), N,N-dimethylaniline (35 µL, 0.279 mmol), $Ca(NTf_2)_2$ (6 mg, 0.00928 mmol), $n$$Bu_4NPF_6$ (4 mg, 0.00928 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (62 mg, 90 %).

RF (3:1 EtOAc:Hept): 0.55

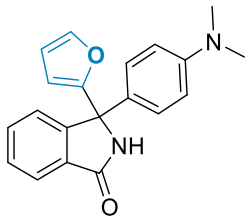
IR ν_{max} (cm^{-1}): 3220, 3047, 2887, 1670, 1608, 1238, 1187, 811.

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_3$ 373.1552; Found 373.1557

^1H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.82 (m, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 7.5, 1.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.80 – 6.74 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.51 (s, 1H), 5.93 (s, 2H), 2.93 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 151.1, 150.2, 148.0, 147.3, 137.4, 132.4, 130.6, 129.8, 128.4, 128.1, 124.4, 124.3, 120.6, 112.3, 108.1, 108.1, 101.4, 70.6, 40.5.

3-[4-(dimethylamino)phenyl]-3-(2-furyl)isoindolin-1-one (609f)



The title compound was prepared according to general procedure **M** from 3-(2-furyl)-3-hydroxy-isoindolin-1-one (100 mg, 0.465 mmol), N,N-dimethylaniline (88 µL, 0.697 mmol), $Ca(NTf_2)_2$ (14 mg, 0.0232 mmol), $n$$Bu_4NPF_6$ (9 mg, 0.0232 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a pink solid (138 mg, 93 %).

RF (1:1 EtOAc:Hept): 0.23

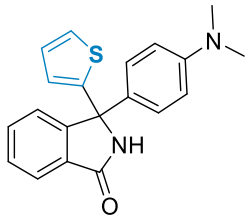
IR ν_{max} (cm^{-1}): 3181, 3058, 2853, 1687, 1520, 1150, 742

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2$ 319.1447; Found 319.1451

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 1H), 7.59 – 7.45 (m, 3H), 7.42 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.78 (s, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.22 (dd, *J* = 3.3, 0.8 Hz, 1H), 2.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 154.2, 150.5, 149.4, 143.3, 132.6, 130.5, 128.8, 127.5, 127.2, 124.2, 124.0, 112.4, 110.2, 108.1, 66.3, 40.5.

3-[4-(dimethylamino)phenyl]-3-(2-thienyl)isoindolin-1-one (609g)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-(2-thienyl)isoindolin-1-one (100 mg, 0.432 mmol), N,N-dimethylaniline (82 µL, 0.649 mmol), $Ca(NTf_2)_2$ (13 mg, 0.0216 mmol), $n$$Bu_4NPF_6$ (8 mg, 0.0216 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (128 mg, 89 %).
RF (1:1 EtOAc:Hept): 0.12

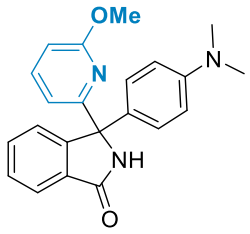
IR ν_{max} (cm^{-1}): 3185, 3056, 2805, 1687, 1519, 1342, 742

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2OS$ 335.1218; Found 335.1224

^1H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.85 (m, 1H), 7.60 – 7.55 (m, 1H), 7.55 – 7.46 (m, 2H), 7.26 – 7.24 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.91 (s, 1H), 6.65 (d, *J* = 9.0 Hz, 2H), 2.95 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 151.2, 150.4, 148.0, 132.5, 130.2, 129.2, 128.7, 127.8, 127.0, 126.4, 125.6, 124.2, 124.2, 112.1, 68.0, 40.5.

3-[4-(dimethylamino)phenyl]-3-(6-methoxy-2-pyridyl)isoindolin-1-one;methane (609h)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-(6-methoxy-2-pyridyl)isoindolin-1-one (100 mg, 0.390 mmol), N,N-dimethylaniline (74 µL, 0.585 mmol), $Ca(NTf_2)_2$ (12mg, 0.0195 mmol), $n$$Bu_4NPF_6$ (8 mg, 0.0195 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (135 mg, 96 %).
RF (3:1 EtOAc:Hept): 0.35

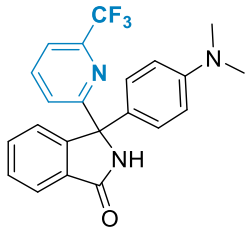
IR ν_{max} (cm^{-1}): 3206, 2943, 2889, 1687, 1602, 1489, 1286, 1025

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}N_3O_2$ 360.1712; Found 360.1718

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.06 (m, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.58 – 7.42 (m, 3H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 3H), 2.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 163.8, 150.7, 150.3, 145.5, 138.1, 132.5, 131. 9, 130.6, 129.0, 128.5, 128.0, 124.4, 124.3, 112.4, 110.9, 68.9, 53.6, 40.5.

3-[4-(dimethylamino)phenyl]-3-[6-(trifluoromethyl)-2-pyridyl]isoindolin-1-one (609i)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-[6-(trifluoromethyl)-2-pyridyl]isoindolin-1-one (100 mg, 0.340 mmol), N,N-dimethylaniline (65 µL, 0.510 mmol), $Ca(NTf_2)_2$ (10 mg, 0.017 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.017 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification

by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (94 mg, 70 %).

RF (3:1 EtOAc:Hept): 0.52

IR ν_{max} (cm^{-1}): 3179, 3062, 2892, 1690, 1608, 1522, 1340, 1113, 814

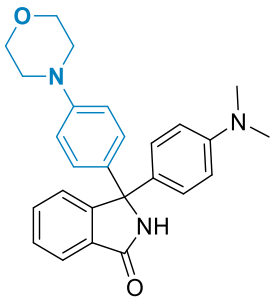
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}F_3N_3O$ 398.1480; Found 398.1473

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.81 (m, 4H), 7.68 (s, 1H), 7.63 – 7.56 (m, 2H), 7.47 (td, *J* = 7.5, 0.8 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 9.0 Hz, 2H), 2.89 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 161.7, 150.1, 149.5, 147.9 (q, *J* = 34.9 Hz), 138.3, 132.5, 130.9, 129.2, 128.8, 127.7, 125.7, 124.0, 123.5, 121.4 (q, *J* = 274.5 Hz), 119.2 (q, *J* = 2.5 Hz), 112.3, 70.9, 40.4.

^{19}F NMR (376 MHz, $CDCl_3$): -67.9.

3-[4-(dimethylamino)phenyl]-3-(4-morpholinophenyl)isoindolin-1-one (609j)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-(4-morpholinophenyl)isoindolin-1-one (40 mg, 0.129 mmol), N,N-dimethylaniline (25 µL, 0.193 mmol), $Ca(NTf_2)_2$ (4 mg, 0.00644 mmol), $n$$Bu_4NPF_6$ (3 mg, 0.00644 mmol) in 1,2-DCE (0.7 mL). Following completion of the reaction (12 h), purification by FCC (3:1 EtOAc:Heptane) afforded the pure compound as a white solid (50 mg, 94 %).

RF (1:1 EtOAc:Hept): 0.26

IR ν_{max} (cm^{-1}): 3252, 2958, 2816, 1684, 1508, 1347, 1187, 923

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}N_3O_2$ 414.2182; Found 414.2175

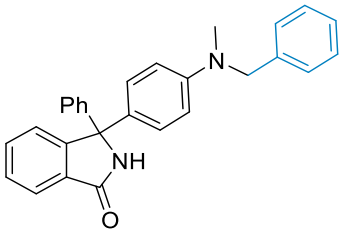
^1H NMR (400 MHz, $CDCl_3$): δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 (td, *J* = 7.4, 1.0 Hz, 1H), 7.39 (dt, *J* = 7.7, 0.8 Hz, 1H), 7.19 (d, *J* =

8.9 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.59 (s, 1H), 3.89 – 3.80 (m, 4H), 3.16 – 3.11 (m, 4H), 2.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 151.5, 150.7, 150.1, 134.2, 132.3, 130.6, 130.2, 128.2, 128.1, 124.4, 124.2, 115.3, 112.2, 70.3, 67.0, 49.0, 40.5.

9.6.7. Functionalised Isoindolinones – Amine Variation

3-[4-[benzyl(methyl)amino]phenyl]-3-phenyl-isoindolin-1-one (610a)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-benzyl-N-methyl-aniline (105 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (128 mg, 89 %).
RF (1:1 EtOAc:Hept): 0.17

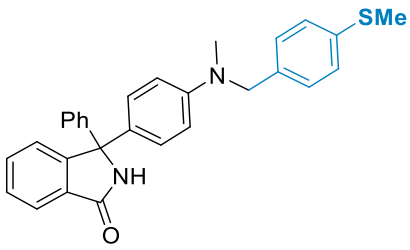
IR ν_{max} (cm^{-1}): 3165, 3053, 2954, 1687, 1519, 1349, 751

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{25}N_2O$ 405.1967; Found405.1963

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.84 (m, 1H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.39 – 7.29 (m, 7H), 7.27 – 7.20 (m, 3H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.77 (s, 1H), 6.66 (d, *J* = 9.0 Hz, 2H), 4.53 (s, 2H), 3.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 151.0, 149.3, 143.3, 138.8, 132.3, 130.7, 130.0, 128.8, 128.6, 128.3, 128.3, 127.9, 127.2, 127.1, 126.7, 124.6, 124.3, 112.1, 70.7, 56.6, 38.7.

3-[4-[methyl-[(4-methylsulfanylphenyl)methyl]amino]phenyl]-3-phenyl-isoindolin-1-one (610b)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-methyl-N-[(4-methylsulfanylphenyl)methyl]aniline (130 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (149 mg, 93 %).

RF (1:1 EtOAc:Hept): 0.18

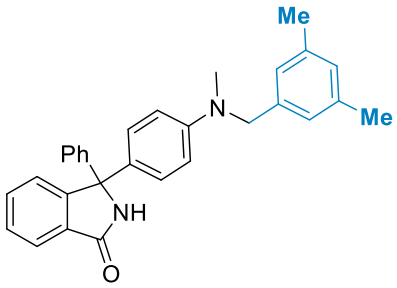
IR ν_{max} (cm^{-1}): 3185, 3055, 2919, 1687, 1517, 1346, 796

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{27}N_2OS$ 451.1844; Found 451.1849

^1H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.84 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.36 – 7.27 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.83 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 4.45 (s, 2H), 2.99 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 151.0, 149.2, 143.3, 137.0, 135.8, 132.3, 130.7, 130.2, 128.6, 128.3, 128.3, 127.9, 127.4, 127.2, 124.6, 124.3, 112.1, 70.7, 56.2, 38.7, 16.2.

3-[4-[(3,5-dimethylphenyl)methyl-methyl-amino]phenyl]-3-phenyl-isoindolin-1-one (610c)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.444 mmol), N-[(3,5-dimethylphenyl)methyl]-N-methyl-aniline (150 mg, 0.666 mmol), $Ca(NTf_2)_2$ (13 mg, 0.022 mmol), $n$$Bu_4NPF_6$ (9 mg, 0.022 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (175 mg, 91 %).

RF (1:1 EtOAc:Hept): 0.25

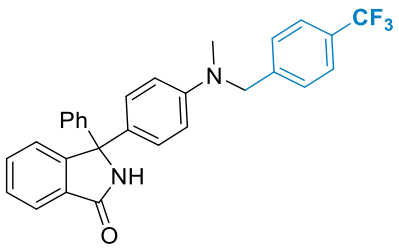
IR ν_{max} (cm^{-1}): 3183, 3055, 2915, 1687, 1517, 1340, 1193, 749

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{29}N_2O$ 433.2280; Found 433.2278

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.36 – 7.27 (m, 5H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 6.82 (s, 2H), 6.64 (d, *J* = 9.0 Hz, 2H), 6.59 (s, 1H), 4.42 (s, 2H), 3.00 (s, 3H), 2.28 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 151.0, 149.5, 143.4, 138.9, 138.4, 132.3, 130.7, 129.9, 128.8, 128.6, 128.4, 128.3, 127.9, 127.2, 124.6, 124.5, 124.3, 112.1, 70.7, 56.7, 38.7, 21.5.

3-[4-[methyl-[[4-(trifluoromethyl)phenyl]methyl]amino]phenyl]-3-phenyl-isoindolin-1-one (610d)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.444 mmol), N-methyl-N-[[4-(trifluoromethyl)phenyl]methyl]aniline (177 mg, 0.666 mmol), $Ca(NTf_2)_2$ (13 mg, 0.022 mmol), $n$$Bu_4NPF_6$ (9 mg, 0.022 mmol) in 1,2-DCE (2 mL). Following completion of the reaction (12 h), purification by FCC (1:3 to 1:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (200 mg, 95 %).

RF (1:1 EtOAc:Hept): 0.16

IR ν_{max} (cm^{-1}): 3187, 3060, 1687, 1608, 1321, 1105, 749

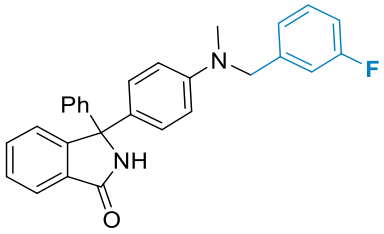
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{24}F_3N_2O$ 473.1841; 473.1834

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.52 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.35 – 7.27 (m, 7H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.98 (s, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 4.54 (s, 2H), 3.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 150.9, 149.0, 143.3, 143.1, 143.1, 132.3, 130.8, 130.7, 129.5 (q, *J* = 32.3 Hz), 128.7, 128.4, 127.9, 127.2, 127.0, 125.8 (q, *J* = 3.7 Hz), 124.6, 124.3, 124.3 (q, *J* = 272.0 Hz), 112.2, 70.7, 56.4, 38.9.

^{19}F NMR (376 MHz, $CDCl_3$): -62.4.

3-[4-[(3-fluorophenyl)methyl-methyl-amino]phenyl]-3-phenyl-isoindolin-1-one (610e)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-[(3-fluorophenyl)methyl]-N-methyl-aniline (115 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a pale yellow solid (139 mg, 93 %).

RF (1:1 EtOAc:Hept): 0.20

IR ν_{max} (cm^{-1}): 3181, 3049, 1687, 1608, 1517, 1341

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{23}FN_2O$ 423.1873; Found 423.1865

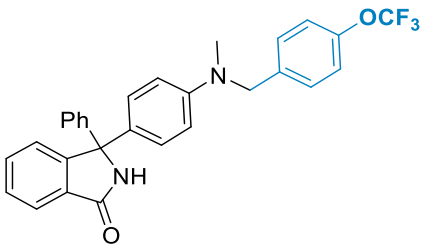
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 7.4, 1.0 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.35 – 7.26 (m, 6H), 7.05 (d, *J* = 9.0 Hz, 2H), 7.01 – 6.96 (m, 1H), 6.96 – 6.86 (m, 2H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.55 (s, 1H), 4.49 (s, 2H), 3.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 163.3 (d, *J* = 246.2 Hz), 151.0, 149.1, 143.3, 141.8, 141.7, 132.3, 130.7, 130.4, 130.3, 130.3, 128.6, 128.3, 127.9, 127.2, 124.4 (d, *J* = 28.6 Hz), 122.2 (d, *J* = 2.8 Hz), 114.0 (d, *J* = 21.3 Hz), 113.6 (d, *J* = 21.7 Hz), 112.1, 70.8, 56.3 (d, *J* = 1.7 Hz), 38.8.

^{13}C NMR (101 MHz, $CDCl_3$) δ

^{19}F NMR (376 MHz, $CDCl_3$): -112.8.

3-[4-[methyl-[[4-(trifluoromethoxy)phenyl]methyl]amino]phenyl]-3-phenyl-isoindolin-1-one (610f)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-methyl-N-[[4-(trifluoromethoxy)phenyl]methyl]aniline (150 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (160 mg, 92 %).

RF (1:1 EtOAc:Hept): 0.22

IR ν_{max} (cm^{-1}): 3185, 3058, 1687, 1608, 1517, 1250, 749

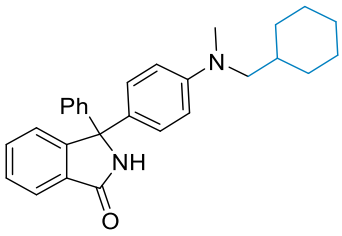
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{24}F_3N_2O_2$ 489.1790; Found 489.1796

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.36 – 7.27 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.17 – 7.12 (m, 2H), 7.10 – 7.04 (m, 3H), 6.62 (d, *J* = 9.0 Hz, 2H), 4.49 (s, 2H), 3.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 150.9, 149.1, 148.3, 148.3, 143.3, 137.6, 132.3, 130.8, 130.5, 128.6, 128.4, 128.0, 127.9, 127.2, 124.6, 124.3, 121.3, 120.6 (q, *J* = 256.9 Hz), 112.2, 70.8, 56.1, 38.7.

^{19}F NMR (376 MHz, $CDCl_3$): -112.8.

3-[4-[cyclohexylmethyl(methyl)amino]phenyl]-3-phenyl-isoindolin-1-one (610g)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-(cyclohexylmethyl)-N-methyl-aniline (108 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (140 mg, 96 %).

RF (1:1 EtOAc:Hept): 0.24

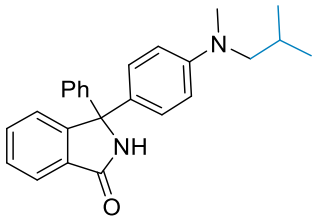
IR ν_{max} (cm^{-1}): 3183, 3055, 2919, 2846, 1687, 1608, 1517, 1340, 747

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{31}N_2O$ 411.2436; Found 411.2439

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.38 – 7.27 (m, 5H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.83 (s, 1H), 6.55 (d, *J* = 9.0 Hz, 2H), 3.08 (d, *J* = 6.8 Hz, 2H), 2.93 (s, 3H), 1.78 – 1.60 (m, 6H), 1.29 – 1.08 (m, 3H), 1.00 – 0.84 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 151.1, 149.2, 143.5, 132.3, 130.8, 128.9, 128.6, 128.3, 128.2, 127.8, 127.2, 124.6, 124.2, 111.4, 70.8, 59.8, 39.8, 37.0, 31.4, 26.6, 26.1.

3-[4-[isobutyl(methyl)amino]phenyl]-3-phenyl-isoindolin-1-one (610h)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-isobutyl-N-methyl-aniline (87 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (126 mg, 96 %).

RF (1:1 EtOAc:Hept): 0.26

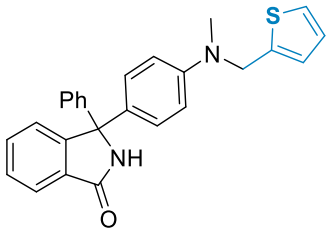
IR ν_{max} (cm^{-1}): 3166, 3053, 2954, 2868, 1694, 1608, 1519, 796

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{27}N_2O$ 371.2123; Found 371.2122

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.38 – 7.26 (m, 5H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.73 (s, 1H), 6.56 (d, *J* = 9.0 Hz, 2H), 3.06 (d, *J* = 7.3 Hz, 2H), 2.93 (s, 3H), 2.01 (hept, *J* = 8.0 Hz, 1H), 0.91 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 151.1, 149.2, 143.4, 132.3, 130.7, 129.0, 128.6, 128.3, 128.2, 127.8, 127.2, 124.6, 124.2, 111.5, 70.8, 60.9, 39.6, 27.5, 20.5.

3-[4-[methyl(2-thienylmethyl)amino]phenyl]-3-phenyl-isoindolin-1-one (610i)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (80 mg, 0.355 mmol), N-methyl-N-(2-thienylmethyl)aniline (108 mg, 0.533 mmol), $Ca(NTf_2)_2$ (11 mg, 0.018 mmol), $n$$Bu_4NPF_6$ (7 mg, 0.018 mmol) in 1,2-DCE (1.8 mL). Following completion of the reaction (12 h), purification by FCC (1:1 EtOAc:Heptane) afforded the pure compound as a white solid (130 mg, 89 %).
RF (1:1 EtOAc:Hept): 0.16

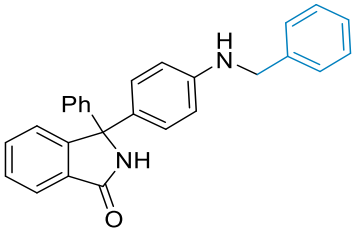
IR ν_{max} (cm^{-1}): 3166, 3053, 2954, 1687, 1517, 1321, 747

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{23}N_2OS$ 411.1531; 411.1539

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.36 – 7.27 (m, 5H), 7.17 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.90 – 6.87 (m, 1H), 6.75 (s, 1H), 6.71 (d, *J* = 9.0 Hz, 2H), 4.63 (s, 2H), 2.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 151.0, 148.8, 143.3, 142.0, 132.3, 130.7, 130.7, 128.6, 128.4, 128.3, 127.9, 127.2, 126.9, 125.0, 124.6, 124.5, 124.3, 112.8, 70.7, 52.0, 38.3.

3-[4-(benzylamino)phenyl]-3-phenyl-isoindolin-1-one (611a)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.222 mmol), N-benzyl-aniline (61 mg, 0.333 mmol), $Ca(NTf_2)_2$ (7 mg, 0.011 mmol), nBu$_4$NPF$_6$ (4 mg, 0.011 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a white solid (84 mg, 94 %).

RF (3:1 EtOAc:Hept): 0.68

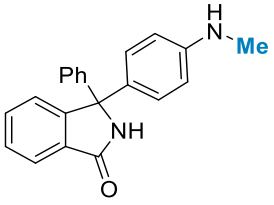
IR ν_{max} (cm^{-1}): 3378, 3058, 2850, 1685, 1608, 1517, 1187, 824

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{23}N_2O$ 391.1810; Found 391.1816

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.54 (s, 1H), 7.72 – 7.64 (m, 1H), 7.62 – 7.52 (m, 2H), 7.47 (ddd, *J* = 7.6, 6.4, 2.0 Hz, 1H), 7.36 – 7.22 (m, 9H), 7.22 – 7.17 (m, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 6.34 (t, *J* = 6.0 Hz, 1H), 4.23 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.5, 147.9, 143.9, 140.2, 131.8, 131.1, 129.9, 128.3, 128.2, 128.1, 127.7, 127.2, 127.2, 126.9, 126.6, 124.7, 123.1, 111.8, 69.8, 46.4.

3-[4-(methylamino)phenyl]-3-phenyl-isoindolin-1-one (611b)



The title compound was prepared according to general procedure **M** from 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.222 mmol), N-methyl-aniline (36 mg, 0.333 mmol), $Ca(NTf_2)_2$ (7 mg, 0.011 mmol), nBu$_4$NPF$_6$ (4 mg, 0.011 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h), purification by FCC (1:1 to 3:1 EtOAc:Heptane) afforded the pure compound as a yellow solid (73 mg, 92 %).

RF (3:1 EtOAc:Hept): 0.62

IR ν_{max} (cm^{-1}): 3407, 3056, 2812, 1664, 1519, 1187, 824

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2O$ 315.1497; Found 315.1502

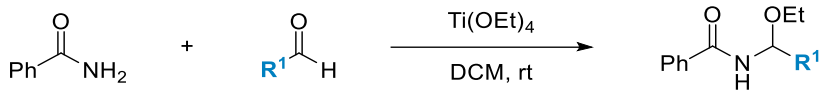
^1H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 – 7.22 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 8.7 Hz, 2H), 5.68 (q, *J* = 4.8 Hz, 1H), 2.63 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.3, 150.6, 149.1, 144.0, 131.8, 131.1, 129.6, 128.2, 128.1, 127.7, 127.2, 126.9, 124.7, 123.1, 111.2, 69.9, 29.7.

9.7. Chapter 7 Experimental

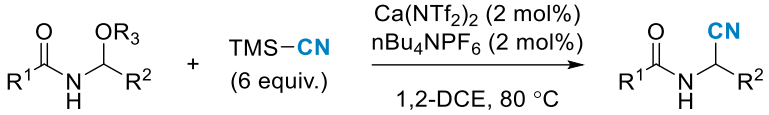
9.7.1. Chapter 7 General Procedures

General Procedure Q



Amide (1.0 equiv.) and aldehyde (1.2 equiv.) were dissolved in anhydrous DCM (0.25M) under an argon atmosphere. $Ti(OEt)_4$ (1.5 equiv.) was added dropwise and the reaction was stirred at room temperature overnight. The reaction was then diluted with ethanol and quenched through dropwise addition of a 0.5M K_2CO_3 solution. The resulting precipitate was then removed via slow filtration through Celite and washed 3 times with ethanol. The solution was then concentrated, and the resulting solid was purified by flash column chromatography (EtOAc:Hex) to afford the pure product.

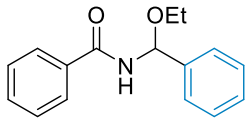
General Procedure R



To a 4 mL vial capped with a capped with teflon cap was added 3-hydroxyisoindolinone or *N*-acyl-*N,O*-acetal (1 equiv.), trimethylsilyl cyanide (TMSCN, 6 equiv.), $Ca(NTf_2)_2$ (2 mol%) and nBu$_4$NPF$_6$ (2 mol%) in 1,2-DCE (0.2 M). The reaction was stirred at 80 °C until TLC analysis indicated full conversion to the product (typically 12 h). The reaction was then quenched with sat. aq. $NaHCO_3$, and extracted into DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was then purified by FCC (EtOAc:Hept) to afford the pure compound.

9.7.2. Synthesis of Starting Materials – N-acyl-N,O-acetals

N-[ethoxy(phenyl)methyl]benzamide (644a)



The title compound was prepared according to general procedure **Q** from benzamide (6 g, 50 mmol), benzladehyde (6.3 g, 60 mmol) and $Ti(OEt)_4$ (17 g, 74 mmol) in DCM (165 mL). Purification by flash column chromatography (1:20 EtOAc:Hex) afforded the pure product as a white solid (4.9 g, 39%).

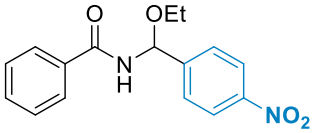
RF (1:3 EtOAc:Hept): 0.30

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.44 (m, 4H), 7.42 – 7.36 (m, 2H), 7.36 – 7.29 (m, 1H), 6.37 (d, *J* = 8.9 Hz, 1H), 3.71 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.57 (dq, *J* = 9.5, 7.0 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.7, 140.1, 133.8, 131.6, 128.3, 128.1, 127.9, 127.7, 126.4, 80.1, 62.9, 15.1.

*Data in accordance with literature[143]

N-[ethoxy-(4-nitrophenyl)methyl]benzamide (644b)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), 4-nitrobenzladehyde (450 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 EtOAc:Hex) afforded the pure product as a pale yellow solid (338 mg, 45%).

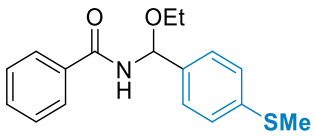
RF (1:3 EtOAc:Hept): 0.31

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.85 – 7.79 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 6.67 (s, 1H), 6.57 (d, *J* = 9.5 Hz, 1H), 3.95 – 3.80 (m, 1H), 3.80 – 3.68 (m, 1H), 1.32 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 148.0, 146.9, 133.3, 132.5, 128.9, 127.3, 123.9, 79.5, 64.7, 15.2.

*Data in accordance with literature[143]

N-[ethoxy-(4-methylsulfanylphenyl)methyl]benzamide (644c)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), 4-(methylthio)benzladehyde (450 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 EtOAc:Hex) afforded the pure product as a white solid (458 mg, 61%).

RF (1:3 EtOAc:Hept): 0.33

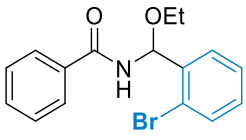
IR ν_{max} (cm^{-1}): 3282, 2973, 2876, 1644, 1519, 1273, 1090

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_2S$ 302.1215; Found 302.1225

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.39 (m, 4H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 9.3 Hz, 1H), 3.83 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.70 (dq, *J* = 9.5, 7.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 139.0, 136.7, 133.9, 132.1, 128.8, 127.2, 126.7, 126.6, 80.1, 64.3, 15.9, 15.3.

N-[(2-bromophenyl)-ethoxy-methyl]benzamide (644d)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), 2-bromobenzladehyde (550 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 to 1:3 EtOAc:Hex) afforded the pure product as a white solid (718 mg, 87%).

RF (1:3 EtOAc:Hept): 0.39

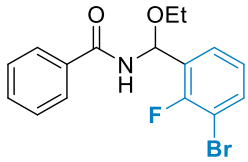
IR ν_{max} (cm^{-1}): 3286, 2973, 2928, 1642, 1517, 1263, 1088

HRMS (APCI) m/z: $[M - C_2H_6O]^+$ Calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0453

^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.72 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H), 6.64 – 6.52 (m, 2H), 3.87 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.73 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 138.7, 133.9, 133.5, 132.1, 130.2, 128.8, 127.9, 127.8, 127.3, 122.8, 80.4, 64.5, 15.3.

N-[(3-bromo-2-fluoro-phenyl)-ethoxy-methyl]benzamide (644e)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), 3-bromo-2-fluorobenzladehyde (603 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 to 1:3 EtOAc:Hex) afforded the pure product as a white solid (163 mg, 19%).

RF (1:3 EtOAc:Hept): 0.18

IR ν_{max} (cm^{-1}): 3267, 2971, 2919, 1643, 1517, 1353, 1051, 841

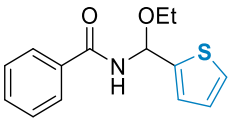
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}BrFNO_2$ 352.0348; Found 352.0358

^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.60 – 7.51 (m, 3H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.09 (td, *J* = 7.9, 0.9 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.62 (d, *J* = 9.4 Hz, 1H), 3.86 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.72 (dq, *J* = 9.5, 7.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 156.8 (d, *J* = 249.5 Hz), 133.9, 133.7, 132.2, 128.8, 127.3, 127.2, 128.5 (d, *J* = 13.8 Hz), 125.4 (d, *J* = 4.4 Hz), 109.9 (d, *J* = 20.9 Hz), 64.5, 15.2.

^{19}F NMR (376 MHz, $CDCl_3$): -110.9

N-[ethoxy(2-thienyl)methyl]benzamide (644)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), 2-thiophenecarboxaldehyde (333 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 to 1:3 EtOAc:Hex) afforded the pure product as a white solid (340 mg, 53%).

RF (1:3 EtOAc:Hept): 0.21

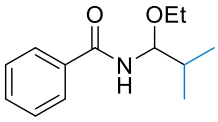
IR ν_{max} (cm^{-1}): 3278, 2976, 1646, 1523, 1273, 1072

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_2S$ 262.0902; Found 262.0900

^1H NMR (400 MHz, DMSO-d_6): δ 9.40 (d, *J* = 8.9 Hz, 1H), 7.97 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.08 (dt, *J* = 3.5, 1.2 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.58 (dd, *J* = 8.9, 0.8 Hz, 1H), 3.70 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.61 (dq, *J* = 9.7, 7.0 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.6, 143.7, 133.5, 131.7, 128.3, 127.8, 126.7, 125.8, 124.7, 77.3, 63.0, 15.0.

N-(1-ethoxy-2-methyl-propyl)benzamide (644g)



The title compound was prepared according to general procedure **Q** from benzamide (300 mg, 2.5 mmol), isobutraldehyde (214 mg, 3.0 mmol) and $Ti(OEt)_4$ (850 mg, 3.7 mmol) in DCM (6 mL). Purification by flash column chromatography (1:20 to 1:3 EtOAc:Hex) afforded the pure product as a white solid (385 mg, 70%).

RF (1:3 EtOAc:Hept): 0.41

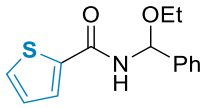
IR ν_{max} (cm^{-1}): 3283, 3058, 2976, 2872, 1633, 1530, 1489, 1092

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}NO_2$ 222.1494; Found 222.1504

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.29 (d, *J* = 9.1 Hz, 1H), 5.18 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.69 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.56 (dq, *J* = 9.7, 7.0 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 134.4, 131.9, 128.8, 127.1, 84.4, 64.2, 33.6, 18.1, 17.6, 15.3.

N-[ethoxy(phenyl)methyl]thiophene-2-carboxamide (654)



The title compound was prepared according to general procedure **Q** from thiophene-2-carboxamide (300 mg, 2.4 mmol), benzaldehyde (300 mg, 2.8 mmol) and $Ti(OEt)_4$ (807 mg, 3.5 mmol) in DCM (6 mL). Purification by flash column chromatography (1:9 to 1:3 EtOAc:Hex) afforded the pure product as a white solid (120 mg, 19%).

RF (1:3 EtOAc:Hept): 0.44

IR ν_{max} (cm^{-1}): 3282, 2972, 1623, 1534, 1280, 1042

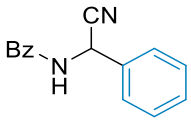
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_2S$ 262.0902; Found 262.0912

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.45 (m, 4H), 7.45 – 7.30 (m, 3H), 7.08 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.43 (s, 2H), 3.86 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.71 (dq, *J* = 9.5, 7.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 139.7, 138.5, 131.0, 128.8, 128.7, 128.7, 127.9, 126.1, 80.3, 64.4, 15.3.

9.7.3. Synthesis of α-amido nitriles – Aldehyde Variation

N-[cyano(phenyl)methyl]benzamide (645a)



The title compound was prepared according to general procedure **R** from N-[ethoxy(phenyl)methyl]benzamide (50 mg, 0.196 mmol), TMSCN (117 mg, 147 µL, 1.18 mmol), $Ca(NTf_2)_2$ (2.4 mg, 0.0039 mmol), nBu$_4$NPF$_6$ (1.5 mg, 0.0039 mmol) in 1,2-DCE (1 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (40 mg, 86 %).

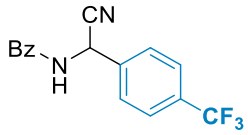
RF (1:3 EtOAc:Hept): 0.26

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dt, J = 8.5, 1.7 Hz, 2H), 7.60 – 7.53 (m, 3H), 7.51 – 7.41 (m, 5H), 6.64 (d, J = 7.0 Hz, 1H), 6.36 (d, J = 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 133.4, 132.7, 132.5, 129.8, 129.6, 128.9, 127.4, 127.2, 117.6, 44.7.

*Data in accordance with literature[210]

N-[cyano-[4-(trifluoromethyl)phenyl]methyl]benzamide (645b)



The title compound was prepared according to general procedure **R** from N-{methoxy[4-(trifluoromethyl)phenyl]methyl}sbenzamide (80 mg, 0.259 mmol), TMSCN (154 mg, 194 µL, 1.55 mmol), $Ca(NTf_2)_2$ (7.8 mg, 0.0129 mmol), nBu$_4$NPF$_6$ (5 mg, 0.0129 mmol) in 1,2-DCE (1.3 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:9 to 1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (56 mg, 71 %).

RF (1:3 EtOAc:Hept): 0.30

IR ν_{max} (cm^{-1}): 3263, 2937, 1646, 1521, 1323, 1113

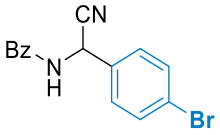
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}F_3N_2O$ 305.0902; Found 305.0912

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.78 (m, 2H), 7.75 – 7.67 (m, 3H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.52 – 7.45 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 133.0, 132.2, 129.1, 129.0, 127.7, 127.4, 127.2, 126.6 (q, *J* = 3.7 Hz), 126.6, 116.9, 44.2.

^{19}F NMR (376 MHz, $CDCl_3$): -62.9

N-[(4-bromophenyl)-cyano-methyl]benzamide (645c)



The title compound was prepared according to general procedure **R** from N-[(4-bromophenyl)(methoxy)methyl]benzamide (25 mg, 0.0781 mmol), TMSCN (47 mg, 60 µL, 0.468 mmol), $Ca(NTf_2)_2$ (2.3 mg, 0.0039 mmol), *n*Bu_4NPF_6 (1.55 mg, 0.0039 mmol) in 1,2-DCE (0.4 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:9 to 1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (19 mg, 77 %).

RF (1:3 EtOAc:Hept): 0.29

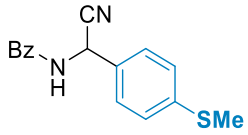
IR ν_{max} (cm^{-1}): 3248, 2917, 1642, 1517, 1325, 1012

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}BrN_2O$ 315.0133; Found 315.0143

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.76 (m, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.46 – 7.39 (m, 3H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H).z

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 132.9, 132.8, 132.5, 132.3, 129.1, 128.9, 127.4, 124.2, 117.1, 44.2.

N-[cyano-(4-methylsulfanylphenyl)methyl]benzamide (645d)



The title compound was prepared according to general procedure **R** from N-[ethoxy-(4-methylsulfanylphenyl)methyl]benzamide (100 mg, 0.333 mmol), TMSCN (198 mg, 250 µL, 2.0 mmol), $Ca(NTf_2)_2$ (4 mg, 0.0066 mmol), $n$$Bu_4NPF_6$ (2.6 mg, 0.0066 mmol) in 1,2-DCE (1.7 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:9 to 1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (72 mg, 77 %).

RF (1:3 EtOAc:Hept): 0.16

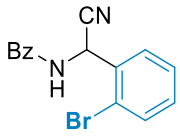
IR ν_{max} (cm^{-1}): 3267, 2917, 1644, 1513, 1489, 1320, 960

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2OS$ 283.0905; Found 283.0895

^1H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.76 (m, 2H), 7.55 (tt, *J* = 2.0, 1.3 Hz, 1H), 7.48 – 7.42 (m, 4H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 8.3 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 166.6, 141.3, 132.7, 132.5, 129.7, 129.0, 127.7, 127.4, 126.9, 117.5, 44.4, 15.5.

N-[(2-bromophenyl)-cyano-methyl]benzamide (645e)



The title compound was prepared according to general procedure **R** from N-[(2-bromophenyl)-ethoxy-methyl]benzamide (100 mg, 0.299 mmol), TMSCN (178 mg, 225 µL, 1.8 mmol), $Ca(NTf_2)_2$ (3.6 mg, 0.006 mmol), $n$$Bu_4NPF_6$ (2.3 mg, 0.006 mmol) in 1,2-DCE (1.5 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:9 to 1:3 EtOAc:Heptane) afforded the pure compound as a white solid (78 mg, 83 %).

RF (1:3 EtOAc:Hept): 0.29

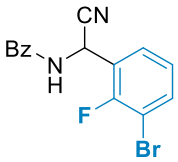
IR ν_{max} (cm^{-1}): 3265, 2920, 1640, 1523, 1325, 1077

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}BrN_2OS$ 315.0133; Found 315.0143

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.73 (m, 3H), 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (tt, *J* = 2.0, 1.3 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.33 (td, *J* = 7.7, 1.7 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 134.2, 132.7, 132.5, 132.4, 131.6, 130.3, 129.0, 128.5, 127.4, 123.4, 116.9, 45.6.

N-[(3-bromo-2-fluoro-phenyl)-cyano-methyl]benzamide (645f)



The title compound was prepared according to general procedure **R** from N-[(3-bromo-2-fluoro-phenyl)-ethoxy-methyl]benzamide (100 mg, 0.284 mmol), TMSCN (169 mg, 213 µL, 1.7 mmol), $Ca(NTf_2)_2$ (3.4 mg, 0.0057 mmol), $n$$Bu_4NPF_6$ (2.2 mg, 0.0057 mmol) in 1,2-DCE (1.4 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (58 mg, 61 %).
RF (1:3 EtOAc:Hept): 0.19

IR ν_{max} (cm^{-1}): 3258, 2920, 1638, 1517, 1456, 1329, 788

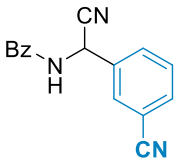
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{11}BrFN_2OS$ 333.0039; Found 333.0039

^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.66 (ddd, *J* = 8.1, 6.7, 1.6 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.14 (td, *J* = 8.0, 0.9 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 135.6, 132.9, 132.3, 129.0, 128.8 (d, *J* = 2.2 Hz), 127.4, 126.1 (d, *J* = 4.7 Hz), 122.6 (d, *J* = 14.4 Hz), 116.3, 110.5 (d, *J* = 20.2 Hz), 40.4.

^{19}F NMR (376 MHz, $CDCl_3$): -109.6

N-[cyano-(3-cyanophenyl)methyl]benzamide (645g)



The title compound was prepared according to general procedure **R** from N-[(3-cyanophenyl)(methoxy)methyl]benzamide (74 mg, 0.278 mmol), TMSCN (165 mg, 209 µL, 1.7 mmol), $Ca(NTf_2)_2$ (8.3 mg, 0.014 mmol), $n$$Bu_4NPF_6$ (5.4 mg, 0.014 mmol) in 1,2-DCE (1.4 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (67 mg, 92 %).
RF (1:3 EtOAc:Hept): 0.10

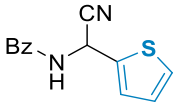
IR ν_{max} (cm^{-1}): 3260, 3036, 2234, 1646, 1517, 1321

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}N_3OS$ 262.0980; Found 262.0973

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.77 (m, 4H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 135.4, 133.3, 133.1, 132.0, 131.7, 130.7, 130.5, 129.1, 127.5, 117.9, 116.7, 113.8, 43.9.

N-[cyano(2-thienyl)methyl]benzamide (645h)



The title compound was prepared according to general procedure **R** from N-[ethoxy(2-thienyl)methyl]benzamide (74 mg, 0.284 mmol), TMSCN (169 mg, 213 µL, 1.7 mmol), $Ca(NTf_2)_2$ (3.4 mg, 0.0057 mmol), $n$$Bu_4NPF_6$ (2.2 mg, 0.0057 mmol) in 1,2-DCE (1.4 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as an orange solid (60 mg, 87 %).
RF (1:3 EtOAc:Hept): 0.21

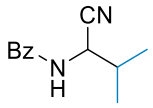
IR ν_{max} (cm^{-1}): 3271, 3107, 2909, 1642, 1508, 1485, 1238, 848

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2OS$ 243.0592; Found 243.0600

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.40 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.36 (dt, *J* = 3.6, 1.1 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.52 (dd, *J* = 8.4, 0.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 135.7, 132.8, 132.4, 129.0, 128.0, 127.8, 127.5, 127.5, 117.0, 40.5.

N-(1-cyano-2-methyl-propyl)benzamide (645i)



The title compound was prepared according to general procedure **R** from N-(1-ethoxy-2-methyl-propyl)benzamide (60 mg, 0.271 mmol), TMSCN (161 mg, 204 µL, 1.6 mmol), $Ca(NTf_2)_2$ (8.1 mg, 0.014 mmol), *n*Bu_4NPF_6 (5.3 mg, 0.014 mmol) in 1,2-DCE (1.4 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (48 mg, 88 %).
RF (1:3 EtOAc:Hept): 0.21

IR ν_{max} (cm^{-1}): 3267, 2969, 2876, 1636, 1522, 1306, 855

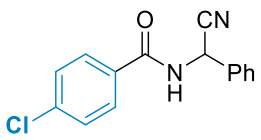
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}N_2O$ 203.1184; Found 203.1189

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 5.03 (dd, *J* = 8.9, 6.4 Hz, 1H), 2.24 – 2.10 (m, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 133.0, 132.5, 129.0, 127.3, 118.0, 47.1, 32.0, 18.8, 18.2.

9.7.4. Synthesis of α-amido nitriles – Amide Variation

4-chloro-N-[cyano(phenyl)methyl]benzamide (657a)



The title compound was prepared according to general procedure **R** from 4-chloro-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (53 mg, 0.174 mmol), TMSCN (104 mg, 131

µL, 1.1 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.0087 mmol), nBu$_4$NPF$_6$ (3.4 mg, 0.0087 mmol) in 1,2-DCE (0.9 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (26 mg, 55 %).
RF (1:3 EtOAc:Hept): 0.30

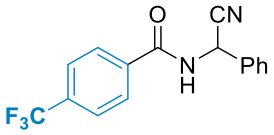
IR ν_{max} (cm^{-1}): 3319, 2917, 1644, 1517, 1482, 1092

HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}ClN_2O$ 271.0638; Found 271.0640

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.60 – 7.52 (m, 2H), 7.51 – 7.38 (m, 5H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.32 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 139.2, 133.1, 130.9, 130.0, 129.7, 129.3, 128.9, 127.3, 117.4, 44.9.

N-[cyano(phenyl)methyl]-4-(trifluoromethyl)benzamide (657b)



The title compound was prepared according to general procedure **R** from N-[ethoxy(phenyl)methyl]-4-(trifluoromethyl)benzamide (56 mg, 0.174 mmol), TMSCN (104 mg, 131 µL, 1.1 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.0087 mmol), nBu$_4$NPF$_6$ (3.4 mg, 0.0087 mmol) in 1,2-DCE (0.9 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a white solid (32 mg, 60 %).
RF (1:3 EtOAc:Hept): 0.44

IR ν_{max} (cm^{-1}): 3241, 2021, 1644, 1528, 1325, 1109, 1062

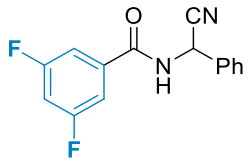
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}F_3N_2O$ 305.0902; Found 305.0898

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.54 (m, 2H), 7.51 – 7.44 (m, 3H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.33 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 135.8, 134.4 (q, *J* = 32.7 Hz), 132.9, 130.0, 129.7, 128.0, 127.3, 126.0 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.7 Hz), 117.4, 44.9.

^{19}F NMR (376 MHz, $CDCl_3$): -63.1.

N-[cyano(phenyl)methyl]-3,5-difluoro-benzamide (657c)



The title compound was prepared according to general procedure **R** from 3,5-difluoro-N-{phenyl[(propan-2-yl)oxy]methyl}benzamide (90 mg, 0.295 mmol), TMSCN (175 mg, 221 µL, 1.8 mmol), $Ca(NTf_2)_2$ (5.7 mg, 0.015 mmol), $n$$Bu_4NPF_6$ (5.7 mg, 0.015 mmol) in 1,2-DCE (1.5 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (31 mg, 38 %).

RF (1:3 EtOAc:Hept): 0.35

IR ν_{max} (cm^{-1}): 3297, 3088, 2924, 1655, 1595, 1526, 1336, 1124, 988

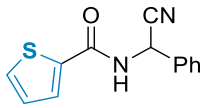
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{11}F_2N_2OS$ 273.0839; Found 273.0827

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 2H), 7.50 – 7.43 (m, 3H), 7.36 – 7.28 (m, 2H), 7.00 (tt, *J* = 8.5, 2.3 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.28 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (101 MHz, CDCl3): δ 164.5 (d, *J* = 12.1 Hz), 164.2, 161.9 (d, *J* = 12.1 Hz), 135.8 (t, *J* = 8.4 Hz), 132.8, 130.1, 129.8, 127.3, 117.2, 110.9 (d, *J* = 7.9 Hz), 110.7 (d, *J* = 7.9 Hz), 108.2 (t, *J* = 25.2 Hz), 45.0.

^{19}F NMR (376 MHz, $CDCl_3$): -107.0

N-[cyano(phenyl)methyl]thiophene-2-carboxamide (657d)



The title compound was prepared according to general procedure **R** from N-[ethoxy(phenyl)methyl]thiophene-2-carboxamide (60 mg, 0.230 mmol), TMSCN (137 mg, 172 µL, 1.4 mmol), $Ca(NTf_2)_2$ (6.9 mg, 0.012 mmol), $n$$Bu_4NPF_6$ (4.5 mg, 0.012 mmol) in 1,2-DCE (1.2 mL). Following completion of the reaction (12 h) and work-up, purification by FCC (1:3 EtOAc:Heptane) afforded the pure compound as a yellow solid (38 mg, 68 %).

RF (1:3 EtOAc:Hept): 0.14

IR ν_{max} (cm^{-1}): 3241, 3029, 1627, 1532, 1299, 853

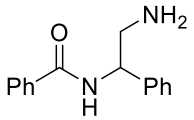
HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2OS$ 243.0592; Found 243.0597

^1H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.52 (m, 4H), 7.50 – 7.40 (m, 3H), 7.10 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 6.33 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 161.0, 136.7, 133.3, 131.8, 129.8, 129.6, 128.1, 127.3, 117.4, 44.6.

9.7.5. Applications of Products

N-(2-amino-1-phenyl-ethyl)benzamide (658)



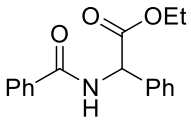
To an oven dried RBF purged with argon was added **745a** (100 mg, 0.42 mmol) and was dissolved in anhydrous THF (2 mL). The solution was cooled to 0 °C and $LiAlH_4$ (161 mg, 1.8 mL, 2.4M in THF, 4.2 mmol) was added dropwise. The reaction was allowed to warm to room temperature and the reaction was stirred until TLC indicated completion of the reaction (1.5 h). Upon completion of reaction, the reaction was quenched with H_2O followed by 15% NaOH followed by a further addition of H_2O and transferred to a separating funnel. The organic layer was extracted into DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by FCC (1:9 MeOH:DCM) to afford the pure product as a white solid (48 mg, 50 %).

RF (1:9 MeOH:DCM): 0.24

^1H NMR (400 MHz, DMSO-d_6): δ 8.72 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 6.9 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 4.96 (dd, *J* = 13.6, 8.2 Hz, 1H), 3.22 (s, 2H), 2.89 (ddd, *J* = 18.4, 13.1, 7.1 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.4, 142.4, 134.7, 131.1, 128.2, 127.4, 126.7, 126.6, 56.7, 47.1.

ethyl 2-benzamido-2-phenyl-acetate (659)



745a (20 mg, 0.085 mmol) was dissolved in a 1:1 solution of conc. HCl (0.7 mL) and EtOH (0.7 mL) and the reaction was heated to reflux overnight. Upon completion of the reaction, indicated by TLC, the reaction was allowed to cool and the pH was adjusted to pH = 9 by slow addition of 1M NaOH. The solution was then transferred to a separating funnel whereby the aqueous layer was extracted into DCM (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by FCC (1:3 EtOAc:Heptane) to afford the pure compound as a white solid (16 mg, 67%).

RF (1:3 EtOAc:Hept): 0.21

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.41 – 7.31 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 4.28 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 166.7, 136.9, 133.8, 132.0, 129.1, 128.8, 128.7, 127.4, 127.3, 62.2, 57.0, 14.2.

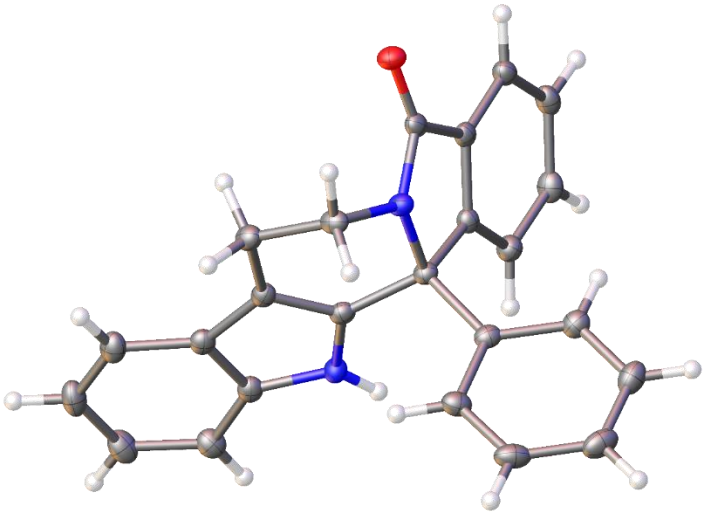
*Data in accordance with literature[211]

9.8. X-ray Data

2-phenyl-10,20-diazapentacyclo[11.7.0.02,10.03,8.014,19]icosa-1(13),3,5,7,14(19),15,17-heptaen-9-one (317a)

A single crystal was selected and mounted, on a Mitegen loop using Paratone-N oil, on a SuperNova, Cu, AtlasS2 diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [1], the structure was solved with the SHELXT [2] structure solution program using Intrinsic Phasing and refined with the SHELXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.



Crystal data and structure refinement for CCDC 2154226, this data is available free-of-charge from www.ccdc.cam.ac.uk.

Identification code	Compound **317a**
Empirical formula	$C_{24}H_{18}N_2O$
Formula weight g/mol	350.40
Temperature/K	100(2)
Crystal system	orthorhombic

Space group	$P2_12_12_1$
a/Å	10.84410(10)
b/Å	11.71540(10)
c/Å	13.6836(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1738.41(3)
Z	4
ρ_{calc} g/cm^3	1.339
μ/mm^{-1}	0.649
F(000)	736.0
Crystal size/mm^3	0.13 × 0.06 × 0.03
Radiation	Cu Kα (λ = 1.54184 Å)
2Θ range for data collection/°	9.94 to 152.482
Index ranges	-12 ≤ h ≤ 13, -14 ≤ k ≤ 11, -16 ≤ l ≤ 17
Reflections collected	19183
Independent reflections	3596 [R_{int} = 0.0270, R_{sigma} = 0.0155]
Data/restraints/parameters	3596/0/245
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0296, wR_2 = 0.0773
Final R indexes [all data]	R_1 = 0.0301, wR_2 = 0.0779
Largest diff. peak/hole / e Å^{-3}	0.22/-0.16
Flack parameter	-0.12(7)

10. Chapter 10: References

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